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Dietary interventions for managing glucose abnormalities in people with cystic fibrosis (Protocol)

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[Intervention Protocol]

Dietary interventions for managing glucose abnormalities in people with cystic fibrosis

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ABSTRACT

Objectives

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

To assess the effects of dietary interventions on glycaemic control and clinical status in people with cystic fibrosis who have dysglycaemia.

BACKGROUND

Cystic fibrosis (CF) is a common, life-limiting, genetic disease, affecting 1 in 2500 live births (Farrell 2008), over 10,500 people in the UK (UK CF Registry 2019), and around 90,000 people worldwide. The highest prevalence is in Europe, North America, and Australia (Bell 2020). It is caused by a mutation of a gene that encodes a chloride transmembrane channel called the cystic fibrosis transmembrane conductance regulator (CFTR), and is characterised by abnormally thick and dehydrated secretions, which lead to organ obstruction, primarily affecting the lungs and digestive system.

Advances in medical management have led to dramatic improvements in survival, such that in the UK, the average life expectancy of people with CF (pwCF) is now 45 years (NICE 2017). The recent introduction of CFTR modulator therapy has resulted in significant improvements in clinical status and quality of life for pwCF (Lopes-Pacheco 2020), and it is anticipated that further advances in life expectancy will be seen (Balfour-Lynn 2020). However, despite improvements in lifespan, CF continues to cause progressive digestive and respiratory dysfunction, and pwCF often experience prolonged periods of ill-health before dying prematurely from lung disease (Bell 2020).

Abnormalities in glucose metabolism are common in CF, and glucose tolerance gradually deteriorates over time, eventually leading to CF-related diabetes (CFRD), the most prevalent complication of CF (Moran 2009). The combination of diabetes and CF is associated with increased mortality, because of detrimental effects on lung function and nutritional status (Chamnan 2010; Lewis 2015). The development of microvascular complications leads to increased morbidity (Schwarzenberg 2007). CFRD is associated with increasing age, affecting approximately 20% of adolescents, and up to half of adults over 40 years (Alexander 2010; Moran 2010). However, youth does not preclude a diagnosis of CFRD, and it can present at any age (O'Riordan 2010). The initial presentation of CFRD is often clinically silent, and progressive pulmonary and nutritional decline may precede the diagnosis of CFRD by several years (Granados 2019). Early diagnosis and optimisation of glycaemic control are needed to improve clinical status and survival; therefore, annual screening, using the oral glucose tolerance test (OGTT), is recommended from 10 years of age (Moran 2010; Ode 2019). The effects of CFTR modulator therapy on glucose metabolism are not yet completely understood, and more research is needed (Merjaneh 2022).

Description of the condition

CFRD is a distinct form of diabetes that shares features of both Types 1 and 2 diabetes. It occurs in association with pancreatic insufficiency, and is primarily caused by the gradual loss of the insulin-secreting beta cells (Bridges 2013). Fluctuating levels of insulin resistance also play a role, and can cause hyperglycaemia to develop at any time (Granados 2019).

During periods of stable health, CFRD can be diagnosed using the same criteria as other forms of diabetes, but testing should be conducted on two separate days (Moran 2010). The diagnostic criteria are: a two-hour plasma glucose level of ≥ 11.1 mmol/L in an OGTT; fasting plasma glucose ≥ 7.0 mmol/L; glycated haemoglobin (HbA1c) ≥ 48 mmol/mol or ≥ 6.5%; polyuria (frequent urination) and polydipsia (an increase in thirst) in the presence of plasma glucose ≥ 11.1 mmol/L (WHO/IDF 2006; WHO 2011). Guidance is also available to help diagnose CFRD during periods of clinical instability, acute exacerbations, pregnancy, and enteral feeding (Moran 2010).

Optimising glycaemic control is known to improve clinical status and reduce mortality (Moran 2009). Insulin therapy is currently the primary means of controlling glycaemia in CFRD. Early abnormalities in glucose tolerance contribute to deterioration in clinical status, and represent a significant risk for the progression to CFRD (Hameed 2010; Schmid 2014). Impaired glucose tolerance (IGT), defined as an OGTT two-hour plasma glucose of 7.8 to 11.1 mmol/L and fasting plasma glucose < 7.0 mmol/L (WHO/IDF 2006), affects approximately 20% of 10-year olds with CF and 82% of the CF population by 30 years of age (Bismuth 2008). The clinical definitions of IGT and CFRD are summarised in Table 1. Evidence is lacking on how best to manage abnormal glucose control before CFRD is diagnosed (Moran 2010; Rana 2010).

Description of the intervention

Dietary management of CFRD aims to normalise blood glucose levels and to achieve and maintain good nutritional status in pwCF (Castellani 2018). Current guidelines are based on clinical consensus rather than empirical evidence, and clinical practice varies (Castellani 2018; Moran 2014). A consistent approach is needed for this vulnerable group.

Low glycaemic index (GI) dietary interventions have demonstrated benefits in non-CF forms of diabetes, and include improved insulin sensitivity, glycaemia, and quality of life in both Types 1 and 2 diabetes (Thomas 2009), and are now recommended as part of the dietary management of these conditions (ADA 2018; Dyson 2011). Carbohydrate counting is also an established nutritional strategy recommended for the management of non-CF forms of diabetes, which can help achieve optimal postprandial blood glucose levels (ADA 2018; Dyson 2011).

Therefore, these dietary interventions may also offer some benefit in managing glucose abnormalities in pwCF.

