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Prebiotics for people with cystic fibrosis (Review)

Williams NC, Jayaratnasingam J, Prayle AP, Nevitt SJ, Smyth AR

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Prebiotics for people with cystic fibrosis.
Cochrane Database of Systematic Reviews 2023, Issue 9. Art. No.: CD015236.
DOI: 10.1002/14651858.CD015236.pub2.

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[Intervention Review]

Prebiotics for people with cystic fibrosis

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Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.
Publication status and date: New, published in Issue 9, 2023.

Citation: Williams NC, Jayaratnasingam J, Prayle AP, Nevitt SJ, Smyth AR. Prebiotics for people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2023, Issue 9. Art. No.: CD015236. DOI: 10.1002/14651858.CD015236.pub2.

ABSTRACT

Background

Cystic fibrosis (CF) is a multisystem disease; the importance of growth and nutritional status is well established given their implications for lung function and overall survivability. Furthermore, it has been established that intestinal microbial imbalance and inflammation are present in people with CF. Oral prebiotics are commercially available substrates that are selectively utilised by host intestinal micro-organisms and may improve both intestinal and overall health.

Objectives

To evaluate the benefits and harms of prebiotics for improving health outcomes in children and adults with CF.

Search methods

We searched the Cochrane Cystic Fibrosis Trials Register compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched the reference lists of relevant articles and reviews. Date of last search: 19 October 2022.

We also searched PubMed and online trials registries. Date of last search: 13 January 2023.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs assessing the efficacy of prebiotics in children and adults with CF. We planned to only include the first treatment period from cross-over RCTs, regardless of washout period.

Data collection and analysis

We did not identify any relevant trials.

Main results

We did not identify any relevant trials for inclusion in this review.

Authors' conclusions

This review did not find any evidence for the use of prebiotics in people with CF. Until such evidence is available, it is reasonable for clinicians to follow any local guidelines and to discuss the use of dietary prebiotics with their patients.

Large and robust RCTs assessing the dietary prebiotics of inulin or galacto-oligosaccharides or fructo-oligosaccharides, or any combination of these, are needed. Such studies should be of at least 12 months in duration and assess outcomes such as growth and nutrition,

gastrointestinal symptoms, pulmonary exacerbations, lung function, inflammatory biomarkers, hospitalisations, intestinal microbial profiling, and faecal short-chain fatty acids. Trials should include both children and adults and aim to be adequately powered to allow for subgroup analysis by age.

PLAIN LANGUAGE SUMMARY

Prebiotics for people with cystic fibrosis

Key messages

Growth and nutritional status can impact lung function and overall survival in people with cystic fibrosis (CF), and prebiotics, a source of food for healthy bacteria in the gut, might be of benefit.

We did not find any trials that looked at how prebiotics affect people with CF, and such trials are needed.

How can prebiotics be used to treat people with CF?

We know that growth and nutritional status are important in CF as they affect lung function and overall survival. People with CF have an imbalance of bacteria and also inflammation in their guts. Oral prebiotics, which are commercially available, may improve both gut health and overall health. The most studied examples of these prebiotics are inulin, fructo-oligosaccharides, galacto-oligosaccharides, and human milk oligosaccharides. Prebiotics may be found naturally in whole plant foods (e.g. chicory root, onions, and bananas), but artificial prebiotic supplements are also available.

What did we want to find out?

Prebiotics have been able to reduce gut symptoms in other conditions, so we wanted to know if they can also help people with CF by improving growth and nutritional status and reducing gut symptoms without any side effects. We also wanted to know if they could improve lung function, reduce the number of flare-ups of the disease and admissions to hospital for CF, and improve the quality of life of people with CF.

What did we do?

We searched for trials comparing individual or multiple combinations of oral (swallowed) prebiotics compared to no treatment or a placebo (treatment with no active ingredient); a single different prebiotic or a combination of other prebiotics; or a probiotic or a symbiotic (a combination of prebiotics and probiotics). We did not restrict trials based on age or how ill or healthy people were with regard to their CF.

What did we find?

We found no trials for inclusion at this time. We did find one trial that is under way, but no results are available yet.

How up-to-date is the evidence?

The evidence is current to October 2022.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a life-limiting genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. It affects approximately 100,000 children and adults worldwide (Bell 2020). CF is a multisystem disease resulting in thick secretions predominantly affecting the lungs, gastrointestinal (GI) tract, pancreas, and liver. Around 84% of people with CF have exocrine pancreatic insufficiency, requiring treatment with pancreatic enzyme replacement therapy (PERT) (Cystic Fibrosis Foundation 2020). Despite treatment with PERT, many people have frequent GI symptoms (Smith 2020). Children with CF may struggle to gain weight adequately, and adults may have difficulty maintaining a healthy weight (Stallings 2008). Growth and nutritional status of people with CF are important as they are major determinants of lung function and survival (Corey 1988; Jadin 2011). Around half of people with CF achieve an adequate nutritional status (McCormick 2010; Turck 2016), and many children with CF fail to achieve catch-up weight gain. However, a new era of CF care has increased lifespan and decreased symptoms in many people with CF, necessitating a re-examination of the legacy diets in CF (McDonald 2021).

