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REVIEW ARTICLE

# Is there an "optimal" diet for prevention of inflammatory bowel disease?

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## Abstract

Nutritional epidemiological studies have evolved from a focus of single nutrients to diet patterns to capture the protective role of healthy diets on chronic disease development. Similarly, in inflammatory bowel disease (IBD), a healthy diet may be protective against its development in individuals with genetic susceptibility, but the definitions of the optimal diet pattern deserve further exploration. Hence, this review article presents evidence, mainly from prospective cohort studies, for the role of diet quality based on adherence to dietary guidelines, traditional and modern diet patterns in the prevention of IBD. Findings from a limited number of studies on diet quality suggest that high diet quality scores are associated with lower risk of developing Crohn's disease, but the data are inconsistent for ulcerative colitis (UC). There are signals that a Mediterranean diet pattern reduces the risk of Crohn's disease but, again, the data are inconsistent and further studies are much needed. Finally, the evidence is conflicting regarding the role of food additives, with difficulties in the assessment of their intake, namely non-nutritive sweeteners and emulsifiers, precluding accurate assessment of a relationship with IBD risk. In contrast, emerging evidence for a role of ultra-processed food in the development of Crohn's disease but not UC is identified. Given the potential influence of diet quality, a Mediterranean diet and ultra-processed food intake on the risk of Crohn's disease, assessment and implementation of dietary advice for these patients need to be tailored. The search for an optimal diet for UC remains elusive and further research for increasing the evidence in the area is greatly needed.

## Introduction

The 2013 Global Burden of Disease study reports poor diet as a leading risk factor for global burden of chronic disease such as cardiometabolic diseases and cancers.[1] Diet is also an important modifiable risk factor for the development of inflammatory bowel disease (IBD). In particular, intake of a Western diet is often implicated,[2–4] but specific dietary components that may directly contribute to the pathogenesis of IBD remain poorly defined. Moreover, identification of the optimal diet, and components thereof, that could protect against IBD should be just as important as identifying the dietary components that are detrimental for IBD.

Historically, the evidence for diet and disease has employed a reductive focus on the role of single nutrients.[5] However, diet consists of nutrients, bioactive components, and food groups. The collective sum of these and their synergistic interactions constitute a diet pattern.[5] Therefore, in defining an optimal diet that protects against IBD development, one should consider evidence from each of these layers as well as the totality of diet,[6] recognizing that an optimal diet pattern can be defined from various perspectives. The first perspective, given the absence of consistent evidence for a specific diet strategy to prevent IBD, is historical and suggests that dietary advice for those at risk of IBD should revert to country-specific healthy eating guidelines.[7] Adherence to these guidelines is measured using diet quality indices. However, it is unclear whether dietary guidelines that are tailored to the general population have a protective role. Second, traditional diet patterns such as the Mediterranean diet are commonly studied in relation to protection against chronic disease,[8] and so this could be a plausible protective diet pattern to consider. Third, the role of industrial food processing in

affecting diet and health has also been increasingly recognized for its contribution to disease development,[9] and may also be important in the context of IBD. Finally, the limited data on *a posteriori* dietary patterns on IBD risk have already been covered elsewhere[10,11] and will not be discussed further in this review.

Hence, this review will describe the evolving definitions of a healthy diet pattern including those based on dietary guidelines designed for the prevention of chronic disease and their associated diet quality indices, traditional and modern diet pattern paradigms. Evidence for each of these approaches in the prevention of IBD will be presented along with practical recommendations for dietitians and other clinicians to enhance preventative care of individuals who are at risk of developing IBD. These at-risk individuals we here define as first- or second-degree relatives of an individual with IBD or those with a family history of IBD that have migrated from countries of low to high incidence of IBD.

## Dietary guidelines and diet quality indices

Dietary guidelines are a set of recommendations that are based on food groups and, more recently, diet patterns, which provide guidance on a healthy diet for the prevention of chronic disease and optimization of nutritional adequacy. These guidelines are synthesized from systematic reviews of epidemiological studies mostly in healthy individuals but also in those individuals at risk of cardiometabolic disease.[12–14] A summary of dietary guidelines from the World Health Organization (WHO) and national guidelines from Australia, the United Kingdom, the United States, and Brazil[14–17] are summarized in Table 1. Of note, there are broad consistencies in the food groups recommended and to be limited, although specific amounts do vary. In contrast, the Brazilian dietary guidelines outline recommendations based entirely on food processing based on the NOVA classification system, regardless of the nutritional content of the food.[18] The NOVA classification system will be furthered discussed in the sections below.