How the intervention might work

Low GI foods consumed evenly throughout the day lead to improved glycaemic control in people with diabetes (Thomas 2009). Therefore, low GI dietary interventions could offer potential benefit to pwCF and dysglycaemia by preventing marked postprandial glucose excursions. The GI is a numerical classification of carbohydrate-containing foods, based on their postprandial effect on blood glucose levels. Carbohydrates that are absorbed rapidly by the body cause higher blood glucose levels after consumption and have high GI ratings, whereas carbohydrates that are absorbed more slowly produce lower postprandial blood glucose excursions and have lower GI ratings (Jenkins 1981; Thomas 2010). The glycaemic response to a food is also affected by other factors, including the method of cooking or processing, degree of ripeness, overall meal size, and the effect of other foods eaten at the same time (Augustin 2002). Combining high GI carbohydrates with fat or protein, or both, lowers the GI, as the fat and protein help to slow the digestion and absorption of the carbohydrate (Atkinson 2008). This approach may help to improve glycaemic control while ensuring sufficient energy, which is needed to optimise nutritional status in pwCF.

Carbohydrate counting is a dietary intervention for managing diabetes, which focuses on the total amount of carbohydrates consumed, and their effect on the postprandial glycaemic response, rather than the source or type of carbohydrate. Two levels of carbohydrate counting have been defined; a basic level and an advanced level (Gillespie 1998). Basic carbohydrate counting aims to increase carbohydrate awareness to improve overall glycaemic control. Advanced carbohydrate counting is used by individuals on insulin therapy; it builds on basic carbohydrate counting and counts the number of grams or portions of carbohydrate eaten, and uses insulin-to-carbohydrate ratios to calculate insulin doses. Carbohydrate counting may be a nutritional approach to assist with improving postprandial blood glucose levels in pwCF with dysglycaemia.

Why it is important to do this review

The treatment and management of pwCF and glucose abnormalities has been identified as a high priority research question, but to date, there has been little research on dietary therapy for pre-diabetes. There are no meta-analyses of dietary interventions for abnormalities in glucose control in pwCF, and due to the lack of empirical evidence, current diagnosis and management of pwCF and glucose abnormalities is based predominantly on the consensus guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD (Moran 2018)).

Low GI dietary interventions have demonstrated improved glycaemic control in non-CF forms of diabetes. However, low GI carbohydrate foods have also been associated with increased satiety and reduced energy intake, which is not consistent with the dietary aims of CF management (Roberts 2003). Energy needs in CF are estimated to be between 110% and 200% of the estimated average requirement (EAR) for healthy individuals of the same age and gender (Stallings 2008). Factors affecting energy requirements include age, gender, nutritional status, chronic and acute infection, and control of malabsorption (Collins 2016). Dietary interventions must be able to incorporate the specific CF aim of optimising nutritional status in addition to achieving good glycaemic control. A previously published systematic review assessed the effect of low GI dietary interventions in young pwCF. They concluded that there was a dearth of evidence in this area, and recommended further scientific study on the clinical utility of a low GI diet in CF to improve glycaemic control (Balzer 2012).

While carbohydrate counting is an established dietary intervention for managing glycaemic control in non-CF diabetes, its use in the management of CFRD is still largely unknown (Bell 2014). It has been proposed that the use of carbohydrate counting to guide insulin doses in people with CFRD can assist with achieving optimal postprandial blood glucose levels, but evidence is lacking (Moran 2010).

This lack of robust evidence for the dietary management of glucose abnormalities in CF must be addressed, and further research into possible nutritional approaches designed to optimise glycaemic control while ensuring sufficient energy to maintain or improve nutritional status, is urgently needed. This Cochrane Review updates the earlier protocol for a systematic review (Birch 2018). It will include any type of dietary intervention for managing glucose abnormalities in pwCF.

OBJECTIVES

To assess the effects of dietary interventions on glycaemic control and clinical status in people with cystic fibrosis who have dysglycaemia.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCT) and non-randomised studies of interventions (NRSI) as described below.

RCT

We will include controlled trials in which allocation was performed by randomisation or a quasi-random rule, e.g. by alternation or Patient ID Number.

NRSI

We will consider including NRSI in this review, as after scoping the available evidence, we only anticipate a small number of RCT (Reeves 2021). We will include NRSI in which participants are allocated to comparison groups using a method that is not random, providing they have the following study design features (Reeves 2017):

- the intervention and comparator was allocated to individuals (rather than to groups of individuals);
- our primary outcome (glycaemic control) was measured in the same individuals at baseline and after either a dietary intervention or a similar period of a comparator intervention; and
- the authors attempted to control for confounding, using at least one of our prespecified covariates (as listed under Assessment of risk of bias in included studies).

We will present and analyse the results for RCT and NRSI separately.

Types of participants

We will include people with cystic fibrosis (pwCF) over five years of age, who have also been diagnosed with either CF-impaired glucose tolerance (IGT) or CF-related diabetes (CFRD). We will not include pregnant women or pwCF post lung transplant.

We present the definitions of CF-IGT and CFRD in Table 1. We will present separate data sets for participants with CF-IGT and CFRD. We will not place any restrictions on upper age, gender, CF mutation, or other demographics.

Types of interventions

We will consider any dietary intervention (e.g. low glycaemic index (GI) diet, carbohydrate counting) assigned for a minimum of two months to manage glucose abnormalities in non-hospitalised pwCF, with or without the use of insulin therapy. The comparators are standard CF dietary therapy (energy dense, high-fat, high-salt diet) for individuals with CF-IGT, and standard CF dietary therapy plus insulin therapy for individuals with CFRD.

Types of outcome measures

We will evaluate the following outcomes separately for participants with CF-IGT and participants with CFRD.

