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Family-based interventions for adults with type 2 diabetes mellitus (Protocol)

Matrook KA, Cowman S, Dovey SM, Smith SM, McGilloway S, Whitford DL

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[Intervention Protocol]

Family-based interventions for adults with type 2 diabetes mellitus

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of family-based interventions to improve outcomes in people with type 2 diabetes mellitus and to consider, where possible, which components of the interventions are most effective.

BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency invariably leads to chronic hyperglycaemia (elevated levels of plasma glucose), with disturbances of carbohydrates, fat, and protein metabolism. There are different types of diabetes mellitus; the most common are type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Type 2 diabetes affects individuals with relative insulin deficiency and insulin resistance. Insulin resistance is characterized by failure of the body tissue to dispose glucose in response to insulin due to excess body weight. Both insulin deficiency and insulin resistance lead to hyperglycaemia in T2DM. Although there are various causes of T2DM, these are still not fully understood. Compared to T1DM, T2DM is often associated with strong genetic risk. The risk of developing T2DM increases with several factors such as age, obesity, lack of physical activity, history of gestational diabetes, dyslipidaemia (abnormal amount of lipids in the blood), and hypertension (ADA 2017).
The prevalence of diabetes is steadily increasing across the globe (IDF 2015). The true global figures of the number of people with diabetes are unknown, but the World Health Organization (WHO) estimated in 2014 that 422 million people were affected (WHO 2016), and the International Diabetes Federation (IDF) estimated that there were 415 million cases in 2015 (IDF 2015), excluding children. These estimates indicate an approximate dou-

bling of the global prevalence (age-standardised) of diabetes from 1980, when there were 108 million cases (WHO 2016). The IDF highlighted that diabetes had affected 9% of adults in 2015 (IDF 2015). The majority of these people (above 90%) have T2DM (ADA 2017; King 1998). The IDF estimates that there will be 642 million people with diabetes in the world by 2040. This means one in every 10 adults will have diabetes. This dramatic growth of diabetic people places serious demands on healthcare services. Health expenditure on diabetes is estimated to be USD 673 billion to USD 1197 billion annually, accounting for up to 12% of overall global health expenditure in 2015 (IDF 2015). Globally, the health expenditure for people with diabetes is two- to three-fold higher than for people without diabetes (IDF 2015).

Diabetes leads to multiple complications that can increase the overall risk of early death. People with T2DM suffer from complications such as microvascular and macrovascular complications as a result of sub-optimal control of blood glucose (ADA 2017; WHO 2016). The development of microvascular complications increases with both the severity and duration of hyperglycaemia, while the risk of macrovascular complications depends on age, gender, genetic factors, and behaviour (e.g. exercise, diet, smoking) (Vermeire 2005). Microvascular complications include retinopathy (retina damage), nephropathy (kidney damage), and neuropathy (nerve damage). The principal mechanism of macrovascular complications is atherosclerosis (narrowing of arteries due to the build up of plaque), which results from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. This leads to narrowing of arterial walls, which can consequently lead to cerebrovascular diseases (e.g. stroke, transient ischemics attack) (ADA 2017; Fowler 2008; WHO 2016). In people with T2DM, prospective trials have demonstrated an association between the degree of hyperglycaemia and the increased risk of microvascular and macrovascular complications, and all-cause mortality (Stratton 2000).

Several trials in T2DM have indicated that the incidence of complications can be improved by metabolic control achieved through a combination of behaviour-changing interventions or pharmacological management, or both (Ohkubo 1995; UKPDS 1998). Therefore, reducing the risk of complications requires continuous medical care and multifaceted risk reduction strategies. Behaviour-changing interventions involve diabetes self-management education (DSME), diabetes self-management support (DSMS), physical activity, nutrition therapy (ADA 2017; Ohkubo 1995; UKPDS 1998), psychosocial care, smoking cessation (ADA 2017), and medication management (Deakin 2005; IDF 2015). Adherence to a diabetes treatment recommendations has been associated with improved outcomes (Sabate 2003; UKPDS 1998; Watkins 2003). Improving glycaemic control in individuals with T2DM reduces the incidence of microvascular complications (Stratton 2000); whether the same is true about macrovascular complications remains uncertain (Stratton 2000)

Description of the intervention

Disease management can be complex for people with diabetes and their families (ADA 2017; WHO 2016). Family-based interventions include supporting family members in caring for patients with chronic illnesses, because disease management mostly takes place within homes and communities (Baig 2015; Fisher 2000). Family members include people who have legal, biological, or emotional relationships with the patient (Baig 2015). Key components of family support may include training family members in supportive communication, providing family members with the necessary tools that assist in monitoring clinical symptoms, and guiding family members to set goals for self-care behaviour (Baig 2015). Family members play direct and indirect roles in disease management (Deakin 2005). Disease management affects family members behaviorally (Rosland 2012), cognitively, and emotionally (Fisher 1998; Fisher 2000). Family-based interventions do not occur in an isolated social context, but rather as an adjunct to usual treatment (Armour 2005; Fisher 2000).

