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Prebiotics for people with cystic fibrosis (Protocol)

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[Intervention Protocol]

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

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 Patient Registry 2020). In spite of 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). The growth and nutritional status of people with CF is 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 (Duytschaever 2011), and high-caloric, high-fat diets (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). Furthermore, 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 by Gibson and Roberfroid (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 *bifidobacteria* and *lactobacilli*). 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". Therefore, the prebiotic concept 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. At present, there are 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. As of 2020, 11 completed randomised controlled trials (RCTs) on probiotics in people with CF had been conducted (Coffey 2020). That Cochrane 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). With 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), and data 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 genuses *Lactobacilli* and *Bifidobacterium*), 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 (SCFAs), 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 wellbeing (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 is a 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 recently one Australian study showed similar with 70% of adults with CF having used probiotics, attributed to GI and antibiotic issues (Anderson 2022). The authors of one recent 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 highlight there is no consensus and direct recommendations on the use of probiotics in CF. GI symptoms are important considerations for adults with CF, further antibiotic use is prevalent and subsequently dietary prebiotics could be suitable adjunct treatments in the disease. Indeed, prebiotic supplementation have been shown to reduce GI symptoms in irritable bowel disease (Silk 2009), and reduce diarrhoea associated with travel (Drakoularakou 2010) and antibiotic use (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 will include RCTs and quasi-RCTs to assess the efficacies of prebiotics in children and adults with CF. 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.

Types of participants

We will include participants who fulfil consensus diagnostic criteria for CF (Farrell 2017). We will place no restrictions for participants in terms of age, gender, genotype, pancreatic exocrine sufficiency status, disease severity, comorbidities, antibiotic use or CFTR modulator therapy.

Types of interventions

We will 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 will include trials where participants could be randomised to a prebiotic-only arm with a suitable comparator.

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

We will 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 will assess the following outcome measures at three-monthly intervals for the first 12 months and then annually thereafter. This will allow us to account for the likelihood of each study reporting outcomes at different durations of fibre-prebiotic interventions. Pooling all outcomes reported from one to three months or from four to six months will allow for comparison between trials. The time points here relate to the duration of the prebiotic intervention.

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 cystic fibrosis (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. forced expiratory volume in one second (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-PK (U/mL)
      iii. 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 will search for all relevant published and unpublished trials without restrictions on language, year 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 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 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 (cfgd.cochrane.org/our-specialised-trials-registers).

We will search the following databases and registries; the search strategies are presented in the appendices (Appendix 1):

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

Searching other resources

We will check the bibliographies of included trials and any relevant systematic reviews identified for further references to relevant trials. We will also contact experts and organisations in the field to obtain additional information on relevant trials.

Data collection and analysis

We will employ the standard methods of the Cochrane Cystic Fibrosis and Genetic Disorders Group and the *Cochrane Handbook of Systemic Reviews of Interventions* (Higgins 2022a).

If an author is involved in any trial identified, they will not participate in decision-making regarding inclusion or exclusion from the review. Furthermore, they will not make any risk of bias assessments or extract data for that trial.

Selection of studies

Once we have identified a complete list of references, one review author (NW) will check and remove duplicates and will then enter the list into the Covidence online software (Covidence). Two review authors (NW and JJ) will independently assess abstracts and titles and exclude obviously relevant trials. We will assess the full text of each remaining trial to determine which satisfy the inclusion criteria. We will discuss any discrepancies, and gain a consensus through the use of a third review author (AP). We will report reasons for exclusion of trialsat the full-text stage in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (NW and JJ) will independently extract data using a standard data extraction form in Covidence (Covidence), and we will pilot this 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-RCT);
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 the use of 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 plan to group outcome data based on the duration of the fibre-prebiotic intervention into three-monthly intervals for the first 12 months and then annually thereafter to allow for comparisons between studies. The impact of intervention duration will be explored further in a subgroup analysis.