Primary outcomes

1. Glycaemic control before and after dietary intervention (measured by standard clinical methods: oral glucose tolerance test (OGTT); glycated haemoglobin (HbA1c); percentage of continuous glucose monitoring (CGM) time above 7.8 mmol/L (Hameed 2010))

Secondary outcomes

1. Nutritional status
   a. weight (kg, or weight-for-age percentile for children and adolescents)
   b. body mass index (BMI; or BMI standard deviation score (SDS) for children and adolescents)
2. Lung function
   a. forced expiratory volume in one second (FEV_1) % predicted
   b. FEV_1 (L)
3. Adverse events
4. Acceptability of dietary intervention
   a. burden of treatment (measured using a standardised scale, e.g. the Treatment Satisfaction Questionnaire for Medication (Regnault 2012))
   b. self-efficacy (measured using a standardised scale, e.g. General Self Efficacy Scale (Jerusalem 1995))
5. Quality of life (measured by a validated disease-specific tool, e.g. CF Questionnaire-revised (CFQ-R (Quittner 2005)))

Search methods for identification of studies

We will search for all relevant published and unpublished studies, with no restrictions on language, year of publication, or publication status.

Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist will conduct a search of the Group's Cystic Fibrosis Trials Register for relevant trials using the terms: cystic fibrosis related diabetes:kw.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL), updated each new issue of the Cochrane Library; weekly searches of MEDLINE; a search of Embase to 1995; and the prospective handsearching of two journals – *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference; and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

We will also search the following electronic databases; please see Appendix 1 for the search strategies.

1. CENTRAL, in the Cochrane Library (www.cochranelibrary.com/);
2. MEDLINE Ovid (1946 to present);
3. Embase Ovid (1974 to present);
4. AMED Ovid (Allied and Complementary Medicines, 1985 to present);
5. Web of Science (1900 to present); Social Citation Index Expanded (SCI-EXPANDED), 1900 to present; Social Science Citation Index (SCI), 1956 to present; Conference Proceedings Citation Index – Social Science & Humanities (CPCI-SSH), 1990 to present; Emerging Sources Citation Index (ESCI), 2007 to present;
6. ISRCTN registry (www.isrctn.com);
7. ANZCTR registry (www.anzctr.org.au);
8. The World Health Organization International Clinical Trials Registry Platform (ICTRP; trialsearch.who.int/);
9. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
10. OpenGrey (www.opengrey.eu/); and
11. Google Scholar (scholar.google.co.uk/; first 20 pages).

Searching other resources

We will handsearch the reference lists of all included articles and relevant systematic reviews identified in the searches listed above, for any additional studies not found through electronic searching.

Data collection and analysis

We plan to present and analyse RCT separately from NRSI; we will also present and analyse data for CF-IGT and CFRD separately. We will initially combine results from different types of dietary intervention, but may use subgroup analysis to observe the effects of specific diets (see Subgroup analysis and investigation of heterogeneity).

We will record any reported, known stressors of glucose metabolism, such as pulmonary exacerbations, corticosteroids, or CFTR modulators, and will perform subgroup analyses as appropriate (see Subgroup analysis and investigation of heterogeneity).

Selection of studies

We will download search results into Endnote x9 (EndNote x9). Two authors (LB, RP) will independently screen the study titles and abstracts for eligibility. We will retrieve and review the full-text versions of potentially eligible articles. We will resolve any disagreements in opinion through discussion, with a third author (DN) to arbitrate, if required. We will download selected studies into Review Manager Web (RevMan Web (RevMan Web 2020)). We will describe the study selection process in a PRISMA flow diagram (Moher 2009).

Data extraction and management

We will use a standardised data extraction template to extract data from included studies. Two review authors (LB, RP) will independently extract data, and resolve any disagreements in opinion through discussion.

We will extract the following data from each included study, where available:

1. study characteristics (author, country, publication year, study design, duration, funding, limitations, conflicts of interest);

2. sample characteristics (size, inclusion and exclusion criteria, sex, age, socioeconomic status);
3. dietary intervention (details of the dietary intervention and comparator(s));
4. analysis methods; and
5. outcome measures (glycaemic control; nutritional status; lung function; adverse events; acceptability of dietary intervention; quality of life).

When multiple papers have reported the same study but different outcomes, we will consider all papers when extracting relevant outcome data. We will report data from participants with CF-IGT separately from data from participants with CFRD.

We plan to report data within one of the following time point ranges, to allow for variation in follow-up between studies: at two months post-baseline; over two months and up to six months; over six months and up to one year; and annually thereafter. However, if investigators record relevant outcome data at other time points, we will consider presenting these as well.

The lead review author (LB) will enter all extracted data into RevMan Web (RevMan Web 2020).

Assessment of risk of bias in included studies

Two review authors (LB and RP) will independently assess the overall risk of bias for each of the included studies using the relevant risk of bias assessment tools outlined below. We will resolve any disagreement(s) by discussion, or by consulting with a third review author (DN).

RCT

For RCT we will use the Cochrane RoB 2 tool for randomised trials (Sterne 2019), outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b). We will use the RoB 2 Excel tool to implement RoB 2.

The intervention effect of interest is the effect of assignment to the interventions (intention to treat) and RoB 2 assesses each study on the following five domains.

1. Domain 1: risk of bias arising from the randomisation process
2. Domain 2: risk of bias due to deviations from the intended interventions
3. Domain 3: risk of bias due to missing outcome data
4. Domain 4: risk of bias in measurement of the outcome
5. Domain 5: risk of bias in selection of the reported result

RoB 2 uses signalling questions and algorithms to reach a proposed risk of bias judgement for each domain. The judgment options are:

1. low risk of bias;
2. some concerns; or
3. high risk of bias.

Risk of bias judgements are then mapped within domains to reach an overall risk of bias. The judgement options for an overall risk of bias are the same as for individual domains.

We will assess the risk of bias for the primary outcome, glycaemic control before and after dietary intervention.