Approaches for supporting people with T2DM to modify and sustain behaviours involve a mix of health service change, education, behavioural interventions, and psychosocial interventions (Thorpe 2013). These interventions have tended to focus on individuals, rather than their families and social environments (Baig 2015; Fisher 2000). Family approaches emphasise addressing educational, relational, and personal needs of both the individual and family members (Armour 2005; Fisher 2000). Unlike usual care, family-based interventions are concerned with the psychosocial and emotional aspects of diseases. This may explain why people with diabetes are less likely to adhere to behaviour-changing modifications without intervention (Deakin 2005). Thus, family approaches to chronic disease management may be promising in complementing traditional treatment strategies (Fisher 1998).

Adverse effects of the intervention

Family relationships can either be protective or a risk factor (Mayberry 2012). Family members can have positive or negative impacts on the health of people with diabetes. For example, family members can facilitate or interfere with self-care activities such as refilling prescriptions or buying groceries (Mayberry 2012). Therefore, recognising which specific family behaviours are linked to better or worse disease management could enable better understanding and inform strategies that families could use to increase their effective support (Rosland 2012).

How the intervention might work

Several conceptual frameworks and theoretical models describe the mechanisms by which family-based interventions influence the outcomes of chronic diseases. Logically, family-based interventions provide an arena where the individual, family members

and healthcare systems intersect. This intersection might provide an ideal environment for meaningful intervention in an appropriate context (Baig 2015). A 2013 systematic review on the role of family in adults with diabetes reported that most intervention studies were based on relatively similar hypotheses (Torenholt 2014). Reviewed intervention studies hypothesise that active family involvement could improve social support (Armour 2005; Baig 2015; Rosland 2012; Torenholt 2014), which can in turn facilitate adopting and maintaining diabetes self-management skills (Armour 2005). Disease outcomes might be improved as a result. Theoretically, family-based intervention studies outline certain models based on the social dimensions. For instance, family system theory describes the influence of emotional interconnectedness on family members' approaches to disease management. Likewise, interdependence theory appreciates that interaction affects both the family and the individual (Rosland 2012; Torenholt 2014).

Key findings suggest two principal mechanisms by which family relationships can influence outcomes in chronic diseases, i.e. family dynamics and social context (Fisher 1998; Fisher 2000).

- Family dynamics are thought to influence outcomes in chronic diseases (Torenholt 2014), due to the vital interaction among three factors. This vital interaction tends to produce lively association between the three principal factors. These factors are: the family's developmental stage (i.e. family's coping skills and conflicts resolution, taking into account social and economic status) (Fisher 1998; Wens 2005); family characteristics (e.g. family organisation, beliefs, emotions, and problem solving skills); and characteristics of diseases (e.g. chronicity, demands for care, typical course) (Fisher 1998). Characteristics of family relationships (e.g. cohesion, stability, family satisfaction, and interpersonal criticalness) can have enhancing or disruptive effects on disease outcomes (Baig 2015; Fisher 1998). For instance, responses from family members to the disease and its management can impact peoples' self-management behaviours (Fisher 2000).
- The family social context of disease management is potentially central to successful adaptation of self-regulation skills (Fisher 1998; Fisher 2000). Family social context includes physical, psychosocial, relational, familial, educational, and personal needs and interests of both the family and the individual. In the case of diabetes, most of the self-regulatory behaviours involved in the self-management of the condition occur in the home environment, and can be therefore be influenced by family members (Fisher 2000). This is particularly true in certain cultures where family is still intact and cohesive (Baig 2015). Fisher and colleagues argue that family social context is the greatest, most pervasive, with the longest lasting influence on the management of T2DM (Fisher 1998). Adopting behavioural self-regulation skills such as taking medication, testing glucose, and modifying diet require a receptive family social context (Fisher 1998; White 2005).

One of the key challenges of disease management for diabetes is that people with diabetes may not perceive many of the behaviour changing modifications required (such as dietary restrictions and exercise) as desirable. This can negatively affect adherence (Armour 2005; Davies 2008; Gonder-Frederick 2002; Keogh 2011). Within the family-based intervention, family and disease outcomes seem to result primarily by the reciprocal determinism between family dynamics and social context (Baig 2015; Fisher 1998; White 2005). In reciprocal determinism a person's behaviour both influences and is influenced by personal factors and the social environment (Bandura 1978). This reciprocal association, in turn, can lead to a greater sense of well-being, improved diabetes self-management behaviours (Torenholt 2014), and potentially improved disease outcomes (Armour 2005; Fisher 2000; Rosland 2012; Torenholt 2014; White 2005). A recent systematic review targeting diabetes outcomes through family-based interventions among adults with diabetes, found evidence for improvement in diabetes-related self-care, diabetes knowledge, perceived social support and self-efficacy (Baig 2015).

