The role of epidemiological evidence from prospective population studies in shaping dietary approaches to therapy in Crohn's disease

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List of abbreviations: CD, Crohn's disease; CDED, Crohn's disease exclusion diet; COSM, Cohort of Swedish Men; SMC, Swedish mammograph cohort; DHA: docosahexaenoic acid; EEN, exclusive enteral nutrition; EPIC, European Prospective Investigation into Cancer and Nutrition; IBD, Inflammatory bowel disease; NHS, Nurses' Health Study; PEN, partial enteral nutrition; RCT: randomised control trial; SFFQ: semi-quantitative food frequency questionnaire

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ABSTRACT

Scope: The concept that dietary factors are key risk and preventive agents in the development of Crohn's disease (CD), while widely believed and supported by epidemiological evidence, has yet to lead to clear identification of those factors through clinical trials. The aims were to examine the strength of the epidemiological evidence of diet and its association with CD, examine how interpretation of mostly epidemiological data has shaped ideas for potential dietary therapies and to explore other factors that have driven the design of dietary clinical trials in CD.

Methods: A literature search was performed in PubMed, Medline, EMBASE and Google Scholar for prospective cohort studies and randomised clinical trials (RCTs) using search terms – 'Crohn's disease', 'diet', 'risk', 'remission', 'treat', 'cohort', 'randomised'.

Results: Only four prospective cohort studies examined the relationship of diet and CD development, but these trials have been largely ignored by dietary RCTs in CD, which have

used predominately exclusion diets in small populations without objective endpoint assessment. Only one demonstrated clinical benefit to intestinal inflammation.

Conclusion: Investment in large multicentre dietary clinical trials that focus on dietary inclusions with objective endpoint assessment are needed to provide safe, sustainable dietary therapy to patients with CD.

The relationship of diet with Crohn's disease: conceptual considerations

Crohn's disease (CD) is a chronic immune-mediated inflammatory disease that results in inflammation and ulceration along any site of the gastrointestinal tract. It is relapsing and remitting in nature. Dietary modification has been heralded as a potential route through which the development of CD might be prevented through, for example, the modification of the gut microbiota or prevention of mucosal barrier dysfunction. Factors associated with the western diet have been considered likely candidates given the difference in the incidence of CD in Europe and North America on the one hand and Asian countries on the other, and the increasing incidence of CD in Asia coinciding with the westernisation of eating habits.^[1]

Migration studies have supported this idea with the observation that CD incidence in first- and particularly second-generation immigrants began to trend towards the CD incidence of their host nation after migration from a low- to high-risk region.^[2-5] Westernisation has had significant impacts on the food supply worldwide with improvements in the agricultural sector, food manufacturing and food storage. This has provided consumers with more food choices that have higher levels of processing and longer shelf life. As a consequence, the western diet has led to increased total calorie intake, lower fibre content, higher glycaemic load, and higher intake of saturated fats, refined carbohydrates and food additives.^[6] It is also associated with altered gut microbial communities with reduced diversity and impaired

intestinal barrier function.^[7, 8] The concept that dietary factors are key risk and preventive agents in the development of CD, while widely believed and supported by epidemiological evidence, has yet to lead to clear identification of those factors through clinical trials.

The second concept that has emerged is that diet can be used as a therapeutic agent to reduce inflammatory burden and prevent relapse when CD has already developed. This is supported by the strong evidence base that major dietary change in the form of exclusive enteral nutrition (EEN) induces remission and healing. However, the nature and mechanistic actions of the inflammatory or anti-inflammatory components of diet remain at best speculative.

The third concept is that, because the causative dietary factors remain in operation after the disease is established, their modification can be used as therapy in induction and/or maintenance of remission. There are precedents for this concept; for example, gluten is the causative agent in coeliac disease and outcomes are markedly improved with adherence to a gluten-free diet, and alcohol is the causative agent in alcoholic hepatitis and removing that causative agent leads to marked improvement of and healing and regeneration in the liver. Thus, one might anticipate that epidemiological evidence for causative associations would have translated in dietary interventional studies in humans.

The aims of this review are to examine the strength of the epidemiological evidence of diet and its association with CD, to examine how our interpretation of mostly epidemiological

data has shaped the ideas for potential dietary therapies and to examine other factors that have driven the design of dietary clinical trials in CD.

Methods

A literature search was performed in PubMed, Medline, EMBASE and Google Scholar for prospective cohort studies and randomised clinical trials using search terms – ‘Crohn’s disease’, ‘diet’, ‘risk’, ‘remission’, ‘treat’, ‘cohort’, ‘randomised’ to examine the epidemiological evidence and dietary clinical trials in relation to CD. For the purposes of this review only prospective cohort studies and randomised clinical trials were examined given the inherent flaws of retrospective cohort studies and case control studies. Studies that examined the effects of nutritional supplements such as vitamins, minerals, prebiotics or probiotics were excluded from this review.

The strengths and flaws of dietary epidemiology studies in CD

There is a profusion of epidemiological data on the association of diet with CD and this has been extensively reviewed elsewhere.^[9] The vast majority of studies have used two methodologies steeped in flaws. First, recall of dietary intake prior to the development of the disease has been utilised frequently in retrospective case control trials or retrospective cohort studies. This methodology in IBD is particularly problematic due to recall bias and is fraught with inaccuracies as reflected in the heterogeneity of the purported associations. Recall bias affects the patient’s recollection of their dietary intake before symptoms of CD develop^[10] describes the effect of recall bias as two-pronged: if individuals are recruited to a

study a long time after diagnosis, they may have considerably changed their diet or preferentially recalled consumption of specific foods that exacerbated their symptoms. Alternatively, the recall of diet a short time after diagnosis is subject to concerns about reverse causation, whereby symptoms preceding diagnosis might cause dietary change.^[10]

Secondly these retrospective studies often assess dietary intake data at one point in time and are unable to account for variations in dietary intake between dietary exposure and disease development. Case control studies can investigate the frequency of exposure to a dietary factor over a number of time points. However, for patients with CD, symptoms can be present for over 12 months before a diagnosis is made and the disease may have been in evolution for longer than that. Therefore, dietary habits may have significantly changed during a technical “disease-free period” due to the presence of as yet unidentified intestinal inflammation.^[11, 12] This delay in diagnosis makes it difficult to identify the true relationship between exposure frequency of a dietary agent and disease development as the true timeline of disease onset is unknown.