NRSI

Potential biases are likely to be greater for NRSI than for RCT, because some of the protections against bias that are available for RCT are not established for NRSI (Reeves 2021). We will use the ROBINS-I tool to assess the internal validity or risk of bias of a specific result from NRSI (Sterne 2016); and we will refer to the *Cochrane Handbook* for guidance on assessing bias in different types of NRSI (Sterne 2021). ROBINS-I also uses signalling questions to reach judgements of bias for each of the seven domains listed below, and these are used to make an overall judgement of bias for each result.

1. Domain 1: risk of bias due to confounding
2. Domain 2: risk of bias in the selection of participants into the study
3. Domain 3: risk of bias in classification of the intervention
4. Domain 4: risk of bias due to deviations from intended interventions
5. Domain 5: risk of bias due to missing outcome data
6. Domain 6: risk of bias in measurement of the outcome
7. Domain 7: risk of bias in selection of the reported result

The categories for risk of bias judgements are low (equivalent to a well-run RCT); moderate; serious; or critical (data are considered to be too problematic to provide any useful evidence (Sterne 2016)).

We will assess the risk of bias for the primary outcome, glycaemic control before and after dietary intervention.

We will summarise the review authors' combined assessments in RevMan Web, and present the risk of bias assessments as supplementary material in an online repository, e.g. Figshare.com.

Possible important confounders we identified include sex, ethnicity, age, use of insulin and mode of delivery, use of other medication for CF management, level of pancreatic insufficiency (measured by Creon® dosage), and evidence of liver disease.

Measures of treatment effect

We will follow the guidance in the *Cochrane Handbook* (Higgins 2021a).

RCT

We will report dichotomous outcomes using risk ratios (RR) or risk differences (RD), with their corresponding 95% confidence intervals (95% CIs), depending on the data reported by each included study. When studies report other measures of effect, e.g. odds ratios, we will extract these and report them separately.

For continuous outcomes, we will report the mean differences (MDs) or standardised mean differences (SMDs), with their corresponding 95% CIs. We will use MDs when all relevant studies measure the same outcome of interest using a comparable or identical scale or standard, and SMDs when relevant studies measure the same outcome of interest using different or incomparable instruments or scales. If not directly reported, we will attempt to use any of the available reported data to derive the required SMD (where applicable), using intention to treat analysis with imputation. To facilitate interpretation of SMD, we will use Cohen's effect sizes guidance: 0.2 represents a small effect; 0.5 a moderate effect; and 0.8 a large effect (Cohen 1988).

NRSI

We will seek estimates of intervention effect that adjust for the maximum number of our prespecified confounders (including baseline measures of glycaemic control). For dichotomous outcomes, these are likely to be odds ratios from regression analyses. Alternatively, they may be ratios of RRs (i.e. RR pre-to-post in intervention group/RR pre-to-post in control group), depending on the data reported. For continuous variables, these are likely to be adjusted MDs or differences in differences.

When there are insufficient data to perform quantitative analyses, we will report the results in a narrative format.

Unit of analysis issues

Where possible, we will use individual participants as the unit of analysis. However, as we may include studies of various designs, we may encounter unit of analysis issues, such as groups of individuals randomised together to the same intervention (i.e. cluster-randomised trials), or multiple observations for the same outcome (e.g. repeated measurements), etc. Should we include any of these study designs in our review, we will follow the advice given in the *Cochrane Handbook,* summarised below (Higgins 2021c).

1. For any cluster study designs, we will extract results adjusted for clustering, and where possible, will re-analyse the data taking clustering into account.
2. For any studies in which participants are randomised more than once, we will make reasonable attempts to contact the study authors to request the data on outcomes associated with the initial randomisation.
3. For any studies with multiple treatment groups, we will include subgroups that are considered relevant to the analysis. When appropriate, we will combine groups to create a single pair-wise comparison. If this is not possible, we will select the most appropriate pair of interventions and exclude the others.
4. For any studies with multiple observations per participant, we will attempt to use the following strategies to conduct their analysis:
   a. obtain individual participant data and conduct an analysis (such as time-to-event analysis) that uses the whole follow-up for each participant;
   b. compute an effect measure for each individual participant that incorporates all time points, such as the total number of events, an overall mean, or a trend over time; or
   c. select a single time point and only analyse data at this time for studies in which it is presented
5. For any other unit of analysis issues arising, we will proceed according to the Cochrane Effective Practice and Organisation of Care (EPOC) recommendations (EPOC 2017).

Dealing with missing data

If data are not available in the format required, we will first contact study authors to obtain the data, otherwise, we will back-calculate the data if possible, e.g. standard deviation (SD) from standard errors or 95% CIs, mean and SD from median and range values, or impute SDs by using SD data from all other trials using the same measurement scale (Furukawa 2006).

We are aware that studies assessing dietary interventions may have issues with non-compliance, which may lead investigators to exclude individual participants, resulting in missing data. We will include these studies, and report reasons for any missing data, but we will not combine data from them with other studies.

Assessment of heterogeneity

If studies are sufficiently homogenous in terms of participants, interventions and outcomes, we will assess statistical heterogeneity between studies by visually inspecting forest plots. We will use the I^2 statistic to quantify the proportion of total variability in point estimates that is due to heterogeneity. We will not use values of I^2 as a basis for deciding whether to undertake meta-analyses, but when the degree of inconsistency is substantial (e.g. greater than 50%), or the directions of effect apparently vary across studies, we will pay particular attention to interpretation of results, ensuring that the amount of heterogeneity is reflected in any conclusions drawn.

Assessment of reporting biases

Provided there are at least 10 studies included in the meta-analysis, we will assess the likelihood of publication bias by visually inspecting funnel plots, and with Egger's regression test (Egger 1997). An asymmetrical funnel plot can be an indicator of publication bias. The degree of observed asymmetry is related to the strength of the influence of bias, but the asymmetry can also be caused by biases in the study results, selective reporting bias, or heterogeneity (Page 2021).