Diet quality indices are used to measure "healthiness" of the overall diet based on adherence to national dietary guidelines or to a healthful diet pattern such as the Mediterranean diet.[19] To measure diet quality, habitual intake is scored against this predefined index comprising encouraged and/or discouraged food and/or nutrients to generate a total score, with higher scores indicative of better diet quality. There are numerous published diet quality indices, including the Healthy Eating Index (HEI), Alternate Healthy Eating Index (AHEI), and the Recommended Food Score that are commonly used. While several of these indices have been validated for predicting chronic disease risk, namely cardiometabolic disease and cancer,[20] their predictive ability can vary depending on how the criteria are scored, as well as the score components (i.e. some may not include dietary components associated with the disease outcome of interest). For example, the AHEI has been shown to have twice the predictive ability to assess the risk of cardiovascular disease compared with the HEI and the Recommended Food Score[21]: the former does not include the same diet components as the latter, including red/processed meats and types of unsaturated fats.

***Can good diet quality based on adherence to dietary guidelines prevent IBD?.*** The first clues for a link between poor diet quality and IBD were identified in a cross-sectional study in which patients with IBD had lower diet quality scores (mean 69.00 ± 16.53 of a total score of 130) as assessed by Dutch Healthy Diet Index 2015 compared with healthy controls (mean 77.34 ± 17.43 respectively; $p \leq 0.001$).[22] Furthermore, diet quality scores in this study were inversely associated with fecal calprotectin levels ($b = -4.009$, $p = 0.006$), raising the potential of a contributory role of diet quality in promoting intestinal inflammation, although reverse association cannot be definitively ruled out.

Four large prospective cohort studies have since supported the inverse relationship between diet quality and IBD. In a UK Biobank cohort ($n = 482\,887$), those with the highest cardioprotective diet scores were associated with a 28% and 21% lower likelihood of developing Crohn's disease (HR 0.72, 95% CI: 0.55–0.95)and UC (HR 0.79, 95% CI: 0.65–0.95) at 12 years, respectively, compared with those with the lowest scores.[23] The Swedish Mammography Cohort and Cohort of Swedish Men study ($n = 83\,147$) reported greater adherence to a Healthful Plant-based Diet Index (HDPI) (HR 0.52, 95% CI: 0.32–0.85) and a nonsignificant trend for AHEI adherence (HR: 0.73, 95% CI: 0.48–1.12) was protective against older-onset Crohn's disease but not against UC at 20 years.[24] Of note, patients with UC had mostly evenly distributed diet quality scores than in the Crohn's cohort, which may explain the lack of association in UC. Interestingly, for every 25% increase in AHEI and HDPI score, there was a lowering of Crohn's disease risk by 42% and 49%, respectively, suggesting that even small modifications in diet quality (equivalent to meeting recommendations for targets in one or two food groups) can have substantial benefits for disease prevention.[24] In another 14-year follow-up of the Lifelines cohort ($n = 125\,445$), a small risk reduction for Crohn's disease was observed with greater adherence to a study-specific Lifelines Diet score (OR: 0.95, 95% CI: 0.92–0.99),[25] while no such association was observed for UC. A limitation of the study, however, was that the diet quality score was modified to align with the dietary data collected, potentially limiting the validity of the diet measures. Finally, similar findings have been reported by a recent EPIC cohort study ($n = 394\,255$) where a lower diet quality, assessed by a the UK Food Standards Agency modified nutrient-profiling system Dietary Index, doubled the risk of CD (HR: 2.04, 95% CI: 1.24–3.36).[26]

There are inherent limitations with observational data presented here and in subsequent sections including residual confounding (e.g. lack of family history data) and dietary data that are limited to a single time point, and these must be considered in their interpretation. Additionally, much of the evidence from Crohn's disease comes from studies in which disease onset occurs later in life, and therefore it is unclear whether this evidence translates to all at-risk individuals. Diet quality indices are also highly heterogeneous in their scoring components, and there may be nutrients or dietary components important for IBD risks that are not captured by current diet quality instruments.

Overall, the totality of the evidence suggests that good diet quality, either via adherence to dietary guidelines, a cardioprotective or healthy plant-based diet, offers protection against

**Table 1** Similarities and differences in healthy eating recommendations of dietary guidelines for the World Health Organization,[17] Australia,[13] United Kingdom,[16] United States,[14] and the NOVA classification in Brazil.[18]