Data that may be closer to meaningful associations comes from large, longitudinal prospective cohort studies in which subjects are recruited when well, allowing associations of dietary patterns and specific nutrient intake to be linked to the subsequent development of CD. The studies that meet these criteria are explored in this review; the Nurses’ Health Study (NHS), European Prospective Investigation into Cancer and Nutrition (EPIC), Cohort of Swedish Men (COSM) and the Swedish Mammography Study (SMC). The details of the methodology, strengths and limitations of these cohort studies can be found in [Table 1](#).

Whilst these studies can provide some insights into the potential role of diet in the development of CD, there are limitations on their translatability to the CD population. The main factor is they all investigate the relationship with diet and the subsequent development of CD in middle-aged to older adults in westernised countries. Given the median age of diagnosis for CD is between 20-30 years of age and up to 80% of cases have disease established by 40 years of age, the relationship from these cohort studies may not be relevant to those patients diagnosed before 40 years old or for those living in developing nations.^[13] Additionally, all cohort studies examined used semi-quantitative food frequency questionnaires (SFFQ) to examine dietary intake over a period of time. However, these SFFQ are validated against weighed food records (WFR) with an adequate correlation between nutrients determined by each method often being defined as low as 0.6. SFFQ rely on the participant having good memory, literacy and numeracy skills to calculate intakes of food over a period of time, which can lead to inaccurate or subjective reporting. SFFQ are also limited by the types of foods that are listed in their questionnaire, do not allow for analysis of an evolving food supply and are generally poorly validated for the intake of many micronutrients, total and specific fibres.^[14, 15] In an Australian study the reliability of the an FFQ was examined and demonstrated that it overestimated the intake of fibre compared to twelve days of WFR, with the FFQ provided higher mean estimates of fibre compared to the WFR ($p < 0.0001$). The FFQ in this study also did not delineated between the different types of fibre or sources of fibre, but it was able to rank individual's intake of fibre.^[14] All of the prospective studies have the same limitations of any observational study of unmeasured or residual confounders that may bias the findings and they only provide strength of association data.

Despite these limitations, such studies do provide the most robust information. There have been four main prospective cohort studies that are evaluable.

Prospective cohort studies

Between NHS and EPIC, these studies have prospectively followed the dietary choices for up to 26 years in over half a million people, examining the relationship of diet with the subsequent development of CD. The SMC and SOCM only examined a few relationships between diet and CD. The structure and methodology used in these studies are outlined in Table 1, while the dietary findings are summarised in [Tables 2](#) and [3](#).

Comparing the results of the NHS and EPIC studies is challenging due to the different dietary methodologies, statistical methodologies and published data. The EPIC methodology incorporated dietary information from eight different countries into one central database whilst only examining dietary intake at one point in time. NHS allowed for changing dietary patterns over time in one population by repeating the SFFQ, and NHS included dietary information about fibre supplements from 1994 allowing for a more accurate assessment of fibre intake.

Different statistical methodologies were applied. NHS used Cox proportional hazards models adjusting for a number of potential confounders, including age, smoking status, body mass index, and use of oral contraceptive hormones, non-steroidal anti-inflammatory drugs

(NSAIDs) and post-menopausal hormone therapy, to estimate the multivariate hazard ratio (HR) and 95% confidence intervals. EPIC used a nested case control study within a prospective cohort study. The odds ratio (OR) for the exposures were calculated using conditional logistic regression adjusting for smoking and total energy intake both of which were measured at recruitment. An example of different published data and dietary analysis is the way each study treated omega-3 polyunsaturated fatty acids; EPIC examined docosahexaenoic acid (DHA) only after adjustment other fatty acids and vitamin D, whereas NHS examined DHA and eicosapentaenoic acid (EPA) combined.

Despite such differences, a few specific nutrient groups had relatively strong relationships with the development of CD ([Table 2](#)) and no positive association was found to be a negative association in another study. Furthermore, there was consistency in multiple nutrients that did not demonstrated a significant relationship with developing CD. These were total fat, total carbohydrates, total sugars, total starches, total omega 6, total monounsaturated fat, total saturated fat, omega 3:6 ratio, fibre from vegetables or legumes, and alcohol intake ([Table 3](#)).

Specific nutrient groups

The only macronutrient to be found to be associated with an increased risk of CD was total protein intake. However, these data came from the French cohort within the EPIC trial, in which only women aged 40-65 years were enrolled at baseline. The highest tertile of protein intake was 2.06 g/kg/d, which is double the recommended intake.^[16] The authors did note that, due to their low incidence rate of CD, analysis could not be performed based on

quartiles and that the sample size had a limited power to detect effects below a relative risk of 2.5. This relationship has not been examined in the NHS cohort.

Dairy intake was cited to be associated with reduced risk of developing CD when comparing no intake against any intake once adjusted for energy intake and smoking status in the EPIC study. This relationship has not been examined in the NHS cohort.