The GI microbiota play a significant role in health and disease, contributing to immunity, inflammation, and metabolic function (Sekirov 2010). People with CF exhibit a disordered gut microbial ecosystem (Burke 2017; de Freitas 2018; Madan 2012; Nielsen 2016; Vernocchi 2018). Evidence suggests that, in CF, gut microbial dysbiosis occurs within the first year of life, and the microbial imbalance develops further with increasing age when compared to healthy people (Nielsen 2016). Alterations of the gut microbiota in CF is likely to be multifaceted, but it is hypothesised to be due to the dehydrated, acidic luminal environment and thick mucous within the gut (Lee 2012), which adheres to the gut wall (Kelly 2022; Snyder 1964). Coupled with frequent antibiotic therapy and high-caloric, high-fat diets (Duytschaever 2011; Sutherland 2018; Tomas 2016), this leads to a dysregulated gut microbiota in CF. The intestinal dysbiosis in children with CF is associated with impaired innate immunity (Ooi 2015). Longitudinal studies on the developing respiratory and intestinal microbiomes in infants and children with CF show that colonisation of pathogenic bacteria precedes in the gut followed by the lungs; increased microbial diversity was associated with better health (Hoen 2015; Madan 2012); and beneficial bacteria were reduced in CF over the first year of life (Antosca 2019).

Modern advances in high-throughput screening have facilitated the fast-tracking of *CFTR* modulators as a treatment. These modulator drugs have the ability to enhance or even restore the functional expression of specific CF-causing mutations. People with CF treated with the *CFTR* modulator ivacaftor for 48 weeks showed a 2.7 kg increase in weight compared to those treated with placebo (Ramsey 2011), and body mass index (BMI) significantly improved after 24 weeks of the *CFTR* modulator combination treatment ivacaftor–tezacaftor–elexacaftor (marketed in the UK and EU as Kaftrio) with a mean treatment difference (z score) of 1.04 relative to placebo (Middleton 2019). Furthermore, emerging evidence suggests that *CFTR*-modulating therapy may improve the irregular pathophysiology of the gut in people with CF and cause a favourable change in the resident gut microbiota (Ooi 2018), and preliminary evidence suggests the use of the CFTR modulator ivacaftor–tezacaftor–elexacaftor may lead to an improvement in gut symptoms (Mainz 2022).

Description of the intervention

Dietary interventions to target the gut microbiota may provide suitable adjunct treatment alongside *CFTR* modulators in people with CF. Dietary strategies to target the gut microbiota include probiotics, defined as live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host (Hill 2014). Alternatively, the concept of a 'prebiotic' was first proposed in 1995 (Gibson 1995). In the decades that followed, prebiotic research focused on substrates that targeted health-promoting groups of bacteria in the gut (commonly those of the genera *Bifidobacterium* and *Lactobacillus*). Prebiotics have been studied for certain health effects such as immune modulation, cardiometabolic health, infection reduction, and mineral availability (Sanders 2019; Scott 2020).

The most up-to-date scientific definition of a prebiotic was developed through the International Scientific Association for Probiotics and Prebiotics in 2016 (Gibson 2017). This current consensus definition is "a substrate that is selectively utilised by host microorganisms conferring a health benefit". The prebiotic concept therefore includes three essential parts: a substance, a physiologically beneficial effect, and a microbiota-mediated mechanism. Prebiotics are frequently equated with dietary fibres, but only a subset of fibres qualify as prebiotics. Prebiotics may be present naturally in whole plant foods (e.g. chicory root, onions, and bananas) or in synthesised forms. Most research into their health effects has focused on isolated substances (Savino 2022). The most studied are the soluble fibre-prebiotic inulin, fructo-oligosaccharides (FOS), and galacto-oligosaccharides (GOS) and, more recently, human milk oligosaccharides (HMOs). Candidate oligosaccharides with less evidence to date include malto-oligosaccharide, isomalto-oligosaccharide, and xylo-oligosaccharide; and candidate non-fibre prebiotics include conjugated linoleic acid, polyunsaturated fatty acids, and polyphenols. There are currently no official dietary recommendations on intake or daily allowances for prebiotics in healthy individuals.

Most dietary 'biotic' research has focused on the use of probiotics in health conditions, with more limited evidence for the use of prebiotics. A Cochrane Review from 2020 reported that 11 completed randomised controlled trials (RCTs) on probiotics in people with CF had been conducted (Coffey 2020). That review highlighted that due to the variability of probiotic composition and dosage, further adequately powered, multicentre RCTs of at least 12 months' duration are required to best assess the efficacy and safety of probiotics for children and adults with CF (Coffey 2020). Given evidence highlighting that prebiotic approaches can target multiple genera of beneficial bacteria (Gibson 2017), they may provide a viable alternative or synbiotic alongside dietary probiotics.

How the intervention might work

The presence of dysregulated intestinal microbial ecosystem and inflammation is well established in CF (de Freitas 2018; Dhaliwal 2015; Nielsen 2016). Prebiotics are hypothesised to alter the microbial growth and activity of beneficial resident microbes in the gut and therefore may restore the gut microbial profile towards

'normal'. There is some emerging evidence to support a potential role for prebiotics in reducing the risk and severity of GI infection and inflammation (Gibson 2005; Licht 2012), including diarrhoea and inflammatory bowel disease (Silk 2009). Prebiotics may also play a role in bone and mineral absorption (Whisner 2018); data also suggest that they reduce the risk of obesity by promoting satiety and weight loss (Kellow 2014), and may improve glycaemic control and gut permeability in type 1 diabetes (Ho 2019).