| | | World Health Organization 2020 | Australian Dietary Guidelines 2013 | The Eatwell Guide (UK) 2016 | Dietary Guidelines for Americans 2020 | Dietary Guidelines for the Brazilian Population 2015 | Mediterranean diet | |
|---|---|---|---|---|---|---|---|---|
| Increase consumption of these core food groups | Fruit<br>Vegetables | ≥400g[†] | 300 g<br>375–450 g | ≥400 g | 300 g<br>~300–525 g from weekly portions of<br>• Red/orange;<br>• Starchy;<br>• Dark-green; and<br>• Other vegetables<br>• Beans, peas, and lentils. | Natural or minimally processed foods | Fruit<br>Vegetables<br><br><br><br><br>Legumes | ≥3 serves[‡‡]<br>≥400 g (at least one portion being raw or as salad)<br><br><br><br><br>≥450 g/week |
| | Grains | Recommends wholegrains but amount not specified. | 4–6 serves[‡] preferably wholegrains/ high fiber. | Starchy carbohydrates as major component of meal. | 184–255 g (6.5–9 ounce equivalents)<br>50% wholegrains | | Wholegrains | Not specified. High intake suggested. |
| | Dairy | — | 2.5–4 serves[§] reduced fat dairy | Not specified. To include low fat milk and low sugar dairy | 3 cups equivalent of low fat, fat- or lactose-free or soy milk | | Olive oil | ≥50 g or 4 Tbsp |
| | Water | — | Plenty | 6–8 cups/day | - | | Red wine | M: 150 mL<br>W: 100 mL |
| | All protein sources (meat, fish, poultry & alternatives) | — | 2–3 serves[¶] lean meat, chicken, fish, eggs and alternatives | Not specified. Beans and pulses. ≥2 × 140 g sustainably sourced fish weekly | 156-184 g from weekly portions of<br>• Egg<br>• Soy products<br>• Nuts, seeds<br>• Beans, peas, and lentils | | Nuts & seeds<br>Fish or shellfish | ≥15 g (or 90 g/ week)<br>≥300 to 450 g fish or 600 g shellfish |
| Moderate intake | Unsaturated fat | Total Fat to <30% TEI | Includes nuts and seeds<br>M: 28–40 g<br>F: 14–20 g | Small amounts | Oils: 27–34 g | Use oils, fats (e.g. butter, lard), salts, and sugar in small amounts | Dairy | Amount not specified but moderate intake. |
| Limit Intake | Red meat | | ≤455 g/week red meat<br>≤2 serves/week full fat cheese | Limit red & processed meat ≤70 g/day | Not specified. | | Red meat, processed meat | ≤100-150 g/ week |

(*Continues*)

**Table 1** (Continued)

| | | World Health Organization 2020 | Australian Dietary Guidelines 2013 | The Eatwell Guide (UK) 2016 | Dietary Guidelines for Americans 2020 | Dietary Guidelines for the Brazilian Population 2015 | Mediterranean diet | |
|---|---|---|---|---|---|---|---|---|
| | Saturated fat | <10% TEI<br><1% TEI Trans Fat. | Limit saturated fat | M: <30 g/day<br>W: <20 g/day | <10% TEI | Processed foods | Butter, margarine or cream | ≤12 g |
| | Sugar | <10% TEI or 50 g free sugar[††] | Minimal added sugar | <30 g free sugar[††] | <10% TEI | | Extras (sweets, sweet carbonated beverages, baked goods including pastries, cakes) | ≤5 serves/ week |
| | Salt | <5 g of iodized salt | Limit added salt | <6 g salt | <2300 mg sodium | | | |
| | Alcohol | — | | | M: ≤2 standard drinks<br>W: ≤1 standard drink | | | |
| | Calories | Limit | | Limit | Limit caloric intake. | | | |
| Avoid consumption | | Industrially processed trans fat | — | — | — | Ultra-processed food | — | — |
| Other recommendations | | Include legumes[§§] | Variety across all food groups | Variety of fruits and vegetables | Variety within certain food groups | — | | |
| | | | Unprocessed foods | Choose packaged foods with green and amber-coded labels on front of pack labeling | Recommendations are tailored to caloric intake | Attention to pleasurable eating including eating in pleasant environments and in company<br>Encourage culinary skills and planning time for meal-related activities (shopping, time to eat) | | |

[†]Excludes potatoes, sweet potatoes, cassava, and starchy roots.
[‡]Serving sizes include 40 g bread, 75-120 g cooked pasta/rice/noodles, 120 g cooked porridge, 30 g cereal etc.
[§]Serving sizes include 250 ml of milk, 40 g hard cheese, 200 g yoghurt.
[¶]Serving sizes include 65 g cooked lean meat, 80 g lean poultry, 100 g fish, 150 g cooked legumes/beans.
[††]Free sugar includes naturally occurring and added sugars.
[‡‡]Serving size not defined.
[§§]Legumes include lentils and nuts.
The Mediterranean Diet recommendations are also provided for comparison (according to that used in the PREDIMED clinical trial[78]). Portion size of food group recommendations, where available, is based on nutritional needs of adults per day (g/day) unless weekly stipulated.
TEI, total energy intake; Tbsp, tablespoon.

the development of Crohn's disease. The findings are inconsistent for the role of diet quality and its association with UC risk.