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

Assessment of risk of bias in included studies

To assess the risk of bias we will use the risk of bias tool described in the Cochrane *Handbook of Systematic Reviews for Interventions* (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 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 do not report these, then we will deem that as a high risk of 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 the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

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, first we will 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 provide only detailed descriptions 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 pairwise 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 from 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 trials) (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); and
4. fibre-prebiotic duration (one to less than six months versus six to 12 months).

Sensitivity analysis

If we identify sufficient studies 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 with a high risk for the domains of performance bias and detection bias.

Summary of findings and assessment of the certainty of the evidence

We propose to generate a summary of findings table for each comparison we present and will report each of 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 relevance to clinicians and patients. 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.

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REFERENCES

Additional references

Anderson 2022

Anderson JL, Tierney AC, Miles C, Kotsimbos T, King SJ. Probiotic use in adults with cystic fibrosis is common and influenced by gastrointestinal health needs: a cross-sectional survey study. *Journal of Human Nutrition and Dietetics* 2022;**35**:444-54. [DOI: 10.1111/jhn.12991]

Antosca 2019

Antosca KM, Chernikova DA, Price CE, Ruoff KL, Li K, Guill MF, et al. Altered stool microbiota of infants with cystic fibrosis shows a reduction in genera associated with immune programming from birth. *Journal of Bacteriology* 2019;**201**(16):e00274-19.

Bell 2020

Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective. *Lancet Respiratory Medicine* 2020;**8**(1):65-124.

Burke 2017

Burke DG, Fouhy F, Harrison MJ, Rea MC, Cotter PD, O'Sullivan O, et al. The altered gut microbiota in adults with cystic fibrosis. *BMC Microbiology* 2017;**17**(1):1-11.

Burokas 2017

Burokas A, Arboleya S, Moloney RD, Peterson VL, Murphy K, Clarke G, et al. Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. *Biological Psychiatry* 2017;**82**(7):472-87.

Coffey 2020

Coffey MJ, Garg M, Homaira N, Jaffe A, Ooi CY. Probiotics for people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2020, Issue 1. Art. No: CD012949. [DOI: 10.1002/14651858.CD012949.pub2]

Corey 1988

Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *Journal of Clinical Epidemiology* 1988;**41**(6):583-91.

Corrêa-Oliveira 2016

Corrêa-Oliveira R, Fachi JL, Vieira A, Sato FT, Vinolo MA. Regulation of immune cell function by short-chain fatty acids. *Clinical & Translational Immunology* 2016;**5**(4):e73.

Covidence [Computer program]

Veritas Health Innovation Covidence. Melbourne, Australia: Veritas Health Innovation. Available at covidence.org.

Cystic Fibrosis Foundation Patient Registry 2020

Cystic Fibrosis Foundation Patient Registry. 2020 Annual data report. www.cff.org/sites/default/files/2021-10/2019-Patient-Registry-Annual-Data-Report.pdf (accessed 17 November 2022).

Deeks 2022

Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

de Freitas 2018

de Freitas MB, Moreira EA, Tomio C, Moreno YM, Daltoe FP, Barbosa E, et al. Altered intestinal microbiota composition, antibiotic therapy and intestinal inflammation in children and adolescents with cystic fibrosis. *PLOS One* 2018;**13**(6):e0198457. [DOI: 10.1371/journal.pone.0198457]

Dhaliwal 2015

Dhaliwal J, Leach S, Katz T, Nahidi L, Pang T, Lee JM, et al. Intestinal inflammation and impact on growth in children with cystic fibrosis. *Journal of Pediatric Gastroenterology and Nutrition* 2015;**60**(4):521-6.

Dinan 2017

Dinan TG, Cryan JF. The microbiome-gut-brain axis in health and disease. *Gastroenterology Clinics of North America* 2017;**46**(1):77-89.

Drakoularakou 2010

Drakoularakou A, Tzortzis G, Rastall R, Gibson GR. A double-blind, placebo-controlled, randomized human study assessing the capacity of a novel galacto-oligosaccharide mixture in reducing travellers' diarrhoea. *European Journal of Clinical Nutrition* 2010;**64**:146-52.