The mechanistic effect of prebiotics to act upon health is multifaceted. Primarily they are selectively utilised by beneficial bacteria within the gut (commonly from the genera *Bifidobacterium* and *Lactobacillus*), increasing the growth and activity of the host's beneficial bacteria. Beneficial bacteria within the gut can then modulate immune function, improve gut barrier integrity, produce antimicrobial compounds, and promote enzyme formation (Sanders 2019). Furthermore, the selective fermentation of prebiotic compounds by beneficial bacteria in the gut results in the production of short-chain fatty acids, which are known to have positive immunomodulatory effects (Corrêa-Oliveira 2016). Prebiotic compounds can also act directly on the intestinal epithelial cells to influence inflammatory signalling (Newburg 2016), and have direct immunomodulatory effects on macrophages (Searle 2012). A diverse and active gut microbial ecosystem will have an impact on intestinal health and homeostasis and confers direct, indirect, and systemic benefits on:

1. lung health (gut–lung axis potentially through immune-mediated cross-talk) (Hoen 2015; Marsland 2015);
2. brain health and mental well-being (gut–brain axis) (Burokas 2017; Dinan 2017; Marques 2014); and
3. general health outcomes such as growth (Dhaliwal 2015).

Why it is important to do this review

Alterations to the host microbiome and intestinal inflammation are largely understudied in people with CF and could be a potential therapeutic target to improve disease management. One 2015 survey found that 60% of children in a CF clinic in the USA were self-medicating with probiotics (Sullivan 2015), and one recent Australian study showed similar results, with 70% of adults with CF having used probiotics, attributed to GI and antibiotic issues (Anderson 2022). The authors of the Cochrane Review on probiotics for people with CF concluded: "To the best of our knowledge, many clinics and people with CF regularly use probiotics, despite the limited evidence. Overall, this approach is likely safe and may have some limited health benefits" (Coffey 2020).

These studies highlight that probiotic use in CF is prevalent, but also that there is no consensus and direct recommendations on the use of probiotics in CF. For adults with CF, GI symptoms are important considerations; furthermore, antibiotic use is prevalent, and subsequently dietary prebiotics could be suitable adjunct treatments in the disease. Indeed, prebiotic supplementation has been shown to reduce GI symptoms in irritable bowel disease (Silk 2009), and reduce diarrhoea associated with travel and antibiotic use (Drakoularakou 2010; Guridi 2020). Given the continued emerging evidence for the importance of diet and the gut microbiota in people with CF (Li 2014; Madan 2012), and positive alterations in gut microbiota and disease outcomes with *CFTR* modulation therapy (Ooi 2018), understanding the current evidence base for prebiotics in CF will be useful for the wider CF community. This could justify future research programmes and application for patient benefit.

OBJECTIVES

To evaluate the benefits and harms of prebiotics for improving health outcomes in children and adults with CF.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include RCTs and quasi-RCTs assessing the efficacy of prebiotics in children and adults with CF. We planned to only include the first treatment period from cross-over RCTs regardless of washout period (Elbourne 2002). A washout phase is designed to limit potential residual treatment effects, but as there is no consensus on washout durations for prebiotic interventions, we have not defined a minimum duration here.

Types of participants

We planned to include participants who fulfilled consensus diagnostic criteria for CF (Farrell 2017). There would be no restrictions on participants in terms of age, gender, genotype, pancreatic exocrine sufficiency status, disease severity, comorbidities, antibiotic use, or *CFTR* modulator therapy.

Types of interventions

We aimed to compare any oral fibre-prebiotic (inulin, FOS and GOS, dose or formulation, without a probiotic) to any other prebiotic formulation, probiotic or synbiotic, or placebo or no control treatment. We planned to only include trials where participants could be randomised to a prebiotic-only arm with a suitable comparator.

We planned to include trials using both single and combined fibre-prebiotic interventions of inulin, FOS, and GOS. We planned to exclude candidate fibre prebiotics of resistant starch, polydextrose, xylo-oligosaccharide, imalto-oligosaccharide, and isomalto-oligosaccharide due to the lack of evidence to accept them as qualified prebiotics. Similarly, we planned to exclude candidate non-fibre prebiotics polyphenolics, and polyunsaturated fatty acids.

We planned to exclude in vitro trials or trials examining the effect of probiotics alone or synbiotics (without adequate description on dose of prebiotic and type of prebiotic used).

Types of outcome measures

We planned to assess the following outcome measures.

Primary outcomes

1. Growth and nutrition (mean change from baseline and post-treatment absolute mean)
   a. height (cm and z score)
   b. weight (kg and z score)
   c. BMI (kg/m^2 and z score)
2. GI symptoms measured using the Multimodal Questionnaire for the Assessment of Abdominal Symptoms in People With CF (CFAbd-Score) (Jaudszus 2019)

3. Adverse events in response to prebiotic feeding, number of participants experiencing an adverse event categorised according to severity
   a. mild transient event (e.g. nausea, diarrhoea)
   b. moderate event (treatment discontinued, e.g. nephrotoxicity)
   c. severe event (e.g. hospitalisations)
   d. adverse events leading to withdrawal