Fibre intake was protective against developing CD in both NHS and EPIC studies, but the source of fibre were conflicted. Estimates of total fibre intake in NHS and EPIC was determined by collecting data from the FFQs and using the Department of Agriculture database or the European Nutrient Database for estimating total dietary fibre intake respectively. The differences in these databases may explain the heterogeneity of the outcomes from the two cohort studies. Additionally, each study analysed the sources of fibre differently; EPIC considered fibre intake from three groups of food (fruit, vegetables, cereals) whereas NHS considered fibre intake from seven groups of foods (fruit, vegetables, cruciferous vegetables, wholegrains, cereals, bran and legumes). Given that EPIC found a protective association from fibre from cereals, there is a possibility that the NHS did not detect this association because the NHS definition of 'cereals' excluded bran and wholegrains. With these considerations in mind, the two studies are consistent in identifying higher dietary fibre intake as protective.

One dietary factor often cited as one of the key drivers of intestinal inflammation, particularly in CD, is the intake of sweetened beverages, largely supported by retrospective case-control studies^[17]. Despite such belief, no such association was identified in EPIC and the two large Swedish cohorts (this has not been examined in the NHS cohort).^[18, 19] A positive association was demonstrated for ulcerative colitis in the EPIC study,^[19, 20] but this finding has now been contradicted by two large Swedish cohorts.^[18] Such conflicting data not only demonstrate the limitations of observational studies, but also highlight the need to differentiate factors associated with ulcerative colitis from those associated with CD, as the risk factors for these diseases differ.

Dietary patterns

The majority of these studies have investigated the impact of individual food groups or nutrients on the risk of developing CD. However, there are considerable complexities of dietary component interactions and synergies, and these may explain the lack of strong associations for macronutrients. Unfortunately, dietary patterns have been poorly studied with respect to risk for CD, with one exception; the Mediterranean diet has been examined in two prospective studies with conflicting results, as outlined in [Table 2](#). The reason for the conflicting results may lie in the methodology of applying the Mediterranean diet score. Whilst both of these studies based their scoring on the same reference source, each study slightly modified this score to suit their population. The main differences included definitions of moderate alcohol consumption and classification of food groups; for example, fruits and vegetables comprised one group in SOCM/SMC while fruits and nuts were linked in EPIC, with vegetables considered separately. Additionally, EPIC may have had reduced power to find any significant associations between Mediterranean diet score and CD incidence due to

the small number of CD cases detected and significant heterogeneity in methods used to collected dietary information across the eight centres in its nested case-control design.

Dietary interventions in Crohn's disease

Multiple diets involving food choice with purported benefits for CD have been described. It might be anticipated the potentially protective food components (such as promoting intake of fibre from a number of different sources and of dairy, and the avoidance of high total protein intake) from these prospective cohort studies may have been translated to such dietary interventions. This premise has been examined in the limited number of diets that have undergone randomised controlled trials (RCTs) that are outlined in [Table 4](#).

A recent Cochrane review has examined the strength 11 of those published clinical trials.^[21] Four showed positive results over the comparator diet, with an additional study with positive results being published consequently.^[22] The quality of the studies were not judged to be high. The primary end-points were disease activity scores, patient tolerance and quality of life, rather than, for all but one,^[23] objective markers such as mucosal healing, and the majority were underpowered, being small in number with high rates of patient drop-out resulting in attrition bias. The control diets were not well-described and some were interventions in their own right and not really control diets. Furthermore, the studies have not detailed the short term or long term nutritional adequacy of their dietary interventions potentially increasing the risk of micronutrient deficiencies in this at risk population.

The standout dietary intervention has been EEN, which is a completely liquid diet that provides 100% of a patient's nutritional requirements. By the nature of the formulas, EEN is made from milk proteins, maltodextrin, vegetables and/or animal fats, emulsifiers, vitamins and minerals. It is gluten-free, fibre-free and low in lactose. EEN was initially used to optimise a patient's nutritional state before surgery for their CD.^[24] An uncontrolled trial in 1973 demonstrated that CD patients on EEN prior to surgery improved their clinical disease activity as well as their nutritional status.^[25] Since then there have been 27 RCTs in adults and children that have investigated the benefit of EEN in inducing remission in CD. EEN is currently the first line therapy in inducing remission in paediatric patients with CD as it has demonstrated mucosal healing in this population.^[24, 26]

There have been three randomised controlled studies of patients with quiescent disease and ongoing symptoms, presumed to be functional gastrointestinal symptoms in which reducing FODMAP content of the diet has alleviated those symptoms.^[27] Such a dietary approach has not been targeted towards inflammation, but toward reducing the functional symptoms. In fact, the degree of inflammation, as shown by faecal calprotectin, has not changed by this dietary strategy. These will not be further discussed.

How have the messages from epidemiological data informed dietary clinical trial design?

Table 5 demonstrates the dietary restrictions examined in RCTs and compares these restrictions with the outcomes of the epidemiological evidence. None have included the favourable dietary factors identified from EPIC, NHS, SMC or COSM in the design of their

active dietary interventions. Some studies were performed prior to the publication of such epidemiological findings and have focussed on one aspect of the findings – the effect of increasing fibre intake.^[23, 28, 29] However, these studies did not measure fibre content and were either of very small sample size^[28] or poor quality with vague end-points dependent upon symptoms and drop-out rates,^[29] and in one study, limited fibre intake to only a single source (Viennese bread) and excluded all fruit and vegetables.^[23] In many studies, including recent ones, potentially beneficial dietary sources of fibre were actually restricted. For example, the trials completed by Levenstein 1985, Lomer 2005, Bartel 2008 and Levine 2019 all restrict different types and sources of fibre.^[22, 23, 30, 31] In the studies of Bartel 2008 and Levine 2019, dairy intake was restricted in contrast to the protective association with dairy intake in EPIC. Rather, the dietary interventions have focused on excluding multiple dietary elements or whole food groups rather than looking at dietary inclusions or methodical elimination of one food component. Depending on the trial, multiple foods or nutrient sources are excluded whether it be fibre, alcohol, red meat, gluten, dairy or food additives.