Duytschaever 2011

Duytschaever G, Huys G, Bekaert M, Boulanger L, De Boeck K, Vandamme P. Cross-sectional and longitudinal comparisons of the predominant fecal microbiota compositions of a group of pediatric patients with cystic fibrosis and their healthy siblings. *Applied and Environmental Microbiology* 2011;**77**(22):8015-24.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140-9.

Farrell 2017

Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. *Journal of Pediatrics* 2017;**181S**:S4-15. [DOI: 10.1016/j.jpeds.2016.09.064]

Fuchs 1994

Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *New England Journal of Medicine* 1994;**331**(10):637-42.

Gibson 1995

Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *Journal of Nutrition* 1995;**125**(6):1401-12.

Gibson 2005

Gibson GR, McCartney AL, Rastall RA. Prebiotics and resistance to gastrointestinal infections. *British Journal of Nutrition* 2005;**93**(S1):S31-4.

Gibson 2017

Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology* 2017;**14**(8):491-502.

Guridi 2020

Guridi CB, Serena AR, Cabrera SG, Fernández IA, Hernández CR, Vivanco BM, et al. Clinical evaluation of the synbiotic Prodefen Plus® in the prevention of the antibiotic-associated diarrhoea in subjects requiring antibiotic treatment. *Beneficial Microbes* 2020;**11**:535-45.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2017

Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). The Cochrane Collaboration, 2017. Available from training.cochrane.org/handbook/archive/v5.2.

Higgins 2022a

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Higgins 2022b

Higgins JP, Eldridge S, Li T, editor(s). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Hill 2014

Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology & Hepatology* 2014;**11**(8):506-14.

Ho 2019

Ho J, Nicolucci AC, Virtanen H, Schick A, Meddings J, Reimer RA, et al. Effect of prebiotic on microbiota, intestinal permeability, and glycemic control in children with type 1 diabetes. *Journal of Clinical Endocrinology & Metabolism* 2019;**104**(10):4427-40.

Hoen 2015

Hoen AG, Li J, Moulton LA, O'Toole GA, Housman ML, Koestler DC, et al. Associations between gut microbial colonization in early life and respiratory outcomes in cystic fibrosis. *Journal of Pediatrics* 2015;**167**(1):138-47.

Jadin 2011

Jadin SA, Wu GS, Zhang Z, Shoff SM, Tippets BM, Farrell PM, et al. Growth and pulmonary outcomes during the first 2 y of life of breastfed and formula-fed infants diagnosed with cystic fibrosis through the Wisconsin Routine Newborn Screening Program. *American Journal of Clinical Nutrition* 2011;**93**(5):1038-47.

Jaudszus 2019

Jaudszus A, Zeman E, Jans T, Pfeifer E, Tabori H, Arnold C, et al. Validity and reliability of a novel multimodal questionnaire for the assessment of abdominal symptoms in people with cystic fibrosis (CFAbd-Score). *Patient* 2019;**12**(4):419-28.

Kellow 2014

Kellow NJ, Coughlan MT, Reid CM. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. *British Journal of Nutrition* 2014;**111**(7):1147-61.

Kelly 2022

Kelly J, Al-Rammahi M, Daly K, Flanagan PK, Urs A, Cohen MC, et al. Alterations of mucosa-attached microbiome and epithelial cell numbers in the cystic fibrosis small intestine with implications for intestinal disease. *Scientific Reports* 2022;**12**(1):6593. [DOI: 10.1038/s41598-022-10328-3] [PMID: 35449374]

Lee 2012

Lee JM, Leach ST, Katz T, Day AS, Jaffe A, Ooi CY. Update of faecal markers of inflammation in children with cystic fibrosis. *Mediators of Inflammation* 2012;**2012**:948367. [DOI: 10.1155/2012/948367] [PMID: 22988347]

Li 2014

Li L, Somerset S. The clinical significance of the gut microbiotain cystic fibrosis and the potential for dietary therapies. *Clinical Nutrition* 2014;**33**(4):571-80.