Secondary outcomes

1. Pulmonary exacerbation defined using consensus criteria, Fuchs' criteria (Fuchs 1994)
   a. number of pulmonary exacerbations
   b. duration of antibiotic therapy (any route) for pulmonary exacerbations (days), separated by route of delivery for intravenous or oral delivery
2. Lung function (mean change from baseline and post-treatment absolute mean)
   a. forced expiratory volume in one second (FEV_1) % predicted
   b. FEV_1 (L)
   c. lung clearance index (LCI)
3. Inflammatory biomarkers (mean change from baseline and post-treatment absolute mean)
   a. intestinal
      i. calprotectin (µg/g)
      ii. M2-pyruvate kinase (M2-PK) (units/mL)
      iii. rectal nitric oxide (rNO) (µmol/L)
   b. serum
      i. C-reactive protein (CRP) (mg/L)
      ii. cytokines (pg/mL)
4. Hospitalisations (all causes)
   a. number
   b. duration (days)
5. Health-related quality of life (HRQoL) measured using a validated questionnaire (e.g. Cystic Fibrosis Questionnaire-Revised (CFQ-R); Quittner 2009)
6. Intestinal microbial profile assessed using next-generation sequencing of stool samples as a change from baseline in response to intervention
   a. alpha diversity (e.g. richness or Shannon index)
   b. beta diversity (e.g. Bray-Curtis dissimilarity)
7. Faecal short-chain fatty acids (mmol/kg): total and individual (acetate, propionate, butyrate) with reference to wet and dry weight
8. Change in body composition (e.g. via iDexa scan, including fat mass and fat-free mass, and mid-arm girth)

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restriction on language, year, or publication status.

Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist conducted a search of the Group's Cystic Fibrosis Trials Register for relevant trials using the following terms: prebiotics.

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 *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.

Date of most recent search: 19 October 2022.

We searched the following databases and registries; the search strategies are presented in Appendix 1:

1. PubMed (from 1946 to 13 January 2023);
2. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (searched on 13 January 2023);
3. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (trialsearch.who.int/) (searched on 13 January 2023).

Searching other resources

We planned to check the bibliographies of any included trials and any relevant systematic reviews identified for further references to relevant trials. Given the comprehensive search strategies employed for different databases, the knowledge of the author team in this relatively new and specialised area of research, and the informal relationships with other researchers in this field, we did not attempt to contact any further experts to identify any unpublished studies.

Data collection and analysis

We planned to employ the standard methods of the Cochrane Cystic Fibrosis and Genetic Disorders Group and the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a).

We planned that if an author was involved in any identified trial, they would not participate in the decision-making regarding inclusion or exclusion from the review. Furthermore, they would not perform risk of bias assessment or data extraction for that trial.

Selection of studies

Once we identified a complete list of references, one review author (NW) checked and removed duplicates before entering the list into Covidence software (Covidence). Two review authors (NW and JJ) independently assessed titles and abstracts, excluding any obviously irrelevant trials. We assessed the full text of each remaining trial for inclusion in the review. We planned to discuss any discrepancies that arose and gain a consensus through consultation with a third review author (AP). We reported the reasons for exclusion of trials excluded at the full-text stage in Characteristics of excluded studies.

Data extraction and management

We were not able to include any trials in this first version of the review; however, if we are able to include trials in future updates of the review, we will follow the methods set out in the sections below.

Two review authors (NW and JJ) will independently extract data using a standardised data extraction form in Covidence (Covidence), which we will pilot on three trials. We will collect data to complete a 'Characteristics of included studies' table on:

1. participant characteristics (e.g. age, gender, genotype, phenotype, pancreatic status);
2. trial characteristics and design (e.g. RCTs or quasi-RCTs);
3. interventions and comparator (e.g. type of fibre-prebiotic, dose, duration);
4. outcome data, reported separately for each outcome.

We will list all treatment arms in the 'Characteristics of included studies' table, even if they are not used in the review.

We will discuss any discrepancies and gain a consensus through consultation with a third review author (AP). Where data may be incomplete, we will contact the primary investigator to request further information and clarification. If we identify multiple publications from one trial, we will group reports.

We will import the extracted data into Review Manager Web for analysis (RevMan Web 2022).

We will report the contribution of a prebiotic (independent of any co-administered agents) to any change in gut symptoms. We will compare any oral fibre-prebiotic (dose or formulation without a probiotic) to any other prebiotic formulation, probiotic or synbiotic, or placebo or no control treatment. This will be followed by subgroup analysis on individual types of prebiotic for outcomes with sufficient data.

We anticipate that studies are likely to report at different time points, therefore we will explore the impact of intervention duration further in a subgroup analysis.

Where studies are not reported in English, we will attempt to perform a translation to allow for appropriate data extraction.

Assessment of risk of bias in included studies

We will use the risk of bias tool described in the *Cochrane Handbook for Systematic Reviews for Interventions* to assess risk of bias (Higgins 2017). Two review authors (NW and JJ) will independently assess the risk of bias for each included trial across the following six domains:

1. sequence generation;
2. allocation concealment;
3. blinding (self-reported and objective);
4. incomplete outcome data;
5. selective reporting; and
6. other potential sources of bias.

We will discuss any discrepancies and gain a consensus through consultation with a third review author (AP). We will judge a trial to have a low risk of bias for randomisation if it describes the randomisation and allocation processes, including concealment from the researchers. If these processes are inadequate, we will deem the trial at high risk of bias, or if unclear we will deem the trial at unclear risk of bias. To assess blinding, we will determine who was blinded, and the method used to determine the risk of bias. Two review authors (NW and JJ) will examine missing data, the distribution of the missing data, and how investigators managed withdrawals and loss to follow-up. If a trial includes an intention-to-treat (ITT) analysis, we will deem this to minimise the risk of bias.

We will assess outcome reporting by reviewing the outcomes to be measured, either in the trial paper or a published protocol. If trial investigators measured relevant outcomes but did not report these, then we will deem the study to have a high risk of reporting bias. We will summarise data from individual trials in a risk of bias table. We will not exclude trials on the basis of risk of bias.