## Traditional paradigms

***The Mediterranean diet.*** The traditional Mediterranean diet hails from the olive-growing regions of the Mediterranean basin in the 1950s and 1960s, particularly Greece and southern Italy. There are several variations based on the Mediterranean region of interest; however, these have been recommended to be viewed as variants of a single entity.[27] The traditional Mediterranean diet consists of an abundance of plant foods (wholegrains, fruit, vegetables, and legumes), olive oil as the principal source of fat, fish in low to moderate amounts (depending on proximity of the specific region to the sea), low to moderate amount of dairy, minimal red meat, and wine consumed with meals,[28] leading to an overall diet that is high monounsaturated fat and fiber. The recommended quantities of fruits, nuts and seeds, legumes, olive oil, and fish in the Mediterranean diet are much higher than those in other national dietary guidelines (see Table 1). The most recent modern Mediterranean diet pyramid includes regular physical activity, sharing culinary activities with family and friends, and choosing local and seasonal foods as central features of the Mediterranean lifestyle.[29]

The earliest and most pivotal research of the Mediterranean diet was a prospective cohort study, the Seven Countries Study, which revealed clear relationships between the aspects of diet pattern (including monounsaturated fat intake) and the extremely low incidence of coronary heart disease and mortality in Mediterranean diet countries compared with non-Mediterranean countries.[30] Since then there has been a plethora of observational and intervention studies examining its role in the prevention of disease, and evidence from meta-analyses reveal wide-ranging benefits of the diet on physical health outcomes, including cardiovascular disease risk factors and reduced risk of cancer,[8] and mental illness such as depression.[31] Surprisingly, little has been published on the underlying mechanisms of the diet as a whole-diet pattern. Beneficial modulation of the microbiome and reducing inflammation have been postulated as major mediating pathways for its benefits on health outcomes,[32–34] raising the possibility of preventative and therapeutic potential in diseases underpinned by inflammation, including IBD.

***Can the Mediterranean diet prevent IBD?.*** There are several lines of evidence supporting the potential role of the Mediterranean diet in preventing IBD. First, the north–south gradient for risk of IBD in Europe is well established.[35,36] There is a lower incidence of IBD in southern European countries, which are mostly located within the Mediterranean basin and therefore, more likely to adhere to a Mediterranean-style diet, compared with northern European countries. Second, as stated earlier, there is evidence for the Mediterranean diet to modulate inflammatory biomarkers, which has strong implications for a condition in which inappropriate immune response is postulated to drive the disease. A recent synthesis of findings reported an anti-inflammatory potential of the Mediterranean diet, but this was mostly from studies in cardiometabolic populations.[33]

The protective effects of a Mediterranean diet for IBD have been studied in three prospective cohort populations. First, analysis of 17-year Swedish registry data ($n = 83\,147$) revealed an association between diet adherence and the risk of CD (HR = 0.42, 95% CI 0.22–0.80), after adjustment for a variety of confounders including smoking and total energy intake.[37] There was no association between Mediterranean diet adherence scores and the risk of UC (HR 1.08, 95% CI 0.74–1.58), or any statistically significant outcomes when examining specific Mediterranean diet score components and risk of CD or UC. A sub-analysis of these data investigating older-onset IBD also shows an association between Mediterranean diet adherence and risk of CD (HR = 0.58, 95% CI 0.32–1.06), but again no association for UC.[24]

Second, the earlier EPIC-IBD study, which examined a sub-cohort of EPIC participants ($n = 366\,351$), failed to find an association between Mediterranean diet adherence and risk of CD or UC, using two modifications of the Mediterranean Diet Score.[38] However, this study included fewer incident IBD cases than the Swedish study, which may have influenced power to identify associations. Finally, a recent prospective analysis of the Lifelines Dutch cohort ($n = 167\,729$) also found no association between Mediterranean diet adherence and risk of CD or UC.[25]

Overall, current evidence suggests that Mediterranean diet pattern may reduce future development of CD, although data are inconsistent. Continued research is required to enable better understanding of the potential preventative role of the Mediterranean diet for the development of IBD, especially in younger cohorts, and which combinations of key foods or food components are primarily responsible for any protective effects.

## Modern paradigms

The last century has seen considerable evolution of the modern food supply. This has included the development of industrial food processing techniques and transformation of food products that are visually attractive, hyper-palatable, and have enhanced texture. These food products contain not only macronutrients, micronutrients, and salt but also a wide variety of food additives to improve their appeal, and to preserve commercial stability. Broadly speaking, a healthy diet can include food products containing additives, but emerging research is questioning their inertness in the diet, particularly at very high intakes. Additionally, classifying individual foods based on the level of processing is challenging due to the complexities of diet and the food supply. Many foods contain additives but are "healthy" based on their overall nutrition composition. For example, flavored yoghurt, which often contains artificial sweeteners, colors, and thickeners, is a rich calcium source that is low in fat and may contain added fiber.

***Food additives.*** Given the incidence of IBD has significantly increased since industrialization in the 1950s, a time in which food additives became available in the food supply, emerging research has investigated the role of additives such as non-sugar sweeteners, emulsifiers, and thickeners in the development of IBD.[39–41] The amount of these additives permitted in food is regulated by international food safety authorities (e.g. US Food and Drug Administration, European Food Safety Authority).

Incorporation of some additives to the food supply, particularly for those that have been shown to be harmful in high doses (in preclinical studies), is regulated by upper limits, such as the European Acceptable Daily Intake (ADI). However, many additives lack an upper limit and are considered generally safe despite being permitted to be added at any dose. In the case of emulsifiers, these include soy lecithin, certain distarch phosphates, xanthan gum, and pectin.