Why it is important to do this review

Although some evidence indicates that family-based interventions are potentially valuable in improving diabetes outcomes (Baig 2015; Fisher 1998; Torenholt 2014), research targeting the interface between adults with chronic diseases and their families is relatively scarce (Torenholt 2014). Despite the wide use of family-based interventions in managing diabetes among children (Armour 2005; Baig 2015 Chesla 2010; Hood 2010), the existing literature suggests their use is limited among adults (Baig 2015; Thorpe 2013; Torenholt 2014), particularly among people with T2DM (Gonder-Frederick 2002; White 2005; White 2007). Although various interventions to improve T2DM outcomes have been developed over the past twenty years (Steed 2003), research on family interventions for chronic diseases remains developmental (Torenholt 2014). Therefore, a comprehensive assessment of the published literature is necessary to assess the effectiveness of family-based intervention in people with T2DM, and to consider where possible which components of the intervention are effective.

A previous systematic review of randomised controlled trials (RCTs) examined the effectiveness of family-based interventions designed to improve outcomes in people with diabetes (Armour 2005). The review was limited in that it included only published trials which used randomised trial designs where family members were residing together. A recent systematic review included all study types (e.g. RCTs, pre-post, pilot) and examined family-based interventions for adults with diabetes (Baig 2015). Limitations of that review were that it included only published studies in English or Spanish, and only studies that were conducted in the United States (Baig 2015). Our proposed review intends to overcome these limitations by: 1) including RCTs and controlled

clinical trial (CCT) designs; 2) including trials of interventions delivered to affected individuals and family members not necessarily residing together; and 3) including trials published in all languages, with no geographical limitations.

OBJECTIVES

To assess the effects of family-based interventions to improve outcomes in people with type 2 diabetes mellitus and to consider, where possible, which components of the interventions are most effective.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and controlled clinical trials (CCTs).

Types of participants

Family members will be adults (aged 18 years or more), and will include any relative in regular contact with the person with type 2 diabetes mellitus (T2DM) and who is significantly involved in supporting the person in the management of their illness. The family member for this review is not necessarily a carer, but someone with whom the person with T2DM has a close relationship. This may include: parent; grandparent; child; grandchild; sibling; aunts; uncles; nieces; nephews; step-parent, or stepchild.

Diagnostic criteria for diabetes mellitus

To be consistent with changes in the classification of and diagnostic criteria for diabetes mellitus over the years, the diagnosis should be established using the standard criteria valid at the time of the trial commencing (for example: ADA 2003; ADA 2017; WHO 1999). Ideally, the diagnostic criteria should have been described. We will use the trial authors' definition of diabetes mellitus if necessary. We plan to conduct a sensitivity analysis according to diagnostic criteria used.
Changes in diagnostic criteria may produce significant variability in the clinical characteristics of the participants included, as well as in the results obtained (which we will also investigate through subgroup analysis).

Types of interventions

We plan to investigate family-based interventions in comparison with a control group. As there is no standard definition for "family-based intervention", for this review we will define these as any interventions designed to improve outcomes in adults (above 18 years) with T2DM, which involve at least one other family member, and are delivered in a community or ambulatory care setting (e.g. home-based). Trials involving interventions delivered to a family member alone will only be included if they assess outcomes for the person with diabetes.

Intervention

- Family-based intervention

Comparator

- Usual care

We will define the control group as having usual care in the setting of T2DM (e.g. team care, specialist care, family physician care, or any other model of care). As there will be differences to what constitutes usual care, we will clearly describe this for all trials included in the review.
Concomitant interventions must be the same in both the intervention and comparator groups to establish fair comparisons. If a trial includes multiple arms, we will include any arm that meets our inclusion criteria.

Minimum duration of intervention

The minimum duration of intervention will be four weeks.

Minimum duration of follow-up

The minimum duration of follow-up will be three months.

Summary of specific exclusion criteria

We will exclude trials:

- that do not include an appropriate comparison group;
- that do not assess outcomes for individuals with T2DM (i.e. they asses outcomes for family members alone);
- where family interventions are delivered only to individuals with T2DM (i.e. not their family members);
- that are targeted to family interventions for individuals with type 1 diabetes mellitus; or
- where family interventions are delivered to individuals with T2DM who are less than 18 years of age.