What has shaped the design of diets in contemporary clinical trials?

Rather than being shaped by epidemiological observations, dietary interventions in CD appear to have been designed on five basic premises. First, aspects of EEN, such as gluten free, fibre free or low lactose, have been a strongly influential. Secondly, there has been extrapolation and translation of pre-clinical trials in animal models of IBD such as the exclusion of emulsifiers, maltodextrins or artificial sweeteners.^[32-35] These pre-clinical studies are fraught with difficulties of translation; the pathogenic basis of the colitis models often bear little similarity to human IBD, the gastrointestinal anatomy and physiology of small animals differs to those of humans, the animal habitual diet is very unhuman-like, and the

doses of fibre or food additives tested in animals are mostly many fold greater than those conceivable in the human diet. The last point has been the subject of a critical review for food thickeners and emulsifiers.^[36] Thirdly, design of dietary studies in CD also appears to have given consideration to community dogma regarding demonised food components, such as gluten, dairy and wholegrains, but without human data to support these restrictions. Fourthly, researchers have incorporated patient's anecdotal reports of food intolerances into models aimed at inducing remission, without setting primary objective endpoints to assess their success, such as the restriction of soy products, which have not been studied in the context of CD. Finally, concepts not based upon rational scientific argument have been followed, such as in those underlying the specific carbohydrate diet.^[37] A research culture has consequently emerged in which complex dietary restriction models are created, feeding the instincts of many of CD patients' to restrict diet when having a flare, regardless of the scientific merit behind this practice.

The strongest evidence of a dietary intervention involved eating food in inducing remission in CD is the CD exclusion diet (CDED) program. This is an example of a dietary structure that has used the evidence of EEN, evidence from pre-clinical trial animal models and anecdotal evidence to develop an extremely restrictive diet that is coupled with partial enteral nutrition (PEN). The murine models used to support the CDED have demonstrated the degradation of the intestinal barrier function, dysbiosis, murine intestinal inflammation, increase bile acid production, increased intestinal permeability and decreased mucous layer when mice are fed maltodextrin, carrageenan, polysorbate 80, carboxymethylcellulose and gluten. These findings have yet to be verified in human subjects. This programme provides patients with 50% of nutritional requirements from PEN and a strict exclusion diet (CDED) that

participants follow for 12 weeks. One of the difficulties with this diet is understanding which dietary restrictions, given there are multiple, play a significant role in the reduction of symptoms and inflammatory markers. Additionally, it leaves clinicians and researchers wondering if the benefit of the CDED programme is due to being provided by PEN, given that the dietary restriction of CDED has not yet been demonstrated to be a successful stand-alone therapy.

Thus, the present status of dietary approaches to modulate inflammation in patients with CD is paradoxical and challenging to understand. The two dietary therapies with evidence of efficacy - EEN, a formulated liquid diet, and CDED coupled with PEN, a combination of foods with a formulated liquid diet - are contrasting in nutritional composition. EEN contains emulsifiers, dairy products, maltodextrin and carrageenan, which are all proposed by the authors of the CDED as inflammatory and are avoided in the CDED. EEN is almost devoid of fibre, but the CDED is described to promote the intake of a limited number of wholefoods, with a focus on soluble fibre, although soluble intake according to the instructions is limited (approximately 4-5 g daily from one apple, two bananas and two potatoes).^[38] These exclusion diets leave clinicians, therefore, pondering their exact mechanism of action, what it means for long-term dietary therapy to sustain remission, the long-term impact on the gut microbiota and the risk of implementing an unsustainable diet in a chronic disease population.

Why does it matter if dietary clinical trials ignore epidemiological evidence?

Epidemiological evidence is beneficial for giving the scientific community signals of possible causal associations between diet and disease, both protective and harmful. However in the case of dietary trials for CD, the RCTs are based on excluding a number of components at once that are not supported by large prospective longitudinal cohort trials. These RCTs have not demonstrated the benefit of excluding each component individually. Therefore, there is a risk for over-restriction of dietary components that is potentially unnecessary in a population that is at risk of malnutrition and micronutrient deficiency.^[39, 40] For example, developing strict exclusion diets focused on a limited number of 'wholefoods' may fuel orthorexic tendencies in a cohort where over 70% of patients already impose self-restrictions on their diet in an attempt to prevent relapse.^[41] There is a risk with these complex restrictive diets that we are limiting food components that may actually have benefits for patients with CD, as we have not examined the impact of these restrictions methodically in human subjects.

Conversely if these restricted components do not have direct benefit for their inflammatory activity, such dietary change may influence the pathogenesis of comorbidities that can be associated with CD, such as osteoporosis, obesity and metabolic syndrome. For example, fibre has demonstrated to have benefits for improved glycaemic control, weight management and bowel cancer risk.^[42] Given that between 40-60% of patients with CD have been reported in westernised cohorts to be overweight or obese, restricting intake of protective food components such as fibre without clear, strong evidence to do so may be causing long term harm for an increasingly co-morbid cohort.^[43-45]

On the other hand, complex interactions between food components may be important, giving rise to the concept of dietary patterns with all their complexity (like the Mediterranean diet) will provide the best anti-inflammatory or protective benefits. If this is the case, then it is essential that the dietary pattern is feasible, nutritionally adequate and enables the patient to enjoy eating especially in a cohort where food is considered potentially dangerous via its putative role in triggering relapse in CD.