Non-sugar sweeteners (NSS) such as sucralose, aspartame, saccharin, and acesulfame potassium are often added to products such as beverages and high protein bars/powders preparations to provide the consumer a sweet taste, but in the form of a low-calorie product. They were originally heralded as a sugar alternative for incorporation into weight loss diets. However, the WHO has recently released recommendations that these products do not confer any long-term benefit in reducing body fat in adults or children and should not be recommended as such.[42]

Dietary emulsifiers and thickeners are the second most widely used group of food additives highly prevalent in packaged foods such as breads, snacks, sauces, desserts, frozen meals, and confectionery.[43] These additives facilitate oil and water emulsion, enhancing the texture, mouthfeel, and palatability of a product without the addition of further calories.[44] A recent audit of the UK food supply reported their presence in 52% of products found in major supermarkets ($n = 12\,844$), and 51 different types of emulsifiers were identified.[43]

The effects of food additives on the development of IBD can be examined in three ways—first, through preclinical models in which additives are fed to mice or applied *in vitro* to specialized intestinal epithelial cells to examine mechanisms leading to intestinal inflammation.[45] Second, using prospective cohort data in which data on food additive intake and development of disease are collected to examine associations, and third, through randomized-controlled feeding trials in healthy individuals to confirm mechanistic effects observed in preclinical studies.

Preclinical models have demonstrated that NSS and emulsifiers may precipitate intestinal inflammation in IBD through mechanisms of bacterial dysbiosis, intestinal barrier dysfunction, and activation of pro-inflammatory pathways. There is wide variability in findings depending on the additive studied, duration of exposure, and mouse model used. Broadly, specific emulsifiers such as polysorbate-80 and glycerol monolaurate lowered microbial diversity and favored a pro-inflammatory bacterial composition in mice.[46] Additionally, supplementation of NSS, aspartame, sucralose, and saccharin at varying doses in animal models decreased the abundance of *Lactobacillus* genus while increasing the representation of *Enterobacteriaceae* and *Clostridiales*.[47] Importantly, *Enterobacteriaceae* has previously been shown to induce metabolic derangements and inflammation.[48] The emulsifiers, polysorbate-80 and carboxymethyl-cellulose (CMC), promote the expression of bacterial flagella and decreased intestinal mucus thickness in a mouse model of IBD, which allows encroachment of bacteria into the epithelial layer.[49] Increased bacterial translocation is thought to be a key mechanism via which emulsifiers may trigger an inflammatory cascade, leading to intestinal inflammation. Increased intestinal permeability, a predisposing factor in the development of Crohn's disease,[50] has also been observed in response to the administration of NSS, aspartame, sucralose,[51] saccharin,[52] polysorbate-80,[45] and thickeners, carrageenan[53] and CMC[49] in animal models. Finally, in mice and rats, there are extensive data reporting the ability of the emulsifiers, polysorbate 80, glyceryl monolaurate, and the thickeners, carrageenan and CMC,[46] to induce colitis. There is less evidence for the role of NNS in inducing colitis. However, sucralose at 1.5 mg/ml, when fed over 6 weeks, exacerbated colitis in a rat model of IBD.[54]

There are significant challenges with understanding the relevance of this preclinical data to human health. Food additives in preclinical research are provided supplementary to food, or added to drinking water, are administered at pharmacological doses, and are often studied in isolation rather than in combination with other additives, which is how they are present in the human food supply.[46] Additionally, there are many common emulsifiers and thickeners that have not yet been studied for their impact on gastrointestinal physiology, such as lecithin, glycerol, and xanthan gum.

Prospective observational dietary data can provide important information about the diet–IBD relationship. However, dietary intake of food additives is inherently difficult to measure. Food labeling laws do not mandate the listing of percentage contribution of food additives to foods on ingredient lists or on nutrition information panels. Hence, food additive composition data are virtually nonexistent, making quantitative assessment of food additive intake from food frequency questionnaires or diet histories near impossible. Currently, food additive intake can only be estimated indirectly through measurement of intake of proxy foods (i.e. those high in additive ingredients). A recent cross-sectional examination of dietary exposure to emulsifiers (frequency of intake per day) in IBD compared with healthy individuals suggests a higher exposure in those with IBD[55]; however, it does not provide us with a temporal relationship between disease development and emulsifier exposure. Additionally, two recent Australian studies in those with and without IBD demonstrated no[55] or rare[56] exposure of polysorbate-80, an emulsifier frequently implicated in the development of IBD through preclinical models, yet it is rarely found in the Australia food supply, indicating a gap between preclinical and food composition data.