Assessment of bias in conducting the systematic review

We will conduct updates of the original review according to the published protocol (Williams 2022), and report any deviations from it in the 'Differences between protocol and review' section.

Measures of treatment effect

For continuous outcomes, we will record the mean change and standard deviation (SD) from baseline for each group (prebiotic and placebo) or mean post-treatment or intervention values and SD or standard error (SE) for each group. We will calculate a pooled estimate of treatment effect for each outcome using mean difference (MD) with 95% confidence intervals (CIs) or standardised mean difference (SMD) with 95% CIs depending on the variability of the outcome measures.

For dichotomous outcomes (e.g. adverse events), we will record the number of participants with an event and the number of participants analysed in each group. Where appropriate, we will present a pooled estimate of the treatment effect for each outcome across trials using risk ratio (RR) with 95% CIs.

Unit of analysis issues

Trials with a parallel-group design will include the individual participant as the unit of analysis.

We will only include the first treatment period from cross-over RCTs, regardless of washout period (Elbourne 2002). A washout phase is designed to limit potential residual treatment effects, but as there is no consensus on washout durations for prebiotic interventions, we will not define a minimum duration here.

In trials with more than one intervention group, we will first determine if all interventions are relevant to this systematic review and meta-analysis, and then determine how we will include a trial with more than one relevant intervention for a particular meta-analysis. For multi-arm trials, the intervention groups of relevance will be those that we can include in a pair-wise comparison of intervention groups that meet the predetermined criteria for inclusion in the review. We will not include comparisons to non-relevant intervention groups. To avoid any confusion over the identity and nature of each trial, we will report all intervention groups of a multi-intervention trial in the 'Characteristics of included studies' table. However, we will only provide detailed descriptions of the intervention groups relevant to the review, and only use these groups in analyses. For multiple-group studies, where all groups have received a relevant intervention compared to

a control, we will combine the intervention groups to create a single pair-wise comparison to the control group (Higgins 2022b).

Dealing with missing data

Initially, if extracted data are insufficient or unclear for the purposes of the review, we will contact the trial investigator(s). We will assess whether they have performed an ITT analysis for missing data and report the number of participants missing from each trial arm where possible. If only means and P values are reported in a trial, we will estimate the SDs using the Review Manager Web calculator (RevMan Web 2022).

Assessment of heterogeneity

We will assess heterogeneity between trials using the Chi^2 and I^2 statistics, and by visual inspection of overlapping CIs on forest plots (Higgins 2003). We will consider a P value of less than 0.1 of interest for the Chi^2 test. Following the *Cochrane Handbook for Systematic Reviews of Interventions*, we will interpret the I^2 statistic as (Deeks 2022):

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity;
4. 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We will attempt to minimise the likelihood of reporting bias from the non-publication of trials or selective outcome reporting by using a broad search strategy, including trial registries. If a sufficient number of trials have reported a given outcome (at least 10) (Sterne 2011), we will use funnel plots to assess for bias.

Data synthesis

Where possible, we will combine trials in a meta-analysis using Review Manager Web (RevMan Web 2022). If different trials use multiple types of prebiotics, then we will use a random-effects model.

Subgroup analysis and investigation of heterogeneity

In the presence of heterogeneity (I^2 statistic of 50% and greater), we will conduct the following subgroup analyses:

1. infants and preschool (aged one to five years) versus older children (aged six to 18 years) versus adults (aged over 18 years);
2. concurrent modulator therapy versus no modulator therapy;
3. fibre-prebiotic type (inulin versus FOS versus GOS);
4. fibre-prebiotic intervention duration; and
5. duration of follow-up.

Sensitivity analysis

If we identify sufficient trials to combine in a meta-analysis, we will undertake a sensitivity analysis including or excluding trials that we judge to have either a high or unclear risk of selection bias (judgement made as detailed in Assessment of risk of bias in included studies). We will conduct a further sensitivity analysis including or excluding trials at high risk of performance bias and detection bias.

Summary of findings and assessment of the certainty of the evidence

We plan to generate a summary of findings table for each comparison evaluated, which will report the following outcomes:

1. change in weight (kg) (follow-up to six months);
2. change in BMI (follow-up to six months);
3. GI symptoms (from the validated CFAbd-Score) (follow-up to six months);
4. adverse events (at four to six months);
5. number of pulmonary exacerbations (at four weeks to 12 months);
6. change in FEV_1 % predicted (at four weeks to 12 months);
7. change in intestinal calprotectin (µg/g) (at four weeks to 12 months); and
8. changes in HRQoL score(s) (at four weeks to 12 months).

The choice of these outcomes is based on their relevance to clinicians and people with CF. Two review authors (NW and JJ) will independently use the GRADE approach to determine the overall certainty of the evidence for each outcome (Schünemann 2022). For each outcome, we will report the population, setting, intervention, comparison, illustrative comparative risks, magnitude of effect (RR or MD or SMD), number of participants and trials, a GRADE score, and additional comments. We will justify downgrading or upgrading the certainty of the evidence in footnotes.