Data synthesis

We will tabulate study characteristics, reporting participant, intervention, comparator, and outcome characteristics of each included study in a characteristics of included studies table. We will compare these characteristics to determine which studies are similar enough to be grouped within each comparison. We will tabulate the extracted data and will present and analyse data for CF-IGT and CFRD separately.

We will undertake meta-analyses only when this is meaningful, i.e. when interventions, participants, etc. are similar enough for combining data to make sense. When there are insufficient data to perform quantitative analyses, we will report the results in a narrative format.

RCT

If we include two or more studies that are sufficiently homogenous in participants, interventions, and outcomes, we will perform a random-effects meta-analysis using RevMan Web, as per the *Cochrane Handbook* (Deeks 2021; RevMan Web 2020). A random-effects meta-analysis weighs studies relatively more equally than a fixed-effect analysis in the presence of heterogeneity (Deeks 2021). We will combine any data from quasi-RCTs with data from RCTs. We will conduct one sensitivity analysis removing the quasi-RCT data (to check whether the lack of blinding in quasi-RCT affects the overall effect estimate), and another one removing RCT assessed at high risk of bias.

If the included studies are not suitable for meta-analysis, i.e. insufficient similarity of populations, interventions, or methods, we will present a narrative review of the findings, structured around the outcomes reported, using the Synthesis Without Meta-analysis (SWiM) reporting guideline (Campbell 2020).

NSRI

We will assess NRSI to see if meta-analysis is feasible as per the *Cochrane Handbook* (Reeves 2021); we will examine features of these studies for homogeneity and risk of bias. If included NRSI are both without critical risk of bias (ROBINS-I judgement of low, moderate, or serious risk of bias), and relatively clinically homogeneous, we will combine data across studies in a meta-analysis, with adjusted effect estimates to control for confounding effects (Taggart 2001). We can perform meta-analysis of adjusted estimates using an inverse-variance weighted average, e.g. using the generic inverse-variance outcome type in RevMan Web, as per the *Cochrane Handbook* (Deeks 2021).

If included NRSI are not sufficiently homogeneous to combine in a meta-analysis, we will present a narrative review of the findings, structured around the outcomes reported, using the SWiM reporting guideline (Campbell 2020). We will display the results of the included studies in a forest plot, suppressing the combined estimate to illustrate how the studies differ.

Subgroup analysis and investigation of heterogeneity

NRSI are eligible for inclusion in this review, therefore, we anticipate the presence of heterogeneity between studies, likely due to variation in design and participant characteristics, resulting from a less controlled design. We will attempt to investigate this heterogeneity by undertaking subgroup analyses if there are sufficient studies (N = 10 (Deeks 2021)). We will base subgroup analyses on:

- dietary intervention type;
- age (children (5 to 18 years of age) versus adults (18 years and over)); and
- gender (males versus females).

We will compare effect estimates between subgroups.

If the details of the study-level characteristics that distinguish studies from one another are not available, we will request further information from the study authors. We will also record any reported, known stressors of glucose metabolism, such as pulmonary exacerbations, corticosteroids, or CFTR modulators, and will undertake subgroup analyses as appropriate.

Sensitivity analysis

We describe our strategy for undertaking sensitivity analyses around risk of bias assessments in the Data synthesis section, above. In addition, it is possible that we will need to make decisions in relation to missing, uncertain, or conflicting information from the studies, for example to impute missing SDs or missing outcome data, and these decisions may significantly affect the combined estimates. Therefore, we will conduct sensitivity analyses to explore the impact of any post hoc decisions we are forced to make, using plausible, yet reasonably extreme, alternative values for any imputed data. Furthermore, we will repeat the meta-analyses by excluding studies in which missing data were imputed. We will examine and report any impact on the results arising from these decisions.

Summary of findings and assessment of the certainty of the evidence

We will generate summary of findings (SoF) tables following the guidance in the *Cochrane Handbook* (Schünemann 2021). We will prepare separate SoF tables for CF-IGT data and CFRD data. We will report outcome data as change from baseline at six months in the SoF tables, and will also record data from any other specified time points to allow for variation in follow-up between studies (over two months and up to six months; over six months and up to one year; and annually thereafter). We will present data from different study designs in the same SoF table, but we will analyse the data from RCT separately from NRSI. We include a template SoF table in Appendix 2.

After generating the SoF tables, we will assess the strength of the overall body of evidence for each of the following outcomes using the GRADE system (GRADEpro GDT; Guyatt 2008):

1. OGTT;
2. HbA1c;
3. % CGM time above 7.8 mmol/L;
4. Weight (kg) for adults;
5. Weight-for-age percentiles for children and adolescents;
6. BMI (kg/m^2); and
7. BMI SDS for children and adolescents.

RCT

We will base the certainty of the body of evidence on the risk of bias of the studies that measured the individual outcome; inconsistency (based on variation in point estimates, overlap of CIs, the P value of heterogeneity, I^2 score, outcome of the subgroup analysis); indirectness (based on differences in interventions and participants, method of measurement of participant-important outcomes, and comparison of interventions); imprecision (based on optimal information size, sample size, overlapping CIs, and judgement on the importance of observed differences); and publication bias (based on funding sources, size of studies, and the comprehensiveness of data search).

Evidence from RCT start at high certainty that the true effect of the intervention lies close to the estimate of the effect. We will downgrade as appropriate after assessing the risk of bias, imprecision, indirectness, inconsistency, and publication bias (Guyatt 2008).

NRSI

Evidence from NRSI start at high certainty of the evidence. We will downgrade as appropriate after assessing the presence of serious concerns and limitations such as indirectness of evidence, heterogeneity, imprecision, or publication bias (Schünemann 2019).