There have been limited prospective cohort studies evaluating the intake of NSS and the onset of IBD. Analysis of the UK Biobank ($n = 121\,490$) over a 10-year follow-up as well as the Cohort of Swedish Men and the Swedish Mammography Study over 17 years ($n = 83\,042$) demonstrated no associations of intake of artificially sweetened beverages with the development of CD (UK Biobank: HR 0.85, 95% CI 0.56–1.28; Swedish Cohort: HR 1.02 [95% CI, 0.60–1.73]) or UC (HR: HR: 1.14 95% CI, 0.83–1.57).[57,58] Of note, incident cases of Crohn's and UC in these studies were low; hence, findings of these studies need to be interpreted with caution. On the other hand, emulsifiers have yet to be examined in any prospective analysis of the development of IBD. This may be due to their ubiquitous nature in the food supply, and therefore, accurately measuring emulsifier intake purely via proxy foods is likely to underestimate intake. This also leads to challenges in analyzing associations between emulsifier intake and development of disease, as it is exceedingly difficult to appropriately adjust for intake of other nutritional confounders in emulsifier-containing foods such as sugar, salt, fiber, and other food additives.

Highly controlled feeding studies in healthy humans, as a way of defining "normal" physiological effects of food additives in a disease-free model, have generated mechanistic insights for their role in early development of IBD. Chassaing et al. fed 16 healthy participants a brownie supplemented with 15 or 0 g/day CMC on a background of emulsifier-free diet for 11 days with no difference in Shannon diversity or bacterial load between groups at the end of the study.[59] However, fecal metabolomic profiles showed depletion of short-chain fatty acid (SCFA) production following CMC versus no supplementation, likely indicating a reduction in SCFA-producing bacteria. No changes in markers of gut permeability, anti-lipopolysaccharide, and anti-flagellin immunoglobulin G antibodies, or serum cytokines, were observed in either group, although CMC did mildly increase abdominal pain compared with the control group. Although this was a seminal first study to report the effect of emulsifiers on gastrointestinal microbiome, the dose of 15 mg CMC is significantly above estimated population intake, potentially limiting its relevance to understanding the role of emulsifiers in GI disease development.[56]

The effect of NNS on the gut microbiome has been evaluated in two human feeding studies with conflicting results. In a 2-week randomized, double-blind, placebo-controlled trial of 54 individuals, Serrano et al.[60] demonstrated no difference in Shannon or Simpson diversity index or major metabolites such SCFAs between four groups who consumed either 400 mg/day saccharin, 670 mg/day lactitol, 800 mg/day saccharin and 1340 mg/day lactitol or placebo. These doses administered were equivalent to maximum ADI levels. However, in a larger but unblinded, parallel RCT[61] ($n = 120$ individuals), four major NNS, aspartame, saccharin, sucralose, and stevia, all significantly altered microbial structure and function when fed at doses varying from 8% to 75% of the ADI. Distinctive effects of each NNS on bacterial composition and fecal metabolomic profiles were noted. For example, sucralose and aspartame mediated functional alterations via pathways associated with purine metabolism, findings that may have relevance in IBD with increased microbial-derived purine metabolites recently implicated in inflammation.[62] Saccharin exposure increased the levels of *Prevotella copri* and *Bacteroides* along with SCFA and plasma indoxyl sulfate, a by-product of tryptophan metabolism. Collectively, these findings suggest that NNS are not physiologically inert as previously assumed. However, a direct link between such microbial changes to the pathogenesis of IBD remains unclear and further studies understanding the impact of such alterations on physiological indices are warranted. Therefore, given the totality of the current evidence, we cannot make specific dietary recommendations for individuals at risk of developing IBD regarding the intake of additives, although reassurance can be provided that food additives can be consumed as part of a healthy diet. Future research is needed to determine whether daily limits are required for specific additives for the prevention of IBD.

***Ultra-processed foods (UPFs).*** Several schemas for classifying foods according to the level of processing have been proposed. However, the NOVA system is the most widely used in nutrition research and policy.[63] The NOVA system categorizes foods according to four distinct levels of processing: Group 1—unprocessed and minimally processed foods; Group 2—processed culinary ingredients; Group 3—processed foods; Group 4—UPFs. As such, the system recognizes that while some types of food processing can contribute to healthy diets, others may be harmful.[63,64] For example, as alluded to earlier, food processing has played an important role in human nutrition and evolution by helping to increase the safety, convenience, and diversity of food products. In the modern, industrialized food system, extensive food processing used to create convenient, hyper-palatable and low-cost products has resulted in a dramatic increase in the availability and consumption of foods that are ultra-processed.[65]

UPFs are formulations of ingredients, mostly of exclusive industrial use, that result from a series of industrial processes (hence "ultra-processed").[66] These formulations of ingredients (e.g. added sugars, oils, fiber extracts, and protein isolates) typically contain cosmetic ingredients such as flavors, colors, and emulsifiers, but rarely include whole foods as ingredients. Examples of UPFs include fast food meals, soft drinks, savory snacks, confectionery, biscuits, sausages and other reconstituted meats, and mass-produced supermarket breads, and convenience foods such as ready-to-eat or ready-to-heat meals, soups, dips, and desserts.