Directions in dietary research in CD

There are three directions in which dietary research is traveling. First, the effects on specific putatively harmful dietary components can be addressed. Food additives are the focus of much attention due largely to the effects of specific types when given in large (pharmacological) doses to animals highly susceptible to developing colitis. This conceptually aligns with an increasingly westernised diet and the increasing incidence of CD since 1950s.^[32, 33, 46] Currently four trials have been registered to investigate the impact of emulsifiers on healthy controls and patients with CD: Alfred Health, Melbourne, Australia (all emulsifier/thickener e-numbers), The Rowett Institute, Aberdeen, United Kingdom (soy lecithin), Kings College London, United Kingdom (low additive diet – not specified) and the Wolfson Medical Center, Israel (emulsifier/bread or emulsifier/ice cream or processed cheese challenge), all hoping to expand our insights if and how emulsifiers impact our gastrointestinal tract and if they play a role in CD pathogenesis. Yet published from results from a study of the impact of carboxymethylcellulose on microbiota, bacterial translocation and intestinal barrier function from the University of Pennsylvania on carboxymethylcellulose and its impact on microbiota, bacterial translocation and intestinal barrier function are eagerly awaited (Registered with clinicaltrials.gov Trial ID NCT03440229).

The second direction is to study complex combinations of dietary changes based loosely or not at all on scientifically-supported rationale. These examine the roles of exclusion diets rather than individual food components or food patterns. There are seven trials either underway or awaiting publication regarding the specific carbohydrate diet and CDED, and their potential role in inducing or maintain remission in CD (Registered with clinical trials.gov Trial ID NCT02213835, Trial ID NCT01749813, Trial ID NCT03058679, Trial ID NCT02610101, Trial ID NCT02412553, Trial ID NCT03301311, Trial ID NCT02231814).

The third approach is to define the pathogenic mechanisms of interest and to design that targets those mechanisms. Such an approach was taken in the development of the FODMAP dietary strategy for functional gut symptoms where dietary factors that led to distension of intestinal lumen were sought and an overall reduction in the intake of the dietary components identified led to alleviation of abdominal symptoms. Examples in CD might include the use of specific prebiotic fructo-oligosaccharides in order to increase the abundance of *Faecalibacterium prausnitzii* in the intestinal lumen (Registered with Clinicaltrials.gov Trial ID NCT02539849)

Conclusion

In nutritional research in CD, there is a clear delineation between studies that have looked at disease development and treatment. For disease development, the messages from large prospective cohort studies indicate that diets high in protein may be a risk factor for

developing CD whilst diets with higher fibre intakes from a variety of food groups and those that include dairy or are high in DHA, and a Mediterranean dietary pattern may be protective. Unfortunately, these messages have not been translated into the design of dietary treatments; quite the opposite has occurred. Whether this is because the signals from prospective population-based epidemiology are viewed with scepticism, or whether they are just ignored is unclear. Data of fair to good quality indicates remission can be induced by using EEN and that similar benefits can be achieved by adding to enteral nutrition consumption of a specific foods and elimination of many others. While such data are groundbreaking and exciting in that they demonstrate the potential power of dietary therapies involving real food, the feasibility of using these restrictive diets repeatedly or on an ongoing for a chronic disease is limited in patients with CD, especially for those who suffer from other co-morbidities. They also provide few clues to what changes in dietary intake are responsible for the benefits so that the design of dietary strategies for future evaluation remains challenging. Research energies are being devoted now to food additives, complex exclusion diets and dietary supplements to alter the role of the gut microbiota. While they provide promise, such strategies should not be incorporated into routine practice on the basis of ideas or animal observations that are difficult to translate. Investment in large multicentre dietary clinical trials that focus on dietary inclusions and that have objective endpoint assessment are needed to provide safe, sustainable dietary therapy to patients with CD.

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Table 1. Summary of the findings in the large prospective epidemiological studies of dietary intake and subsequent development of Crohn's disease.

Study type	Population	Dietary methodology	Incident cases of Crohn's disease	Strengths	Limitations
European Prospective Investigation into Cancer and Nutrition (EPIC)					
Population-based prospective cohort trial	<ul style="list-style-type: none"> N = 401,326 Age 20-80 8 European countries Healthy community dwelling participants Each case CD or UC was matched with 4 randomly-selected controls matched for gender, age at recruitment [$\pm$ 6 months], centre and recruitment date [$\pm$ 3 months] 	<ul style="list-style-type: none"> Country-specific validated food frequency (FFQ) questionnaires. Recordings of foods converted to nutrient intake using the European Nutrient Database 	<p>N = 104</p> <ul style="list-style-type: none"> 73% women Age at diagnosis = mean 55 [SD 11] y Time between recruitment and diagnosis = median 5.3 [range 1.5–12.3] y 	<ul style="list-style-type: none"> 8 Western European countries with similar dietary patterns Men and women (except for France – female teachers only from health insurance scheme; and from Utrecht – women from breast screening program) 	<ul style="list-style-type: none"> Low number of cases No assessment of fibre supplement intakes One-off dietary assessment Variations in dietary intakes predict, at best, no more than 50% of the underlying variation^[47] Half of 50070 participants from Oxford were vegans, lacto-ovo vegetarians or fish eaters (7% total cohort) = over-represented compared with national data^[48] 65% of total cohort women of middle age
Nurses' Health Study (NHS)					
Population based prospective cohort trial	<p>N=170,776</p> <ul style="list-style-type: none"> Age 25–55 y USA Healthy community-dwelling, female registered nurses 	<ul style="list-style-type: none"> Validated semi-quantitative FFQ completed every 4 y Nutrient intakes calculated by multiplying the frequency of consumption of each food item by the nutrient content based on tables provided 	<p>N = 269 (incidence 8/100,000 person-y)</p> <ul style="list-style-type: none"> 100% women Age at diagnosis = mean 54 y 	<ul style="list-style-type: none"> Repeated assessment of FFQ to account for changing in dietary behaviour Fibre supplement intake assessed after 1994 Prospective Long follow up 	<ul style="list-style-type: none"> Correlation between total dietary fibre intake measured by the FFQ and weighted records was 0.61 Female nurses only