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ADDITIONAL TABLES

Table 1. Definitions of glucose abnormalities

	CF-IGT	CFRD
OGTT	2-h plasma glucose 7.8 to 11.1 mmol/L	2-h plasma glucose ≥ 11.1 mmol/L (WHO/IDF 2006)
HbA1c		≥ 48 mmol/mol or ≥ 6.5% (ADA 2018; WHO 2011ADA 2018)
Fasting plasma glucose		≥ 7.0 mmol/L (WHO/IDF 2006)
CGM		time above 7.8 mmol/L ≥ 4.5% (Hameed 2010)

CF-IGT: cystic fibrosis impaired glucose tolerance
CFRD: cystic fibrosis-related diabetes
CGM: continuous glucose monitoring
HbA1c: glycated haemoglobin
OGTT: oral glucose tolerance test

APPENDICES

Appendix 1. Electronic search strategies

Database	Search strategy
Cochrane Library	ID Search
	#1 MeSH descriptor: [Food] explode all trees
	#2 nutrition* near/1 manag*:ti,ab
	#3 MeSH descriptor: [Diet] explode all trees
	#4 diet*:ti,ab

(Continued)

#5 nutri*:ti,ab

#6 MeSH descriptor: [Diet, Carbohydrate-Restricted] explode all trees

#7 MeSH descriptor: [Nutritional Support] explode all trees

#8 macronutrient*:ti,ab

#9 sugar*:ti,ab

#10 glyc*mic near/1 index:ti,ab

#11 dietary near/1 manipulation*:ti,ab

#12 dietary near/1 intervention*:ti,ab

#13 low near/1 GI near/1 diet*:ti,ab

#14 carbohydrate near/1 count*:ti,ab

#15 MeSH descriptor: [Energy Intake] explode all trees

#16 #1 or #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 #17 cystic near/1 fibrosis:ti,ab

#18 MeSH descriptor: [Cystic Fibrosis] explode all trees

#19 CF:ti,ab

#20 #17 or #18 or #19

#21 CFRD:ti,ab

#22 CF-IGT:ti,ab

#23 pre-diabetes:ti,ab

#24 dysglyc*mia:ti,ab

#25 altered near/1 glucose near/1 handling:ti,ab

#26 impaired near/1 glucose near/1 toleranc*:ti,ab

#27 diabetes:ti,ab

#28 insulin near/1 resistance:ti,ab

#29 glucose near/1 metabolism:ti,ab

#30 glucose near/1 tolerance:ti,ab

#31 glyc*mic near/1 control:ti,ab

#32 glyc*mia:ti,ab

#33 glucose near/1 handling:ti,ab

#34 MeSH descriptor: [Diabetes Mellitus] explode all trees

#35 "cystic fibrosis related diabetes":ti,ab

#36 MeSH descriptor: [Insulin Resistance] explode all trees

#37 MeSH descriptor: [Blood Glucose] explode all trees

#38 MeSH descriptor: [Glucose Tolerance Test] explode all trees

(Continued)

	#39 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 #40 #16 and #20 and #39
MEDLINE Ovid	1. Cystic Fibrosis/ 2. (cystic adj1 fibrosis).tw. 3. Mucoviscidos*.tw. 4. cf.ti. 5. 1 or 2 or 3 or 4 6. exp Glucose Metabolism Disorders/ 7. CFRD.tw. 8. (CF-IGT or "CF IGT" or CFIGT).tw. 9. diabet*.tw. 10. (pre-diabetes or pre-diabetic or prediabet* or "pre diabetes" or "pre diabetic").tw. 11. exp diabetes mellitus/ 12. (glucose or insulin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 13. (glycaemi* or glycemi* or hyperglycaemi* or hyperglycemi* or Hypoglycaemi* or Hypoglycemi* or Dysglycaemi* or Dysglycemi*).tw. 14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 15. exp Diet/ 16. exp Diet Therapy/ 17. diet*.tw. 18. exp Nutritional Sciences/ 19. Nutritional Status/ 20. nutri*.tw. 21. (food* or eat or eats or fed or feed).tw. 22. "low GI".tw. 23. (beverage* or drink*).tw. 24. exp Dietary Carbohydrates/ 25. exp Dietary Proteins/ 26. exp Dietary Fats/ 27. (carbohydrate* or protein* or fat*).tw. 28. macronutrient*.tw. 29. sugar*.tw.

(Continued)

	30. 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. animals/ not humans/
	32. (rat or rats or mouse or mice or ferret* or rabbit*).ti.
	33. 31 or 32
	34. 5 and 14 and 30
	35. 34 not 33
AMED	1. (food and beverages).mp. [mp=abstract, heading words, title]
	2. food$.ti,ab.
	3. (nutrition* adj1 manag*).ti,ab.
	4. diet/
	5. diet$.ti,ab.
	6. exp nutrition/
	7. nutri$.ti,ab.
	8. exp protein/
	9. exp carbohydrate/
	10. exp drinking/
	11. macronutrient$.ti,ab.
	12. sugar$.ti,ab.
	13. (glycemic adj1 index).ti,ab.
	14. (dietary adj1 manipulation$).ti,ab.
	15. (dietary adj1 intervention$).ti,ab.
	16. (low adj1 GI adj1 diet$).ti,ab.
	17. (carbohydrate adj1 count*).ti,ab.
	18. 1 or 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
	19. exp Cystic Fibrosis/
	20. (cystic adj1 fibrosis).ti,ab.
	21. CF.ti,ab.
	22. 19 or 20 or 21
	23. exp Diabetes Mellitus/ or exp Diabetes Complications/ or exp Diabetes Mellitus, Experimental/
	24. CFRD.ti,ab.
	25. CF-IGT.ti,ab.
	26. pre-diabetes.ti,ab.