Types of outcome measures

We will not exclude any trial on the basis that it does not report one or several of our primary or secondary outcome measures in the publication. Should none of our primary or secondary outcomes be reported in a trial, we will not include the trial but will provide some basic information in an additional table.
We will investigate the following outcomes using the methods and time points specified below.

Primary outcomes

- Glycaemic control
- Diabetic complications
- Adverse evens

Secondary outcomes

- All-cause mortality
- Health-related quality of life
- Social support
- Health behaviour
- Diabetes knowledge
- Socioeconomic effects

Method of outcome measurement

- Glycaemic control: measured by glycosylated haemoglobin A1C (HbA1c).
- Diabetic complications: defined as angina pectoris, myocardial infarction, stroke, peripheral vascular disease, neuropathy, nephropathy, retinopathy, diabetic foot and lower limb amputation, and heart failure, measured in the long term.
- Adverse events: such as family non-supportive behaviours (e.g. sabotaging behaviours, and miscarried helping behaviours. Sabotaging behaviours occur when family members are well-informed about diabetes but do not help participants to perform diabetes self-care behaviours. For example, disrupting diabetic participant's attempt to change eating habits. Miscarried behaviours happen when family members attempt to help with diabetes self-care, but do so in an inadequate or incorrect manner. For instance, couples experience conflicts when a husband attempts to modify the wife's diet, but the wife does not appreciate husband's attempt to do so).
- All-cause mortality: defined as death from any cause.
- Health-related quality of life: evaluated with a validated generic or disease-specific instrument (e.g. Audit of Diabetes-Dependent Quality of Life (ADDQoL) (Wee 2006), 36-Item Short Form Health Survey (SF-36) (McHorney 1993).
- Social support: defined as emotional or practical support, and measured using a validated instrument (e.g. Short-form Social Support Questionnaire (SSQ-6) (Sarason 1983), or any other validated scale).
- Health behaviour: defined as self-care behaviours, evaluated with a validated instrument (e.g. Summary of Diabetes Self-care Activities measure (Toobert 2000), or any other validated scale).
- Diabetes knowledge: evaluated with validated instrument (e.g. Diabetes Knowledge Questionnaire (Garcia 2001), or any other validated scale).
- Socioeconomic effects: defined as the costs of treatment and visits to clinic or hospital, such as hospital admissions, accident and emergency visits, length of stay in hospital, or visits to general practitioner.

Timing of outcome measurement

- We will include outcomes that are measured for as long as follow-up is carried out at any given time point. We will classify the outcome measurement as short-, medium-, or long-term. We will define short-term as less than six months; medium-term as between six months and less than 12 months; and long-term as 12 months or more.
- HbA1c should be measured at least three months after the intervention.
- We will measure adverse events and all-cause mortality at any time after participants were randomised to intervention or comparator groups.

Search methods for identification of studies

Electronic searches

We will search the following sources from the inception of each database to the specified date, and will place no restrictions on the language of publication.
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO);
- MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE; from 1946 onwards);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
- PsycINFO Ovid;
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/).

We will continuously apply a MEDLINE (via Ovid SP) email alert service established by the Cochrane Metabolic and Endocrine Disorders (CMED) Group to identify newly published trials, using the same search strategy as described for MEDLINE (Appendix 1). After we submit the final review draft for editorial approval, the CMED Group will perform a complete search update on all

databases available at the editorial office and will send the results to the review authors. Should we identify new trials for inclusion, we will evaluate these, incorporate the findings into our review and resubmit another Cochrane Review draft (Beller 2013).

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, systematic reviews, meta-analyses and health technology assessment reports. In addition, we will contact authors of included trials to identify any additional information on the retrieved trials and establish whether we may have missed further trials.

We will not use abstracts or conference proceedings for data extraction unless full data are available from trial authors because this information source does not fulfil the CONSORT requirements which consist of "an evidence-based, minimum set of recommendations for reporting randomised trials" (CONSORT; Scherer 2007). We will list key data from abstracts in an appendix. We will present information on abstracts or conference proceedings in the 'Characteristics of studies awaiting classification' table.

Data collection and analysis

Selection of studies

Two review authors (KM, SD) will independently screen the abstract, title, or both, of every record we retrieve in the literature searches, to determine which trials we should assess further. We will obtain the full text of all potentially relevant records. We will resolve any disagreements through consensus or by recourse to a third review author (SC). If we cannot resolve a disagreement, we will categorise the trial as a 'study awaiting classification' and will contact the trial authors for clarification. We will present an adapted PRISMA flow diagram to show the process of trial selection (Liberati 2009). We will list all articles excluded after full-text assessment in a 'Characteristics of excluded studies' table and will provide the reasons for exclusion.