Globally, UPFs are ubiquitous and consumed at levels that have been associated with detrimental health outcomes.[63] In high-income countries such as Australia, the United States, the United Kingdom, and Canada, ultra-processed foods contribute approximately half of total energy intake.[67] Lower rates (20–30% of TEI) of UPF consumption are observed in low- and middle-income countries.[67] However, the nutrition transition currently underway in these countries has seen a rapid shift from traditional diets based on whole foods to diets that are higher in UPFs.[68,69]

Meta-analyses of large-scale population and experimental studies indicate a dose–response association between UPF consumption and over 15 chronic disease-related outcomes.[70,71] In IBD, the evidence of an association with UPF consumption is still emerging. A meta-analysis of four prospective cohort studies,[72] consisting of more than 1 million participants (9- to 22-year follow-up), has found an increased risk of developing CD (HR 1.71; 95% CI: 1.37–2.14) among the highest quartile of UPF intake (~46–51% energy intake) compared with the lowest quartile of intake (~13–21% of total energy intake). Significant associations were not observed for UC, which may be explained by its shorter preclinical period and a more acute presentation compared with CD, among other factors alluded to earlier.[72]

The mechanisms underlying the association between IBD and UPF consumption are unclear, but the unique chemical compositions and physical structures of these foods provide plausible explanations.[73] Greater intake of UPF is associated with increased intake of free sugars, sodium, saturated and trans-fat, and decreased intake of vitamins and phytochemicals, some of which have been implicated in IBD development.[67] Physical and chemical modifications including the deconstruction of the food matrix, presence of industrial ingredients used, and the presence of contaminants from high-tech manufacturing processes (e.g. advanced glycation end-products) and packaging (e.g. phthalates) may also contribute to adverse health effects.[73] As a result, UPFs are often less satiating and may impair endocrine function and gut–brain satiety signaling, contributing to

excessive consumption.[73,74] The increased exposure to non-nutritive food substances, particularly emulsifiers and thickeners (as previously explored), has potential detrimental effect on gut microbiome and may promote overall inflammation.[73] Finally, the displacement of unprocessed and minimally processed foods reduces the exposure to beneficial micronutrients and phytochemicals.[67]

In summary, higher intakes of UPFs have been linked to increased risk of CD, supported by plausible biological mechanisms. Nevertheless, this evidence is based on a relatively small number of studies, mostly from high-income countries (despite including large number of participants); most of the dietary assessment tools were not developed to measure UPFs and misclassification of items cannot be ruled out; therefore, the findings need to be interpreted with caution.[75] Some have suggested that not all foods classified as ultra-processed pose the same health risk and can be consumed as part of a healthy diet (e.g. wholegrain bread or breakfast cereals, and flavored yoghurt).[76] Others have argued that a whole dietary patterns approach should be considered; thus, the harms of specific subgroups may be attenuated by the higher intakes of whole foods in diets that are not UPFs.[77] Further research is needed to define the levels of UPF consumption and combinations of food items recommended for CD prevention.

***Recommendations for practice.*** Based on the evidence reviewed above, there are several recommendations that can be proposed for individuals who are interested in reducing their risk of Crohn's disease through dietary approaches. Overall, a high-quality diet, a diet in line with Mediterranean diet principles, and a healthy diet pattern that limits the intake of UPF can reduce the risk of developing Crohn's disease. Recommendations for limiting UPF intake should be tailored for the individual based on other physical health needs and socioeconomic factors including food security. Figure 1 proposes specific dietary recommendations for this group and tools that are available for assessment and monitoring in clinical practice.