(Continued)

	27. Dysglyc*mia.ti,ab. 28. (altered adj1 glucose aj1 handl*).ti,ab. 29. "cystic fibrosis related diabetes".ti,ab. 30. (impair* adj1 glucose adj1 toleranc*).ti,ab. 31. exp Insulin Resistance/ or exp Blood Glucose/ or exp Glucose Intolerance/ or exp Glucose Tolerance Test/ 32. diabetes.ti,ab. 33. (insulin adj1 resistance).ti,ab. 34. (glucose adj1 metabolism).ti,ab. 35. (glucose adj1 tolerance).ti,ab. 36. (glycemic adj1 control).ti,ab. 37. glycaemia.ti,ab. 38. (glucose adj1 handling).ti,ab. 39. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 40. 18 and 22 and 39 41. animals/ not humans/ 42. (rat* or mouse or mice).ti. 43. 41 or 42 50. 40 not 43
Web of Science	1. TS=(food) 2. TS=(nutrition* near/1 manag*) 3. TS=(diet*) 4. TS=(nutriti*) 5. TS=(macronutrient*) 6. TS=(sugar*) 7. TS=(glyc*mic near/1 index) 8. TS= (dietary near/1 manipulation*) 9. TS=(low near/1 GI near/1 diet*) 10.TS= (dietary near/1 intervention*) 11.TS=(low near/1 GI near/1 diet*) 12.TS=(carbohydrate near/1 count*) 13.TS=(appetite*) 14.TS=(energy near/1 intake) 15.#14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 16.TS=(cystic near/1 fibrosis) 17.TS=(Cystic) 18.#17 OR #16 19.TS= (pre-diabetes) 20.TS= (dysglyc*mia or diabetes or glyc*mia) 21.TS=(altered near/1 glucose near/1 handl*)

(Continued)

22.TS=(impaired near/1 glucose near/1 toleranc*)
23.TS= (insulin near/1 resistance or glucose near/1 metabolism)
24.TS= (glucose near/1 tolerance)
25.TS=(glyc*mic near/1 control or glucose near/1 handl*)
26.TS = ("cystic fibrosis related diabetes")
27.TS= (blood near/1 glucose or glucose near/1 tolerance near/1 test)
28.#27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16
29.#28 AND #18 AND #15

1. #28 AND #18 AND #15
2. **Refined by:** [excluding] **WEB OF SCIENCE CATEGORIES:** (PALEONTOLOGY OR BIODIVERSITY CONSERVATION OR SURGERY OR PATHOLOGY OR RESPIRATORY SYSTEM OR OCEANOGRAPHY OR ANTHROPOLOGY OR AGRICULTURE DAIRY ANIMAL SCIENCE OR GENETICS HEREDITY OR AGRICULTURAL ENGINEERING OR CHEMISTRY ORGANIC OR SOIL SCIENCE OR CHEMISTRY INORGANIC NUCLEAR OR MARINE FRESHWATER BIOLOGY OR GEOSCIENCES MULTIDISCIPLINARY OR PSYCHIATRY OR REPRODUCTIVE BIOLOGY OR ENVIRONMENTAL SCIENCES OR DERMATOLOGY OR VETERINARY SCIENCES OR TRANSPLANTATION OR EVOLUTIONARY BIOLOGY OR CHEMISTRY MEDICINAL OR CARDIAC CARDIOVASCULAR SYSTEMS OR OTORHINOLARYNGOLOGY OR ECOLOGY OR PERIPHERAL VASCULAR DISEASE OR FISHERIES OR SPORT SCIENCES OR PARASITOLOGY OR ZOOLOGY OR BIOPHYSICS OR ENERGY FUELS OR AGRICULTURE MULTIDISCIPLINARY OR ENGINEERING ENVIRONMENTAL OR HEALTH POLICY SERVICES OR ENTOMOLOGY OR HEMATOLOGY OR PLANT SCIENCES OR GEOGRAPHY PHYSICAL OR LIMNOLOGY OR ENGINEERING CHEMICAL OR WATER RESOURCES OR ALLERGY OR ECONOMICS OR DENTISTRY ORAL SURGERY MEDICINE OR ENGINEERING BIOMEDICAL OR AGRONOMY OR FORESTRY OR BIOTECHNOLOGY APPLIED MICROBIOLOGY OR ELECTROCHEMISTRY OR OBSTETRICS GYNECOLOGY OR MYCOLOGY OR ONCOLOGY OR SPECTROSCOPY OR NUCLEAR SCIENCE TECHNOLOGY OR CELL BIOLOGY OR HORTICULTURE OR DEVELOPMENTAL BIOLOGY OR BIOLOGY OR RADIOLOGY NUCLEAR MEDICINE MEDICAL IMAGING OR MATERIALS SCIENCE BIOMATERIALS OR TOXICOLOGY OR GREEN SUSTAINABLE SCIENCE TECHNOLOGY OR OPHTHALMOLOGY OR CHEMISTRY APPLIED OR CHEMISTRY PHYSICAL OR PSYCHOLOGY BIOLOGICAL OR CHEMISTRY MULTIDISCIPLINARY OR POLYMER SCIENCE OR SUBSTANCE ABUSE OR CHEMISTRY ANALYTICAL)

1. TS=(animals NOT humans)
2. #30 not #31
3. #30 not #31
4. **Refined by:** [excluding] **WEB OF SCIENCE CATEGORIES:** (STATISTICS PROBABILITY OR ENGINEERING MULTIDISCIPLINARY OR BIOCHEMICAL RESEARCH METHODS OR GERONTOLOGY OR PSYCHOLOGY CLINICAL OR TROPICAL MEDICINE OR MEDICINE LEGAL OR COMPUTER SCIENCE INTERDISCIPLINARY APPLICATIONS OR INSTRUMENTS INSTRUMENTATION OR MATHEMATICAL COMPUTATIONAL BIOLOGY OR OPTICS OR RHEUMATOLOGY OR PSYCHOLOGY EXPERIMENTAL OR EDUCATION SCIENTIFIC DISCIPLINES OR PSYCHOLOGY MULTIDISCIPLINARY OR EDUCATION SPECIAL OR REMOTE SENSING OR VIROLOGY)