Data extraction and management

For trials that fulfil our inclusion criteria, two review authors (KM, SD) will independently extract key participant and intervention characteristics. We will describe interventions according to the 'template for intervention description and replication' (TIDieR) checklist (Hoffmann 2014; Hoffmann 2017).

We will report data on efficacy outcomes and adverse events using standardised data extraction sheets from the Cochrane Metabolic and Endocrine Disorders Group. We will resolve any disagreements by discussion or, if required, we will consult a third review author (SC).

We will provide information about potentially relevant ongoing trials, including the trial identifiers, in the 'Characteristics of ongoing studies' table and in a joint appendix, 'Matrix of trial endpoint (publications and trial documents)'. We will try to find the protocol for each included trial and we will report primary, secondary and other outcomes in comparison with data in publications in a joint appendix.

We will email all authors of included trials to enquire whether they would be willing to answer questions regarding their trials. We will present the results of this survey in an appendix. We will thereafter seek relevant missing information on the trial from the primary trial author(s), if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary trial, we will maximise the information yield by collating all available data, and we will use the most complete data set aggregated across all known publications. We will list duplicate publications, companion documents, multiple reports of a primary trial, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included trial. Furthermore, we will also list duplicate publications, companion documents, multiple reports of a trial, and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded trial.

Data from clinical trials registers

If data from included trials are available as study results in clinical trials registers, such as ClinicalTrials.gov or similar sources, we will make full use of this information and extract the data. If there is also a full publication of the trial, we will collate and critically appraise all available data. If an included trial is marked as a completed study in a clinical trial register but no additional information (study results, publication or both) is available, we will add this trial to the table 'Characteristics of studies awaiting classification'.

Assessment of risk of bias in included studies

Two review authors (KM, SD) will independently assess the 'Risk of bias' of each included trial. We will resolve any disagreements by consensus or by consulting a third review author (SC). In the case of disagreement, we will consult the remainder of the review author team and make a judgment based on consensus. If adequate information is not available from the publications, trial protocols or other sources, we will contact the trial authors for more detail to request missing data on 'Risk of bias' items.

We will use the Cochrane 'Risk of bias' assessment tool (Higgins 2011a; Higgins 2017) to assign assessments of low, high or unclear risk of bias (for details see Appendix 2). We will evaluate individual

bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* according to the criteria and associated categorisations contained therein(Higgins 2017).

Summary assessment of risk of bias

We will present a 'Risk of bias' graph and a 'Risk of bias' summary figure.
We will distinguish between self-reported and investigator-assessed and adjudicated outcome measures.
We will consider the following self-reported outcomes.

- Diabetes knowledge
- Health behaviour
- Health-related quality of life
- Social support

We will consider the following outcomes to be investigator-assessed.

- Adverse events
- All-cause mortality
- Diabetic complications
- HbA1c
- Socioeconomic effects

Risk of bias for a trial across outcomes: some 'Risk of bias' domains, such as selection bias (sequence generation and allocation sequence concealment), affect the risk of bias across all outcome measures in a trial. In case of high risk of selection bias, we will mark all endpoints investigated in the associated trial as being at high risk of bias. Otherwise, we will not perform a summary assessment of the risk of bias across all outcomes for a trial.
Risk of bias for an outcome within a trial and across domains: we will assess the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both trial-level entries and outcome-specific entries). We consider low risk of bias to denote a low risk of bias for all key domains, unclear risk to denote an unclear risk of bias for one or more key domains, and high risk to denote a high risk of bias for one or more key domains.
Risk of bias for an outcome across trials and across domains: these are the main summary assessments that we will incorporate into our judgements about the quality of evidence in the 'Summary of findings' tables. We will define outcomes as being at low risk of bias when most information comes from trials at low risk of bias, unclear risk when most information comes from trials at low or unclear risk of bias and high risk when a sufficient proportion of information comes from trials at high risk of bias.

Measures of treatment effect

When at least two included trials are available for a comparison and a given outcome, we will try to express dichotomous data as a risk ratio (RR) or odds ratio (OR) with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale (e.g. HbA1c) we will estimate the intervention effect using the mean difference (MD) with 95% CIs. For continuous outcomes that measure the same underlying concept (e.g. health-related quality of life) but use different measurement scales, we will calculate the standardised mean difference (SMD). We will express time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We will take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised controlled trials (RCTs), and multiple observations for the same outcome. If more than one comparison from the same trial is eligible for inclusion in the same meta-analysis, we will either combine groups to create a single pair-wise comparison or appropriately reduce the sample size so that the same participants do not contribute data to the meta-analysis more than once (i.e. splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons (Higgins 2011b).
We will attempt to re-analyse cluster-RCTs that have not appropriately adjusted for potential clustering of participants within clusters in their analyses. The variance of the intervention effects will be inflated by a design effect. Calculation of a design effect involves estimation of an intracluster correlation coefficient (ICC). We will obtain estimates of ICCs through contact with authors, or impute them by using either estimates from other included trials that report ICCs or external estimates from empirical research (e.g. Bell 2013). We plan to use sensitivity analyses to examine the impact of clustering.