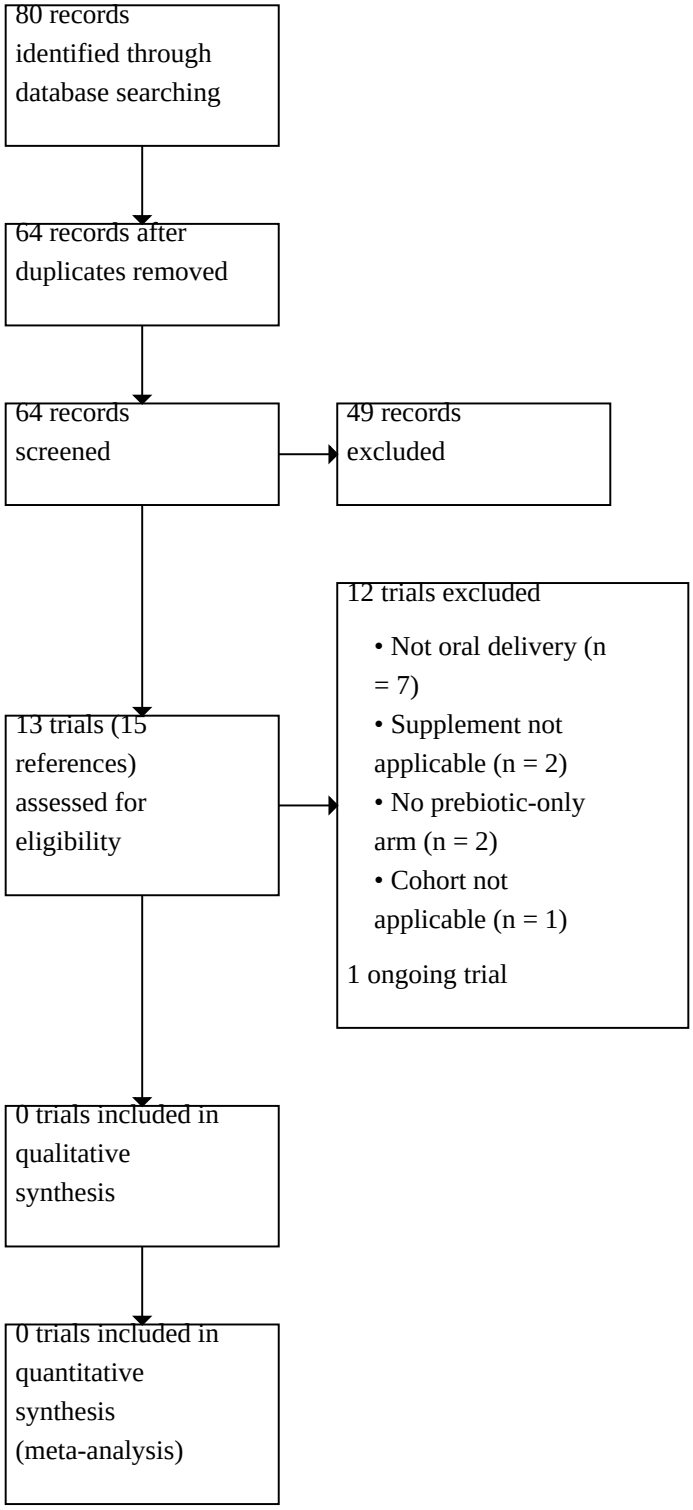
RESULTS

Description of studies

Results of the search

The electronic searches initially generated 80 results from the three databases. After removal of duplicates, we screened 64 records and found 13 trials (15 references) to be potentially eligible after preliminary screening. We excluded 12 trials after full-text screening, and listed one trial as ongoing. No trials were eligible for inclusion in the review (Figure 1).

Figure 1. Study flow diagram.



Included studies

No trials were eligible for inclusion in the review.

Excluded studies

We screened the full texts of 13 trials and subsequently excluded 12 trials, as follows.

1. Intervention was not delivered orally (seven trials) (EUCTR2010-023090-19-GB; Fischer 2022; NCT00970346; NCT01465529; NCT02157922; NCT03698448; NCT03822455).
2. No prebiotic-only arm (two trials) (de Freitas 2018; IRCT2017011732004N1).
3. Did not use an applicable oral supplement (two trials) (Kentrup 1999; NCT01737983).
4. Participants did not have CF (one trial) (Maretti 2017).

Ongoing studies

We identified one protocol of an ongoing randomised, double-blind, parallel-assignment trial that is potentially eligible for inclusion in a future update of this review (NCT04118010). This phase 4 clinical trial, 'Vitamin D and prebiotics for intestinal health in cystic fibrosis', aims to recruit 40 adults (over 18 years old) with CF. The trial will compare high-dose vitamin D and a commonly used prebiotic (inulin) to reduce gastrointestinal dysbiosis and improve critical intestinal functions in CF. The primary outcome for this study is the change from baseline in gastrointestinal microbiota composition, which will be determined using 16S ribosomal ribonucleic acid (rRNA) gene sequencing and microbiome-dependent metabolites; secondary outcomes are listed in Characteristics of ongoing studies. The trial registry entry states that the trial began in October 2019, with an estimated primary completion date of December 2022, but as yet no update has been provided.

Risk of bias in included studies

We included no trials in the review.

Effects of interventions

We included no trials in the review, therefore we could not present any data or narrative information on effects of the interventions.

DISCUSSION

We did not include any trials in the review, therefore insufficient evidence precluded a determination of the impact of prebiotics on people with CF.

Summary of main results

We did not identify any RCTs meeting our eligibility criteria. We screened 64 records, with 15 references to 13 trials found to be potentially eligible after preliminary screening. We screened 13 trials at the full-text stage and found none to be eligible for inclusion in the review.

Overall completeness and applicability of evidence

We did not include any trials in the review, hence there is no evidence to assess.

Quality of the evidence

We did not include any trials in the review, hence there is no evidence to assess.

Potential biases in the review process

This work represents an extensive review of the Cochrane Cystic Fibrosis and Genetic Disorders Group's CF Trials Register and online trials databases. Two review authors independently screened the results against the eligibility criteria for the review, which were published in a peer-reviewed protocol (Williams 2022).