Licht 2012

Licht TR, Ebersbach T, Frøkiær H. Prebiotics for prevention of gut infections. *Trends in Food Science & Technology* 2012;**23**(2):70-82.

Madan 2012

Madan JC, Koestler DC, Stanton BA, Davidson L, Moulton LA, Housman ML, et al. Serial analysis of the gut and respiratory microbiome in cystic fibrosis in infancy: interaction between intestinal and respiratory tracts and impact of nutritional exposures. *MBio* 2012;**3**(4):e00251-12. [DOI: 10.1128/mBio.00251-12]

Mainz 2022

Mainz JG, Zagoya C, Polte L, Naehrlich L, Sasse L, Eickmeier O, et al. Elexacaftor-tezacaftor-ivacaftor treatment reduces abdominal symptoms in cystic fibrosis-early results obtained with the CF-specific CFAbd-score. *Frontiers in Pharmacology* 2022;**13**:877118. [DOI: 10.3389/fphar.2022.877118]

Marques 2014

Marques TM, Cryan JF, Shanahan F, Fitzgerald GF, Ross RP, Dinan TG, et al. Gut microbiota modulation and implications for host health: dietary strategies to influence the gut–brain axis. *Innovative Food Science & Emerging Technologies* 2014;**22**:239-47.

Marsland 2015

Marsland BJ, Trompette A, Gollwitzer ES. The gut–lung axis in respiratory disease. *Annals of the American Thoracic Society* 2015;**12**(2):S150-6.

McCormick 2010

McCormick J, Mehta G, Olesen HV, Viviani L, Macek M Jr, Mehta A, et al. Comparative demographics of the European cystic fibrosis population: a cross-sectional database analysis. *Lancet* 2010;**375**(9719):1007-13. [DOI: 10.1016/S0140-6736(09)62161-9]

McDonald 2021

McDonald CM, Bowser EK, Farnham K, Alvarez JA, Padula L, Rozga M. Dietary macronutrient distribution and nutrition outcomes in persons with cystic fibrosis: an evidence analysis center systematic review. *Journal of the Academy of Nutrition and Dietetics* 2021;**121**(8):1574-90.e3. [PMID: 32532674]

Middleton 2019

Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. *New England Journal of Medicine* 2019;**381**(19):1809-19.

Newburg 2016

Newburg DS, Ko JS, Leone S, Nanthakumar NN. Human milk oligosaccharides and synthetic galactosyloligosaccharides contain 3'-, 4-, and 6'-galactosyllactose and attenuate inflammation in human T84, NCM-460, and H4 cells and intestinal tissue ex vivo. *Journal of Nutrition* 2016;**146**(2):358-67.

Nielsen 2016

Nielsen S, Needham B, Leach ST, Day AS, Jaffe A, Thomas T, et al. Disrupted progression of the intestinal microbiota with age in children with cystic fibrosis. *Scientific Reports* 2016;**6**:1-11. [PMID: 27143104]

Ooi 2015

Ooi CY, Pang T, Leach ST, Katz T, Day AS, Jaffe A. Fecal human β-defensin 2 in children with cystic fibrosis: is there a diminished intestinal innate immune response? *Digestive Diseases and Sciences* 2015;**60**(10):2946-52.

Ooi 2018

Ooi CY, Syed SA, Rossi L, Garg M, Needham B, Avolio J, et al. Impact of CFTR modulation with ivacaftor on gut microbiota and intestinal inflammation. *Scientific Reports* 2018;**8**(1):17834.

Quittner 2009

Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire – Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic Pseudomonas aeruginosa airway infection. *Chest* 2009;**135**(6):1610-8.

Ramsey 2011

Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *New England Journal of Medicine* 2011;**365**(18):1663-72.

RevMan Web 2022 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 4.2.0. The Cochrane Collaboration, 2022. Available at revman.cochrane.org.

Sanders 2019

Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. *Nature Reviews Gastroenterology & Hepatology* 2019;**16**(10):605-16.