Dealing with missing data

If possible, we will obtain missing data from the authors of the included trials. We will carefully evaluate important numerical data such as screened, randomly assigned participants as well as intention-to-treat (ITT), and as-treated and per-protocol populations. We will investigate attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we will critically appraise issues concerning missing data and use of imputation methods (e.g. last observation carried forward).
In trials where the standard deviation (SD) of the outcome is not available at follow-up or cannot be recreated, we will standardise by the average of the pooled baseline SD from those trials that reported this information.
Where included trials do not report means and SDs for outcomes and we do not receive the necessary information from trial authors, we will impute these values by estimating the mean and variance from the median, range, and the size of the sample (Hozo 2005). We will investigate the impact of imputation on meta-analyses by performing sensitivity analyses and we will report per outcome which trials were included with imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we will not report trial results as the pooled effect estimate in a meta-analysis.

We will identify heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi² test with a significance level of $\alpha = 0.1$. In view of the low power of this test, we will also consider the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

When we identify heterogeneity, we will attempt to determine the possible reasons for it by examining individual trial and subgroup characteristics.

Assessment of reporting biases

We will use funnel plots to assess small-trial effects, as indicated by the number of trials. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. Therefore we will interpret the results carefully (Sterne 2011).

Data synthesis

We plan to undertake (or display) a meta-analysis only if we judge participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful. Unless good evidence shows homogeneous effects across trials of different methodological quality, we will primarily summarise low risk of bias data using a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration to the whole distribution of effects and present a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval needs at least four trials to be calculated and specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events such as event rates below 1%, we will use the Peto's odds ratio method, provided that there is no substantial imbalance between intervention and comparator group sizes and intervention effects are not exceptionally large. In addition, we will perform statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and we plan to carry out the following subgroup analyses including investigation of interactions (Altman 2003).

- Level of glycaemic control (e.g. HbA1c less than 8.5% versus HbA1c 8.5% or more)
- Intervention duration (e.g. less than three months versus 3 months or more)
- Age (e.g. less than 65 years versus 65 years or more)
- Gender (e.g. male versus female individuals with T2DM)

Sensitivity analysis

We plan to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting the analysis to:

- published trials;
- effect of risk of bias, as specified in the Assessment of risk of bias in included studies section;
- very long or large trials (to establish the extent to which they dominate the results);
- trials using the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other), or country.

We will also test the robustness of results by repeating the analyses using different measures of effect size (RR, OR, etc.) and different statistical models (fixed-effect and random-effects models).

Certainty of evidence

We will present the overall certainty of evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results. Two review authors (KM, SD) will independently rate the certainty of evidence for each outcome. Differences in assessment will be solved by discussion or consultation with a third researcher (SC).

We will include an appendix entitled 'Checklist to aid consistency and reproducibility of GRADE assessments', to help with standardisation of the 'Summary of findings' tables (Meader 2014). Alternatively, we will use the GRADEpro Guideline Development Tool (GDT) software and will present evidence profile tables as an appendix (GRADEproGDT 2015). We will present results for the outcomes as described in the Types of outcome measures section. If meta-analysis is not possible, we will present the results in a narrative format in the 'Summary of findings' table. We will justify all decisions to downgrade the quality of trials using footnotes, and we will make comments to aid the reader's understanding of the Cochrane Review where necessary.

'Summary of findings' table

We will present a summary of the evidence in a 'Summary of findings' table. This will provide key information about the best estimate of the magnitude of the effect, in relative terms and as absolute differences, for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome and a rating of overall confidence in effect

estimates for each outcome. We will create the 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011) using Review Manager (RevMan 5.3) table editor (RevMan 2014). We will report the following outcomes, listed according to priority.

- Diabetic complications
- Health-related quality of life
- Social support
- All-cause mortality
- Adverse events
- HbA1c
- Socioeconomic effects

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

MEDLINE (OvidSP)
1. exp Family/ 2. Family Therapy/ 3. Family Health/ 4. ((famil* or parent or parents or parental or marriage or marital or couple or couples or spouse or spouses or caregiver? or care giver? or relatives) adj4 (therap* or based or focus* or educat* or management or support* or involv* or integrat* or participat* or counsel*)).tw 5. ((famil* or parent or parents or parental or marriage or marital or couple or couples or spouse or spouses or caregiver? or care giver? or relatives) adj6 (intervention? or program*)).tw 6. or/1-5

(*Continued*)