		by the Department of Agriculture		<ul style="list-style-type: none"> NHS 2 included younger women aged 25-46 y 	
Cohort of Swedish Men (COSM) and the Swedish Mammography Study (SMC).					
<p>Population-based longitudinal cohorts</p> <ul style="list-style-type: none"> SMC 1987-1990 Follow up = 11 y COSM 1997 Follow up = 17 y (1998-2017) 	<p><i>Sweetened beverages:</i></p> <p>N = 83,042</p> <ul style="list-style-type: none"> Age 44-83 y Sweden Healthy community-dwelling participants <p><i>Mediterranean diet:</i></p> <ul style="list-style-type: none"> N = 83, 147 Age 47 – 83 Sweden <p>Healthy community dwelling participants</p>	<ul style="list-style-type: none"> Examination into relationship between sweetened beverages used one off FFQ from 1997 (validated against 4-week food records in 129 people and 24-h recalls Calculated Mediterranean diet score from FFQ 	<p><i>Sweetened beverages:</i></p> <p>N = 143 (11 cases/100,000 person-years)</p> <ul style="list-style-type: none"> Age at baseline = median 60 (range, 44–83) y <p><i>Mediterranean diet:</i></p> <p>N = 164 (28 cases/100,000 person years)</p>	<ul style="list-style-type: none"> Reasonable incidence rate Prospective Long follow up The Spearman coefficient correlations between SFFQ and 14 24-h recall interview 0.70-0.81 for intakes of total carbohydrate, fat, fibre and alcohol 	<ul style="list-style-type: none"> One-off FFQ from 1997 - could have used additional FFQs from 1987 and 2009 Median age does not reflect that of CD diagnosis worldwide^[49] Did not differentiate between artificially sweetened soft drinks and regular soft drinks Juice not included

Table 2. Outcomes of large prospective epidemiological studies of dietary intake and subsequent development of Crohn's disease.

Nutrient	Unit / adjustment / comparison	Increased risk	Decreased risk	No difference	Not reported
Total protein intake	<ul style="list-style-type: none"> g/kg body weight energy adjusted third vs first tertile of intake 	EPIC ^[50] <ul style="list-style-type: none"> HR 2.63 95% CI, 1.23-5.59; $P=0.008$. Significant dose-effect relationship was observed ($P=0.04$) 		EPIC <ul style="list-style-type: none"> Dose effect relationship not but observed for animal protein ($P=0.33$). 	NHS COSM SMC
Dairy intake	<ul style="list-style-type: none"> Consumers vs non consumers when adjusting for energy intake and smoking status 		EPIC ^[51] <ul style="list-style-type: none"> OR 0.30 [95% CI, 0.13–0.65] 		NHS COSM SMC
Omega 3	<ul style="list-style-type: none"> g/d DHA only after adjustment other fatty acids and vitamin D lowest quintile vs highest quintile 		EPIC ^[52] <ul style="list-style-type: none"> OR 0.07 [0.02- 0.81] Trend across quintiles - OR 0.54 [0.30-0.99] 	NHS ^[53] <ul style="list-style-type: none"> Long chain omega 3 = DHA & EPA combined 	COSM SMC
Total fibre	<ul style="list-style-type: none"> g/d energy-adjusted lowest quintile vs highest quintile multivariate analysis 		NHS <ul style="list-style-type: none"> HR 0.59 [0.39–0.90] 	EPIC ^[54]	COSM SMC
Total fibre from fruit	<ul style="list-style-type: none"> g/d energy adjusted lowest quintile vs highest quintile multivariate analysis* 		NHS ^[55] <ul style="list-style-type: none"> HR 0.57 [0.38 – 0.85] 	EPIC ^[54]	COSM SMC
Total fibre from cereals	<ul style="list-style-type: none"> g/d smokers+ex smokers vs never smokers lowest quintile vs highest quintile multivariate analysis* 		EPIC <ul style="list-style-type: none"> OR 0.12 [0.02–0.75] ($p = 0.023$) Trend across quartiles: HR 0.50 [0.29 –0.86] ($p = 0.017$)^[54] 	NHS ^[55]	COSM SMC
Mediterranean diet (MED) score			SMC/SOMC ^[56] <ul style="list-style-type: none"> Adjusted HR for MED score: <ul style="list-style-type: none"> 3-4: 0.69 [0.48-0.99] 5: 0.78 [0.49- 	EPIC ^[19]	NHS COSM SMC

			<ul style="list-style-type: none"> ○ 1.24] 6-8: 0.42 [0.22-0.80] • for every one-unit increase in MEDI score, the adjusted HR of CD was 0.87 [0.78-0.96] 		
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Abbreviations: HR, hazard ratio; OR, odds ratio; EPIC, European prospective investigation into cancer and nutrition; NHS, Nurses Health Study; COSM, Cohort of Swedish men; SMC, Swedish mammography study; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

* Adjusted for age, cohort, smoking (never, past, current), body mass index (<20 kg/m², 20–24.9kg/m², 25–29 kg/m², > 30kg/m²), oral contraceptive use (never, ever), use of postmenopausal hormone therapy (premenopausal, postmenopausal hormone never user, past user, current user), regular use of NSAIDs (yes, no), regular use of aspirin (yes, no).