Savino 2022

Savino F. Prebiotics in Pediatrics. In: Guandalini S, Dhawan A, editors(s). Textbook of Pediatric Gastroenterology, Hepatology and Nutrition. Berlin (Germany): Springer, 2022:713-9.

Schünemann 2022

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Scott 2020

Scott KP, Grimaldi R, Cunningham M, Sarbini SR, Wijeyesekera A, Tang ML, et al. Developments in understanding and applying prebiotics in research and practice – an ISAPP conference paper. *Journal of Applied Microbiology* 2020;**128**(4):934-49.

Searle 2012

Searle LE, Jones G, Tzortzis G, Woodward MJ, Rastall RA, Gibson GR, et al. Low molecular weight fractions of BiMuno® exert immunostimulatory properties in murine macrophages. *Journal of Functional Foods* 2012;**4**(4):941-53.

Sekirov 2010

Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. *Physiological Reviews* 2010;**90**(3):859-904.

Silk 2009

Silk DB, Davis A, Vulevic J, Tzortzis G, Gibson GR. Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics* 2009;**29**(5):508-18.

Smith 2020

Smith S, Rowbotham N, Davies G, Gathercole K, Collins SJ, Elliott Z, et al. How can we relieve gastrointestinal symptoms in people with cystic fibrosis? An international qualitative survey. *BMJ Open Respiratory Research* 2020;**7**(1):e000614. [DOI: 10.1136/bmjresp-2020-000614]

Snyder 1964

Snyder WH, Gwinn JL, Landing BH, Asay LD. Fecal retention in children with cystic fibrosis: report of three cases. *Pediatrics* 1964;**34**:72-7. [PMID: 14181988]

Stallings 2008

Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *Journal of the American Dietetic Association* 2008;**108**:832-9.

Sterne 2011

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002. [DOI: 10.1136/bmj.d4002]

Sullivan 2015

Sullivan JS, Hounchell J, Pecott-Grimm H, Cowan K, Lahiri T. Probiotic use and antibiotic associated gastrointestinal symptoms in pediatric patients with cystic fibrosis. *Pediatric Pulmonology* 2015;**50**(Suppl 41):407. [ABSTRACT NO: 567]

Sutherland 2018

Sutherland R, Katz T, Liu V, Quintano J, Brunner R, Tong CW, et al. Dietary intake of energy-dense, nutrient-poor and nutrient-dense food sources in children with cystic fibrosis. *Journal of Cystic Fibrosis* 2018;**17**(6):804-10.

Tomas 2016

Tomas J, Mulet C, Saffarian A, Cavin JB, Ducroc R, Regnault B, et al. High-fat diet modifies the PPAR-γ pathway leading to disruption of microbial and physiological ecosystem in murine small intestine. *Proceedings of the National Academy of Sciences of the USA* 2016;**113**(40):E5934-43. [DOI: 10.1073/pnas.1612559113]

Turck 2016

Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. *Clinical Nutrition* 2016;**35**(3):557-77.

Vernocchi 2018

Vernocchi P, Del Chierico F, Russo A, Majo F, Rossitto M, Valerio M, et al. Gut microbiota signatures in cystic fibrosis: loss of host CFTR function drives the microbiota enterophenotype. *PLOS One* 2018;**13**(12):e0208171. [DOI: 10.1371/journal.pone.0208171]

Whisner 2018

Whisner CM, Castillo LF. Prebiotics, bone and mineral metabolism. *Calcified Tissue International* 2018;**102**(4):443-79.

APPENDICES

Appendix 1. Electronic search strategies

Database	Search strategy
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]

(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)
WHO ICTRP (trialsearch.who.int/)	[Basic Search] (Cystic fibrosis OR mucoviscidosis) AND (prebiotic OR synbiotic OR galactooligosaccharide OR fructooligosaccharide OR Inulin OR oligosaccharide)

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. Providing prebiotic product for previous research trial (Williams 2016).

JJ: none.

AP Conflicts of interest TBC.

SN: none.

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

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