7. exp Diabetes Mellitus, Type 2/
8. (MODY or NIDDM or T2DM or T2D).tw.
9. diabet*.tw.
10. or/7-9
11. 6 and 10
[12-19: Cochrane Handbook 2008 RCT filter - sensitivity max. version - adapted for more sensitivity]
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. random*.ab.
15. placebo.ab.
16. drug therapy.fs.
17. trial.ab.
18. groups.ab.
19. or/12-18
20. exp animals/ not humans/
21. 19 not 20
22. 11 and 21
[23-28: Wong 2006a*- systematic reviews filter - specificity max. version]*
23. cochrane database of systematic reviews.jn.
24. search*.tw.
25. meta analysis.pt.
26. medline.tw.
27. systematic review.tw.
28. or/23-27
29. 11 and 28
30. 22 or 29
31. ((type 1 or type I) not (type 2 or type II)).ti,ab.
32. 30 not 31
33. (gestational diabetes or family history or case control or cross sectional or observational study).ti. or (case reports).pt
34. 32 not 33

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online)

1. MESH DESCRIPTOR Family EXPLODE ALL TREES
2. MESH DESCRIPTOR Family Therapy
3. MESH DESCRIPTOR Family Health
4. ((famil* or parent or parents or parental or marriage or marital or couple or couples or spouse or spouses or caregiver? or care giver? or relatives) ADJ4 (therap* or based or focus* or educat* or management or support* or involv* or integrat* or participat* or counsel*)):TI,AB,KY
5. ((famil* or parent or parents or parental or marriage or marital or couple or couples or spouse or spouses or caregiver? or care giver? or relatives) ADJ6 (intervention? or program*)):TI,AB,KY
6. #1 OR #2 OR #3 OR #4 OR #5
7. MESH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES
8. (MODY or NIDDM or T2DM or T2D):TI,AB,KY
9. diabet*:TI,AB,KY
10. #7 OR #8 OR #9
11. #6 AND #10

PsycINFO (Ovid SP)

(*Continued*)

1. Family/
2. exp Family Therapy/
3. Family Intervention/
4. Family Relations/
5. ((famil* or parent or parents or parental or marriage or marital or couple or couples or spouse or spouses or caregiver? or care giver? or relatives) adj4 (therap* or based or focus* or educat* or management or support* or involv* or integrat* or participat* or counsel*)).tw
6. ((famil* or parent or parents or parental or marriage or marital or couple or couples or spouse or spouses or caregiver? or care giver? or relatives) adj6 (intervention? or program*)).tw
7. or/1-6
8. Type 2 Diabetes/
9. (MODY or NIDDM or T2DM or T2D).tw.
10. diabet*.tw.
11. or/8-10
12. 6 and 11
[13-16: Eady 2008 *"PsycInfo Search Strategies" filter - best sensitivity version]*
13. control*.tw.
14. random*.tw.
15. exp Treatment/
16. or/13-15
17. 12 and 16
18. ((type 1 or type I) not (type 2 or type II)).ti,ab.
19. 17 not 18
20. (gestational diabetes or family history or case control or cross sectional or observational study or case report).ti
21. 19 not 20
22. book.pt.
23. 21 not 22

CINAHL (Ebsco)

S1. MH "Family+"
S2. MH "Family Therapy"
S3. MH "Family Coping"
S4. MH "Family Relations"
S5. MH "Family Services"
S6. MH "Patient-Family Relations"
S7. MH "Family Involvement (Iowa NIC)"
S8. MH "Family Support (Iowa NIC)"
S9. MH "Family Therapy (Iowa NIC)"
S10. TI ((famil* or parent or parents or parental or marriage or marital or couple or couples or spouse or spouses or caregiver# or care giver# or relatives) N4 (therap* or based or focus* or educat* or management or support* or involv* or integrat* or participat* or counsel*))
S11. AB ((famil* or parent or parents or parental or marriage or marital or couple or couples or spouse or spouses or caregiver# or care giver# or relatives) N4 (therap* or based or focus* or educat* or management or support* or involv* or integrat* or participat* or counsel*))
S12. TI ((famil* or parent or parents or parental or marriage or marital or couple or couples or spouse or spouses or caregiver# or care giver# or relatives) N6 (intervention# or program*))
S13. AB ((famil* or parent or parents or parental or marriage or marital or couple or couples or spouse or spouses or caregiver# or care giver# or relatives) N6 (intervention# or program*))

(*Continued*)