Agreements and disagreements with other studies or reviews

To the best of our knowledge, this is the first published systematic review to examine this topic.

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of evidence from randomised controlled trials (RCTs), clinicians should follow any local guidelines and discuss the use of dietary prebiotics with their patients.

Implications for research

This review found a paucity of evidence regarding the use and impact of dietary prebiotics in people with cystic fibrosis (CF). As absence of evidence is not necessarily evidence of absence of effect, it is hoped that publication of this review will raise the profile of the question at hand and generate future research to provide an evidence base for the use of dietary prebiotics in people with CF.

This gap in evidence would be best addressed by large and robust RCTs utilising dietary prebiotics of inulin or galacto-oligosaccharides or fructo-oligosaccharides, or any combination of these. Adequately powered, multicentre RCTs of at least 12 months in duration would be required to best assess the efficacy and safety of prebiotics for people with CF. The outcomes of greatest interest in future trials include growth and nutrition, gastrointestinal symptoms, pulmonary exacerbations, lung function (e.g. forced expiratory volume in one second (FEV_1) % predicted), inflammatory biomarkers (e.g. intestinal calprotectin and serum C-reactive protein), hospitalisations, intestinal microbial profiling, and faecal short-chain fatty acids (total and individual concentrations of acetate, propionate, and butyrate). Trials that include both children and adults should aim to be adequately powered to allow for the performance of a subset analysis for age. Given the potential variability in dietary prebiotic composition and dose, a large number of RCTs will be required to make adequate general recommendations. Furthermore, with gut dysbiosis evident in people with CF, future prebiotic intervention work should consider how the gut microbiota, dietary prebiotics, and CF modulators combine to influence CF. The interactions of diet and cystic fibrosis transmembrane conductance regulator (*CFTR*) modulators on gastrointestinal symptoms in people with CF warrant further investigation.

Given the limited evidence of prebiotic composition and dose, a thorough examination of all possible treatment regimens will be extremely challenging. Animal models or in vitro epithelial cell-line models are both likely needed to develop and optimise

a clearer understanding of prebiotic formulations in CF. Trials evaluating the longer-term clinical benefits of dietary prebiotics on intestinal inflammation and gut microbial composition in healthy controls and other disease populations are also necessary, and likely beneficial to our understanding for their use in CF.

ACKNOWLEDGEMENTS

The authors would like to thank Nikki Jahnke and the Cochrane Cystic Fibrosis and Genetic Disorders Group for their help and support of this review. They would like to thank Lisa Winer, Cochrane Central Production Service, for copy editing the manuscript.

This project was supported by the National Institute for Health and Care Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service, or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
de Freitas 2018	No prebiotic-only arm
EUCTR2010-023090-19-GB	Not oral delivery
Fischer 2022	Not oral delivery
IRCT2017011732004N1	No prebiotic-only arm
Kentrup 1999	Supplement not applicable – alpha-glucosidase inhibitor, which is not a prebiotic
Maretti 2017	Cohort not applicable – participants do not have cystic fibrosis
NCT00970346	Not oral delivery
NCT01465529	Not oral delivery
NCT01737983	Supplement not applicable, not a prebiotic
NCT02157922	Not oral delivery
NCT03698448	Not oral delivery
NCT03822455	Not oral delivery

Characteristics of ongoing studies *[ordered by study ID]*

NCT04118010

Study name	Vitamin D and prebiotics for intestinal health in cystic fibrosis
Methods	Randomised, double-blind, parallel-assignment intervention trial Duration: 12 weeks
Participants	**Inclusion criteria** 1. Males and females (age > 18 years) with confirmed CF by genetic mutation or sweat chloride testing, or both 2. Not currently on oral or systemic antibiotics for pulmonary exacerbation 3. Vitamin D deficient/insufficient (25(OH)D, 6 to 30 ng/mL) with most recent 25(OH)D in the past 12 months 4. Use of cystic fibrosis transmembrane conductance regulator (*CFTR*) modulator therapy is allowed **Exclusion criteria** 1. Severe vitamin D deficiency 25(OH)D ≤ 5 ng/mL or hypocalcaemia or hypercalcaemia 2. Active GI disease, abdominal pain and/or diarrhoea 3. Chronic kidney disease worse than stage 3 (eGFR < mL/min per 1.73 m^2) 4. Any vitamin D supplement use > 2000 IU or vitamin D analogue (patients who are taking more than 2000 IU of vitamin D must agree to stop the vitamin D for 6 weeks and take less than 2000 IU of vitamin D during the study) 5. Use of immunosuppressants or history of organ transplantation 6. Current use of probiotics or prebiotics Estimated enrolment: 40 adults
Interventions	**Intervention**: vitamin D_3 50,000 IU/week and 12 g/day chicory-derived prebiotic inulin **Control**: placebo vitamin D_3 capsules and 12 g/day corn-derived maltodextrin as the prebiotic placebo
Outcomes	**Primary outcome measure** 1. Change from baseline in GI microbiota composition at 12 weeks, measured using 16S rRNA gene sequencing and microbiome-dependent metabolites pathways in stool and plasma using high-resolution metabolomics analysis and reported as a percentage of bacteria **Secondary outcome measures** 1. Change from baseline in GI microbiota diversity at 12 weeks, measured using 16S rRNA gene sequencing and microbiome-dependent metabolites pathways in stool and plasma using high-resolution metabolomics analysis and reported as the Shannon Index 2. Change from baseline in GI microbiota richness at 12 weeks, measured using 16S rRNA gene sequencing and microbiome-dependent metabolites pathways in stool and plasma using high-resolution metabolomics analysis and reported as a number of populations of micro-organisms 3. Change from baseline in calprotectin level in the stool at 12 weeks (calprotectin is a protein released by a type of white blood cell called a neutrophil; when there is inflammation in the GI tract, neutrophils move to the area and release calprotectin, resulting in an increased level in the stool.) 4. Change from baseline in lipocalin-2 blood level at 12 weeks (LCN2, also known as oncogene 24p3 or NGAL, is a protein that in humans is encoded by the lipocalin 2 (*LCN2*) gene. NGAL is involved in innate immunity by sequestrating iron that in turn limits bacterial growth. It is expressed in neutrophils and in low levels in the kidney, prostate, and epithelia of the respiratory and alimentary tracts. NGAL is used as a biomarker of kidney injury.)