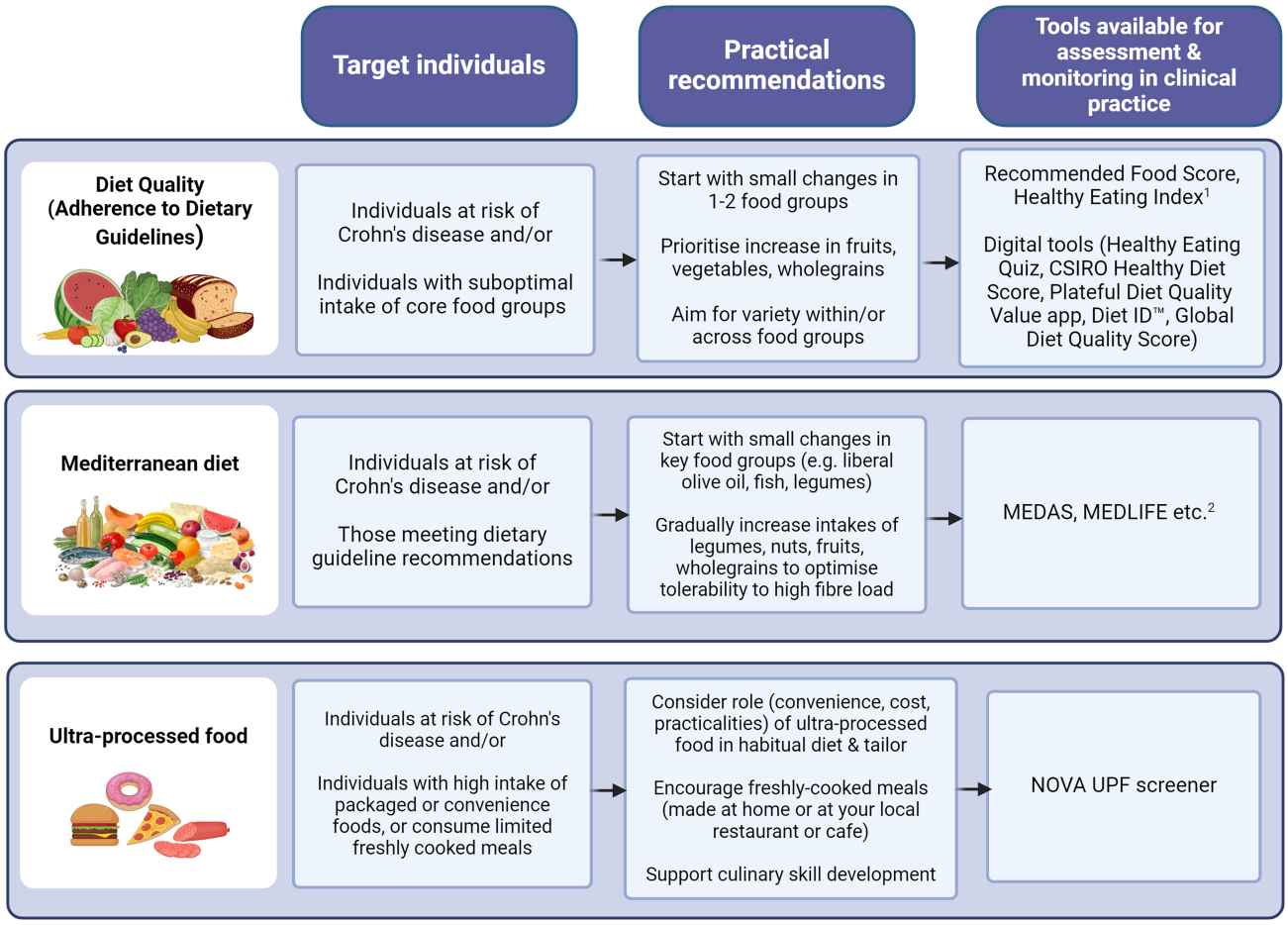


**FIGURE 1** A summary of recommendations for individuals wishing to reduce their risk of Crohn's disease through diet. While there are a plethora of tools that are available for assessing diet quality or adherence to a Mediterranean diet, only tools that are practical for use in the clinic (where nutritional analysis may not always be viable) are listed. Additional diet quality indices and Mediterranean diet tools have been comprehensively reviewed elsewhere.[79,80] UPF, ultra-processed food; CSIRO, Commonwealth Scientific Industrial Research Organization. Some of the recommendations for reducing UPF intake have been adapted from this publication by the British Nutrition Foundation.[81] Figure created using BioRender.com

Broadly, these approaches share several overarching and consistent themes that can be summarized as follows:

- Increase consumption of fruits and vegetables (≥400 g/day), whole grains (≥50%);
- weekly incorporation of nuts (90 g/week), seeds, and legumes (450 g/week);
- achieve adequate intake of dairy from low fat sources;
- moderate intake of oil and unsaturated fats;
- eating from a wide variety either from within each or across all food groups;
- limiting intake of red meat, sugar, salt, and alcohol.

There is no evidence that UC can be prevented with the above strategies. However, healthy eating recommendations are applicable to the general population and could be adapted according to the epidemiological evidence in UC for specific food groups or nutrients and according to clinical judgment. For example, these may include limiting the intake of total and red meat and increasing the intake of omega-3 polyunsaturated fatty acids.

## Conclusion

The concept of a healthy diet pattern has evolved considerably beyond history healthy eating recommendations. According to the evidence presented here, the optimal diet for people at risk of Crohn's disease is not a one-size-fits-all diet but one that conforms to national dietary guidelines, aligns with Mediterranean diet principles, and is not high in UPFs. Crucially, even small modifications to align with healthy guidelines may have substantial benefit for disease prevention. This advances the previous paradigm in which dietary guidelines was the default in the absence of any other evidence for alternative recommendations. The search for an optimal diet for UC remains elusive. Whether diet does not influence risk of UC at all or whether there are weaker influences of diet on UC disease risk only detectable once diet methodological challenges in dietary assessment are addressed is unclear. Further research is needed to address this gap. Finally, the definition of a healthy diet for IBD will continue to evolve as personalization of diets based on specific genetic, biochemical, or microbial signatures becomes an exciting possibility and may improve the prediction of IBD risk in future.

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