S14. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S15. MH "Diabetes Mellitus, Type 2"
S16. TI (MODY or NIDDM or T2DM or T2D)
S17. AB (MODY or NIDDM or T2DM or T2D)
S18. TI diabet*
S19. AB diabet*
S20. S15 OR S16 OR S17 OR S18 OR S19
[S21-S24: Wong 2006b *"therapy studies" filter - SDSSGS version]*
S21. MH "treatment outcomes+"
S22. MH "experimental studies+"
S23. random*
S24. S21 OR S22 OR S23
S25. S20 AND S24
S26. TI ((type 1 or type I) NOT (type 2 or type II))
S27. AB ((type 1 or type I) NOT (type 2 or type II))
S28. S26 OR S27
S29. S25 NOT S28
S30. TI ("gestational diabetes" OR "family history" OR "case control" OR "cross sectional" OR "observational study" OR "case report")
S31. S29 NOT S30

ICTRP (Standard search)

family based AND diabet* OR
family focus* AND diabet* OR
family oriented AND diabet* OR
family intervention AND diabet* OR
family therapy AND diabet* OR
family counseling AND diabet* OR
family based AND T2D* OR
family focus* AND T2D* OR
family oriented AND T2D* OR
family intervention AND T2D* OR
family therapy AND T2D* OR
family counseling AND T2D*

ClinicalTrials.gov (Advanced Search)

Conditions: (diabetes OR diabetic OR T2D OR T2DM) AND NOT ("type I" OR "type 1" OR gestational)
Intervention/treatment: (family or families OR spouse OR spouses OR marriage OR marital OR "couple" OR "couples" OR caregiver OR "care giver" OR caregivers OR "care givers") AND NOT (coupled OR coupling)

Appendix 2. Selection bias decisions

Selection bias decisions for trials that reported unadjusted analyses: comparison of results obtained using method details alone with results using method details and trial baseline information[a]

Reported randomisation and allocation concealment methods	Risk of bias judgement using methods reporting	Information gained from study characteristics data	Ris of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable (s)	**High risk**
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable (s)	**Unclear risk**[b]
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables[c]	Low risk
		No baseline details	**Unclear risk**
Sequence is not truly randomised, or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable (s)	High risk
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited baseline details, showing balance in some important prognostic variables[c]	**Unclear risk**
		No baseline details	High risk

[a] Taken from Corbett 2014; judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias, compared with using methods reporting alone.
[b] Imbalance identified that appears likely to be due to chance.
[c] Details for the remaining important prognostic variables are not reported

Appendix 3. Assessment of risk of bias

Risk of bias domains

Random sequence generation (selection bias due to inadequate generation of a randomised sequence)
For each included trial, we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups

- Low risk of bias: the trial authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the trial. We will consider the use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)
We will describe for each included trial the method used to conceal allocation to interventions prior to assignment and we will assess whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We will also evaluate trial baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgment for selection bias (Corbett 2014). Chance imbalances may also affect judgments on the risk of attrition bias. In the case of unadjusted analyses, we will distinguish between trials that we rate as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and trials that we judge as being at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We will reclassify judgements of unclear, low or high risk of selection bias as specified in Appendix 2.

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the trial)
We will evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self-reported, investigator-assessed or adjudicated outcome measures (see below)

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judge that the outcome is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the trial does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of trial participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment
We will evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self-reported, investigator-assessed or adjudicated outcome measures (see below)

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is unlikely to have been influenced by lack of blinding.

(*Continued*)

- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to amount, nature or handling of incomplete outcome data)

For each included trial and/or each outcome, we will describe the completeness of data, including attrition and exclusions from the analyses. We will state whether the trial reported attrition and exclusions, and report the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We will also note if the trial reported the reasons for attrition or exclusion and whether missing data were balanced across groups or were related to outcomes. We will consider the implications of missing outcome data per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between trial arms)

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias; the trial did not address this outcome.
- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes enough to induce clinically-relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting)

We will assess outcome reporting bias by integrating the results of the appendix 'Matrix of trial endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009), with those of the appendix 'High risk of outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) classification' (Kirkham 2010). This analysis will form the basis for the judgement of selective reporting

- Low risk of bias: the trial protocol was available and all the trial's prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all the trial's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely so that we cannot enter them in a meta-analysis; the trial report failed to include results for a key outcome that we would expect to have been reported for such a trial (ORBIT classification).

Other bias

- Low risk of bias: the trial appears to be free from other sources of bias.
- Unclear risk of bias: there was insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the trial had a potential source of bias related to the specific trial design used; the trial was claimed to be fraudulent; or the trial had some other serious problem.

CONTRIBUTIONS OF AUTHORS

All review authors contributed to, read and approved the final protocol draft.

DECLARATIONS OF INTEREST

Khadija A Matrook: none known.

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NOTES

We have based parts of the Methods, as well as Appendix 1, Appendix 2 and Appendix 3 of this Cochrane protocol on a standard template established by the CMED Group.