Table 3. Nutrients that demonstrated no difference in increasing the risk of CD incidence from major epidemiology studies

Nutrient	Studies where assessed
Omega 6	NHS ^[53] EPIC ^[52]
Total mono-unsaturated and total saturated fat	NHS ^[53] EPIC ^[52]
Total fibre from vegetables	NHS ^[55] EPIC ^[54]
Total fat	EPIC ^[52] Q5 vs Q1 Adjust OR 1.42 (0.26–7.67), NHS ^[53] Q5 vs Q 1 Adjust OR 0.98 (0.66–1.45)
Alcohol	EPIC ^[57]
Total carbohydrates, starch or sugar	EPIC ^[58] Q5 vs Q1 Adjust OR 0.87 (0.24–3.12)
Omega 3:6 ratio	NHS ^[53]
Fibre from legumes, wholegrains, bran, cruciferous vegetables	NHS ^[55]

Table 4. Randomised control trials methodologies addressing induction to remission and/or maintenance of remission in Crohn's disease.

Author, year, design, N	Group 1 (G1)	Group 2 (G2)	Methodology	Site, duration	Population	Drop out	Endpoint/s	Results
Induce remission								
Levenstein 1985 ^[30] Single-blinded N=36	Low fibre 3 g/d (legumes, whole grains, nuts, fruits, vegetables excluded, except ripe bananas and skinned potatoes)	Habitual fibre (normal Italian diet) 13 g/d N=35	Written diet information Encouraged to buy a centrifuge in order to prepare solid-free extracts of fruits and vegetables	Italy – multi-centre 29 months	Not stated n=58 active n=12 in remission	n=13	Surgery vs no surgery Recurrence vs no recurrence	No differences between groups in • requirement for surgery (G1: 14% vs G2 17%) • recurrence rates (2/6 in each group)
Lomer 2005 ^[31] Single-blinded N=83	Normal calcium and low microparticle diet N=20	Normal calcium and normal microparticle diet N=20	Dietary counselling	UK – multicentre Intervention for 16 weeks Follow up week 52	18-70 y Active (histological /endoscopic or CDAI >150) Steroid dependent	n=8	CDAI <150, Clinical response = decrease in CDAI from baseline ≥ 60 @ week 16	No differences in: • Response: 16/42 vs 17/41 (p=0.8) • Remission: 16/42 vs. 13/41 (p=0.1)
Bartel ^[23] 2008 Double-blinded N=18	High fibre 46 g/d from sourdough spelt bread; avoid fruit/vegetables; meat fried in rape seed oil + butter, 6 weeks then stepwise introduction of organic produce	Reduced fibre 16 g/d; avoid fruit/vegetables Low fat, high carbohydrate; no red meat. 6 week then avoid fibre-rich fruit and vegetables, include red meat	Dietary counselling	Austria – 6 weeks with follow up at 24 weeks	CDAI 150-220 Adults	Multiple withdrawals	CDAI <150, remission MRI or endoscopic improvement	No differences • Remission - 4/5 vs. 7/9 (week 6) & 4/5 vs 5/7 (week 24) • MRI improvement - 3/4 vs 1/9 (week 6) (p = 0.027)
Brotherton 2014 ^[28] Single-blinded N=7	High-fibre, reduced refined carbohydrate diet with daily servings of whole wheat bran cereal N=4	Low-fibre diet N=3	Dietary counselling	Cleveland clinic, USA 4 weeks	HBI score ≥3 ≥4 weeks of stable drug therapy Biologic naïve Age 18-64 y	Powered to recruit 22	IBDQ HBI	Remission: 4/4 vs. 0/3 (week 4) Change in HBI Intervention 5.8 to 0.5 vs. comparator 5.2 to 3.5 (P = 0.008)

Levine 2019 ^[22] randomised but blinding not stated) N= 74	'CDED+PEN' Multiple changes* (CDED) <i>plus</i> 50% nutritional requirements from enteral nutrition (PEN) N= 40	'EEN' (exclusive enteral nutrition) N= 34	Dietary counselling + PEN provided	Israel 12 weeks	<ul style="list-style-type: none"> PCDAI 10-40 CRP >5 g/L or ESR >20 mm/h or FC >200 µg/g, < 36 months from diagnosis Age 4–18 y	N=4	Primary <ul style="list-style-type: none"> dietary tolerance Secondary: @ weeks 6 and 12 <ul style="list-style-type: none"> remission (PCDAI <10) corticosteroid-free remission 	<i>Primary:</i> CDED + PEN 98% vs EEN 74% (p=0.002); OR = 13.9 [95% CI 1.7-115.1] <i>Secondary:</i> corticosteroid-free remission: @ week 6: 75% 59% (P = 0.38); @ week 12 76% vs (P = 0.01)
Sustain remission								
Brandes ^[59] 1981 Randomised but blinding methods not specified) N=23	45% carbohydrates, 25% protein, 30% fat; Nil with high content of refined carbohydrates ± high/ low calorie diet depending on weight N=10 (5 remission, 5 active)	60% carbohydrates, 15% protein, 25% fat; High levels of refined carbohydrates ± high/ low calorie diet depending on weight N= 10 (6 remission, 4 active)	Dietary counselling provided by dietitian	24 months	CDAI <200 Adults	n=3	CDAI reduction	<ul style="list-style-type: none"> Clinical relapse in those in remission 1/5 vs 1/6 = RR 1.2 [0.1-14.69] Decreased disease activity in 4 of 5 with active CD in Group 1; 4 in group 2 increasing activity
Jones ^[60] 1985 open label N=20	Exclusion diet: identification of specific food intolerance	High residue, low refined carbohydrate diet	Dietary counselling	UK 6 months	CDAI <150 0-49 years	n = 0	CDAI >150	Exclusion diet: 7/10 patients on an exclusion diet remained well @ 6 months (p <0.05). High residue diet: 8 relapsed within 2 months, 10/10 within 6 months