ISRCTN registry	Cystic fibrosis
ANZCTR registry	Cystic fibrosis
WHO ICTRP	**Advanced Searches** **Search 1** [in the Title] Cystic fibrosis OR CF OR mucoviscidose OR mucoviscidosis [in the Condition] diabetes OR diabetic OR glucose OR glycaemia OR glycemia OR glycaemic OR glycemic OR hyperglycaemia OR hyperglycemia OR hyperglycaemic OR hyperglycemic OR hypoglycaemia OR hypoglycemia OR hypoglycaemic OR hypoglycemic

(Continued)

	Recruitment status: ALL **Search 2** [in the Title] Cystic fibrosis OR CF OR mucoviscidose OR mucoviscidosis [in the Condition] dysglycaemia OR dysglycemia OR dysglycaemic OR dysglycemic Recruitment status: ALL
ClinicalTrials.gov	**Basic Searches** **Search 1** Status: All studies Condition or disease: Cystic fibrosis OR CF OR mucoviscidose OR mucoviscidosis Other terms: (diet OR nutrition OR food OR feed OR eat OR drink OR beverage) AND (diabetes OR diabetic OR glucose OR glycaemia OR glycemia OR glycaemic OR glycemic) **Search 2** Status: All studies Condition or disease: Cystic fibrosis OR CF OR mucoviscidose OR mucoviscidosis Other terms: (diet OR nutrition OR food OR feed OR eat OR drink OR beverage) AND (hyperglycaemia OR hyperglycemia OR hyperglycaemic OR hyperglycemic OR hypoglycaemia OR hypoglycemia OR hypoglycaemic OR hypoglycemic) **Search 3** Status: All studies Condition or disease: Cystic fibrosis OR CF OR mucoviscidose OR mucoviscidosis Other terms: (diet OR nutrition OR food OR feed OR eat OR drink OR beverage) AND (dysglycaemia OR dysglycemia OR dysglycaemic OR dysglycemic)
OpenGrey	(Cystic fibrosis OR mucoviscidose OR mucoviscidosis) AND (diabetes OR diabetic OR glucose OR glycaemia OR glycemia OR glycaemic OR glycemic OR hyperglycaemia OR hyperglycemia OR hyperglycaemic OR hyperglycemic OR hypoglycaemia OR hypoglycemia OR hypoglycaemic OR hypoglycemic OR dysglycaemia OR dysglycemia OR dysglycaemic OR dysglycemic)
Google Scholar	**Advanced Search** With all of the words: (Cystic fibrosis OR mucoviscidose OR mucoviscidosis) AND (diet OR dietary OR nutrition OR nutritional OR nutrients OR fat OR protein OR carbohydrate OR sugar OR food OR feed OR eat OR drink OR beverage) AND (diabetes OR diabetic OR glucose OR glycaemic OR glycemic OR hyperglycaemic OR hyperglycemic OR Hypoglycaemic OR Hypoglycemic OR dysglycaemia OR dysglycemia OR dysglycaemic OR dysglycemic) Where my words occur: in the title of the article

Appendix 2. Blank summary of findings table

Dietary intervention to manage glucose abnormalities in CF compared with standard CF dietary therapy
Patient or population: pwCF and CF-IGT or CFRD

(Continued)

Settings: outpatients, community

Intervention: dietary intervention to manage glucose abnormalities in CF, with or without the use of insulin therapy

Comparison: standard CF dietary therapy for individuals with CF-IGT, and standard CF dietary therapy plus insulin therapy for individuals with CFRD

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard CF dietary therapy	Dietary intervention to manage glucose abnormalities in CF				
Glycaemia - OGTT (mmol/L) change from baseline at 6 months						
Glycaemia - HbA1c (mmol/mol) change from baseline at 6 months						
Glycaemia - CGM (% time above 7.8mmol/L) change from baseline at 6 months						
Weight - adults (kg) change from baseline at 6 months						
Weight - children and adolescents (weight-for-age percentiles) change from baseline at 6 months						
BMI SDS - children and adolescents change from baseline at 6 months						
BMI - adults (kg/m^2) change from baseline at 6 months						

(Continued)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) will be provided in footnotes. The **corresponding risk** (and its 95% CI) will be based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Abbreviations: **BMI**: body mass index; **CF**: cystic fibrosis; **CF-IGT**: cystic fibrosis impaired glucose tolerance; **CFRD**: cystic fibrosis-related diabetes; **CGM**: continuous glucose monitoring; **CI**: confidence interval; **OGTT**: oral glucose tolerance test; **pwCF**: people with CF; **SDS**: standard deviation score.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

CONTRIBUTIONS OF AUTHORS

Task	Author(s)
Draft the protocol	LB, RP, JHS, JH
Review the draft protocol	LB, RP, JHS, JH, FL, SLH, FF, DN
Develop and run the search strategy	RP
Obtain copies of studies	LB
Select which studies to include (2 people)	LB, RP
Extract data from studies (2 people)	LB, RP
Enter data into RevMan	LB
Carry out the analysis	LB, RP
Interpret the analysis	LB, RP, JHS, JH
Draft the final review	LB, RP, JHS, JH, FL, SLH, FF, DN

LB will act as guarantor of the review.

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SLH declares the receipt of speaker fees from Vertex Ltd.

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