NCT04118010 *(Continued)*	5. Change from baseline in serum CRP blood level at 12 weeks (CRP is produced by the liver in response to inflammation; a high level of CRP in the blood is a marker of inflammation.) 6. Change from baseline in TNF blood level at 12 weeks (TNF is a multifunctional cytokine that plays important roles in diverse cellular events such as cell survival, proliferation, differentiation, and death. As a pro-inflammatory cytokine, TNF is secreted by inflammatory cells, which may be involved in inflammation-associated carcinogenesis.) 7. Change from baseline in IL-6 blood level at 12 weeks (IL-6 is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine.) 8. Change from baseline in IL-8 blood level at 12 weeks (IL-8 is a chemotactic factor that attracts neutrophils, basophils, and T-cells, but not monocytes. It is also involved in neutrophil activation. It is released from several cell types in response to an inflammatory stimulus.)
Starting date	13 March 2020
Contact information	Vin Tangpricha, MD (vtangpr@emory.edu)
Notes	

25(OH)D: 25-hydroxy vitamin D
CF: cystic fibrosis
CRP: C-reactive protein
eGFR: estimated glomular filtration rate
GI: gastrointestinal
IL-6: interleukin 6
IL-8: interleukin 8
IU: international units
LCN2: lipocalin-2
NGAL: neutrophil gelatinase-associated lipocalin
rRNA: ribosomal ribonucleic acid
TNF: tumour necrosis factor

APPENDICES

Appendix 1. Electronic search strategies

Database	Search strategy	Date last searched
PubMed (from 1946 to present)	#1 Cystic fibrosis OR mucoviscidosis #2 prebiotic OR synbiotic OR galactooligosaccharide OR fructooligosaccharide OR Inulin OR oligosaccharide #3 randomized controlled trial [pt] #4 controlled clinical trial [pt] #5 randomized [tiab] #6 placebo [tiab] #7 drug therapy [sh] #8 randomly [tiab] #9 trial [tiab] #10 groups [tiab]	13 January 2023

(Continued)

	#11 #3 OR #4 OR #5 OR #6 OR#7 OR #8 OR #9 OR #10 #12 animals [mh] NOT humans [mh] #13 #11 NOT #12 #14 #1 AND #2 AND #13 Note: Lines #3 -#13 are the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format. Available from: https://training.cochrane.org/handbook/version-6/chapter-4-tech-suppl, page 60	
ClinicalTrials.gov (www.clinicaltrials.gov)	[Advanced Search] Condition or disease: Cystic fibrosis OR mucoviscidosis Other terms: prebiotic OR synbiotic OR galactooligosaccharide OR fructooligosaccharide OR Inulin OR oligosaccharide Study type: Interventional Studies (Clinical Trials)	13 January 2023
WHO ICTRP (trialsearch.who.int/)	[Basic Search] (Cystic fibrosis OR mucoviscidosis) AND (prebiotic OR synbiotic OR galactooligosaccharide OR fructooligosaccharide OR Inulin OR oligosaccharide)	13 January 2023

HISTORY

Protocol first published: Issue 12, 2022

CONTRIBUTIONS OF AUTHORS

Task	Author(s) responsible
Protocol stage: draft the protocol	NW, JJ
Review stage: select which trials to include (2 + 1 arbiter)	NW, JJ, AP
Review stage: extract data from trials (2 people)	NW, JJ
Review stage: enter data into Review Manager Web	NW, JJ
Review stage: carry out the analysis	NW, JJ
Review stage: interpret the analysis	NW, JJ, SN, AP, AS
Review stage: draft the final review	NW, JJ, AP, SN, AS
Review stage: draft the final review	NW, JJ, AP, SN, AS
Update stage: update the review	NW, JJ

DECLARATIONS OF INTEREST

NW has received prebiotic supplement in-kind support from Clasado Biosciences, which provided prebiotic product for previous research trial (Williams 2016).

JJ: none.

AP reports grants from Vertex, as well as travel expenses from Vertex to attend national and international meetings.

SN: none.

AS reports grants from Vertex, as well as speaker honoraria and expenses from Vertex and Teva, outside the submitted work. In addition, AS has a patent issued "Alkyl quinolones as biomarkers of Pseudomonas aeruginosa infection and uses thereof".

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

  This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We previously planned to report results by time point, but on the advice of the statistical peer reviewer at full-review stage, we now plan to report all results together regardless of trial duration.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cystic Fibrosis; Feces; Hospitalization; Inflammation; Nutritional Status; Prebiotics

MeSH check words

Adult; Child; Humans