Ritchie ^[29] 1987 Single blinded RCT N= 352	Carbohydrate intake in its natural unrefined state only; avoiding all products containing sugar or white flour. N=190	Carbohydrate in its refined form (e.g. white flour and rice); avoiding unrefined carbohydrate foods. Sugar intake unrestricted N = 162	Dietary counselling by dietitian	UK 24 months	Clinically well and on no treatment other than oral nutritional supplements, antidiarrhoeal drugs or sulphasalazine	N =56 (n=24: 14 non compliant, 18 unrelated)	Clinical deterioratio n (need for increased medical or surgical therapy) or worsening of symptoms enough to withdraw from trial	No differences • 52/162 vs 66/190 (p = > 0.05)
Riordan ^[61] 1993 Single blinded RCT N=78	Placebo with dose reduction <i>plus</i> Elemental diet with reintroduction of single food each day and exclusion provoked symptoms N=40	Prednisolone 40 mg/d – 3-months weaning dose if remained in remission <i>plus</i> General dietary advice from dietitian N=38	Face to face dietary counselling by dietitian	UK 24 months or until relapse	HBI > 6 who achieved remission HBI < 3 after elemental diet	N =14 (7 non- compliant, 3 other illness, 2 steroid side effects, 2 pregnancy)	HBI > 6 or unwillingne ss by the patient to continue, surgery, medication complicatio ns, steroid side effects severe enough to warrant withdrawal	Intervention between two groups RR 0.67 [0.47-0.93] 21/40 intervention group 30/38 in control group.
Lorenz- Meyer ^[62] 1996 Single blinded RCT	Low carbohydrate diet < 84g/d N=69	General nutrition guidelines from the German Society of Nutrition N=65	Written information	12 months	Steroid-induced remission CDAI <150 adults	Powered for n=200 N= 2 drop out	Relapse (increase of CDAI > 200 and by > 60 points above baseline plus increase in CRP 2 SD above the mean of the healthy population	No differences • (RR 0.92 [0.75-1.12]) • Control 45/69 vs vs 46/65
Allenberg ^[63] 2019 Single blinded RCT N = 659	≤1 serving/month of red meat or processed meat and minimum of 16 oz of water per day. N=96	≥2 servings of red meat or processed meat each week and minimum of 16 oz of water per day. N = 118	Web-based written information	49 weeks	CDAI <150 18 years and old	Powered for n = 194	Increase in CDAI by ≥ 70 points and to >150 or self- reported initiation or increased dose of an IBD medication or surgery for a flare of CD.	No differences • RR 1.03 [9.85-1.26] • group 1 63/96 vs group 2 74/118

* Crohn' disease Exclusion Diet (CDED): limits red meat, restricts insoluble fibre, animal/dairy fat, high fat from other sources, wheat, processed meat/protein sources rich in

taurine, emulsifiers, artificial sweeteners, carrageenans, sulphites; allows some soluble fibre & resistant starch

Table 5. Comparison of epidemiological study outcomes and dietary clinical trial methodologies of RCTs that excluded groups of foods

Nutrient/food	Cohort studies			Induce remission					Sustain remission					
	Study	EPIC	NHS	SCS/SCM	Levenstein	Loimer	Bar tel	Brother ton*	Levin e*	Brand es	Jone s*	Ritch ie	Lore nz-Meye r	Albe nberg
Protein	↑	⊖	⊖											
Dairy intake#	↓	⊖	⊖											
Omega 3	↓	↔	⊖											
Total fibre	↔	↓	⊖											
Fruit fibre	↔	↓	⊖											
Cereals fibre	↓	↔	⊖											
MED diet	↔	⊖	↓											
Omega 6	↔	⊖	⊖											
Total Mono	↔	↔	⊖											
Total sat fat	↔	↔	⊖											
Veg fibre	↔	↔	⊖											
Total fat	↔	↔	⊖											
Alcohol	↔	⊖	⊖											
CHO, total	↔	⊖	⊖											
Omega 3:6	⊖	↔	⊖											
Bev, sweet	↔	⊖	↔											

What informs dietary strategies for

How do we design diets that might help reduce the gut inflammation in people with Crohn's disease? Many diets have been designed on ideas not based upon scientific data, some are based upon the findings in animal studies that mostly do not mimic the human situation and some incorporate our current understanding of how food influences gut inflammation. However, information from large population studies that relate dietary habits of individuals with development of Crohn's disease over subsequent decades is not being incorporated into the diets under investigation.

Jessica Wood is an Accredited Practising Dietitian who has a special interest in providing evidence-based care to patients who live with gastrointestinal disorders such as inflammatory bowel disease, irritable bowel syndrome and coeliac disease. After completing a Masters of Clinical Research Methods in which she explored body composition in patients with inflammatory bowel disease, she is now undertaking a PhD with Monash University investigating the potential role of emulsifiers in the pathogenesis of Crohn's disease. She is the founder of the Dietitians Crohn's and Colitis Australian Network (DECCAN) and has contributed to Australian guidelines treating patients with Crohn's disease.

Dr Emma Halmos is an Accredited Practising Dietitian who completed a PhD with Monash University conducting the pivotal study on the low FODMAP diet in irritable bowel syndrome and Crohn's disease, and the effects on gut microbiota. This work earned Emma the Ken Heaton prize from the Rome Foundation for most cited paper and the Douglas Piper Young Investigator Award by the Gastroenterological Society of Australia. After post-doctoral work in coeliac disease at the Walter and Eliza Hall Institute of Medical Research, she has returned to Monash University to investigate the role of dietary emulsifiers in Crohn's disease.

Peter Gibson is Professor and Director of Gastroenterology at The Alfred and Monash University, having previously been Professor of Medicine at Eastern Health and Head of the Eastern Health Clinical School. He is a Past-President of the Gastroenterological Society of Australia. He directs a program of translational research in inflammatory bowel disease and irritable bowel syndrome. Major foci of his work include the use of diet to improve outcomes in chronic intestinal conditions, and the optimisation of clinical management in inflammatory bowel disease. Amongst his achievements, he led the team that developed the FODMAP diet.

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