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Exploring Long-Term Dietary Diversity in Irish Patients with Inflammatory Bowel Disease and Its Relationship with Disease Activity and Treatment Response

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ABSTRACT

Inflammatory Bowel Disease (IBD) is a chronic inflammatory condition that primarily acts on the digestive system causing phases of discomfort and flare-ups. Its two main forms include Crohn's disease (CD) and ulcerative colitis (UC). While diet is known to influence disease progression, the impact of specific dietary patterns and components on treatment outcomes is not yet understood.

Therefore, the aim of the study is to investigate the long-term eating habits of Irish patients with IBD and evaluate the possible associations between dietary choices, disease activity, and response to advanced therapy.

Diet was assessed either by analyzing the intake of specific food groups and components or by summarizing dietary patterns into scores, such as the Healthy Food Diversity Index (HFD), Healthy Eating Index (HEI), Empirical Dietary Inflammatory Index (EDII), and a simple dietary diversity score. The intention was the identification of potential associations between dietary patterns, disease activity and therapy response. In order to explore these associations statistical analyses were used.

A total of 92 patients with IBD, 37 UC and 55 CD cases, were assessed at three timepoints: baseline, 2 weeks after the beginning of biologic treatment and 6 weeks after treatment initiation. Disease activity was measured via the Harvey-Bradshaw Index (HBI) for CD and the Simple Clinical Colitis Activity Index (SCCAI) for UC. A decrease in HBI and SCCAI scores of more than 3 points at the third timepoit determined the treatment response. Long-term dietary habits were captured with a food frequency questionnaire (FFQ).

Diet is pivotal in managing IBD, underlining the possibility for dietary choices to enhance medical treatments and improve the outcomes for the patients.

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INTRODUCTION

UNDERSTANDING INFLAMMATORY BOWEL DISEASE: PREVALENCE, IMPACT, AND CONTRIBUTING FACTORS

Inflammatory Bowel Disease (IBD) includes a variety of chronic, non-infectious inflammatory disorders affecting mainly the intestinal tract, usually characterized by intermittent discomfort and flare-ups. Ulcerative Colitis (UC) and Crohn's Disease (CD) are the two most common types of IBD[1,2]. UC was first documented in 1859 by Wilks[3], and usually, it manifests in the colon. Its typical features, besides from blood in the stool, include, abdominal pain, mucus in stools, and weight loss. Usually, the inflammation is superficial and it can be classified according to its extent: when the inflammation is confined to the rectum it is called "proctitis", inflammation limited to the descending colon is termed "left-sided colitis", while inflammation extending from the rectum to the hepatic flexure is classified as "pancolitis" [4]. CD was described by Dalziel in 1913[5], but was later named after Dr. Crohn, who initially reported it[6]. This IBD subtype can affect any part of the gastrointestinal tract, but it most commonly occurs in the terminal ileum. It is commonly presented by abdominal pain, diarrhea and weight loss. The inflammation is focal, segmental and transmural, and frequent complications may be fissures, fistulas, abscesses, and intestinal obstruction[4]. It is classified as "ileal CD" or "colonic CD" when it manifests in the ileulm and the colon respectively, while when it is displayed in a combination of those locations it is classified as "ileocolonic CD"[7]. The etiology of IBD is still substantially unknown, however it is likely to be multifactorial, involving complex interaction between the genetic, environmental or microbial factors and the immune responses[8].

IBD has emerged as a pubblic health challenge, effecting approximately 6.8 milion people worldwide[9]. North America and Europe report the highest incidence and prevalence rates of IBD [10]. However it has emerged in newly industrialised countries and it has developed into a global disease with rising prevalence in every continent[11,12]. Although IBD can occur at any age, it most commonly appears in early adulthood and peaking during the second to fourth decades, with some keeping down in older adults[13].

Studies show that individuals with IBD, both adults and children, experience significantly poorer quality of life compared to healthy individuals. A decrease in life quality may be associated with disruption to usual life activities, given the impact of the disease on education, employability, and social and interpersonal functioning, as well as stigma and disability[14]. IBD patients exhibit significantly higher rates of anxiety, depression, and post-traumatic stress disorder compared to the general population. Thus a growing evidence for the correlation between IBD disease activity and these psychiatric comorbidities was shown[15–17]. Additionally, the economic burden of IBD is high. In Europe there is an annual direct cost that is estimated to be around 3.500€ and 2.000€ for patient suffering from CD and UC, respectively. This is mostly due to medication expenses because of biologic therapies[18].

In light of the considerable psychosocial and economic burdens of IBD, an increasing interest has been pointed out regarding the understanding of the contribution of biological factors to the onset and the course of the disease, especially those linked to the gut microbiota. An imbalance in microbial homeostasis facilitates the invasion and colonization of opportunistic pathogens in the gut, contributing to IBD development[19]. The term “microbiota” refers to living microorganisms that coexist in a shared environment. The human microbiota includes 10-100 trillion microorganisms within and on the body. It includes bacteria, virus, protozoa, and fungi, with bacteria being the most abundant. The majority of the bacteria belong to the phyla *Firmicutes*, *Bacteroides*, *Proteus*, and *Actinomycetes*, whereas *Firmicutes* and *Bacteroides* are dominant in the gut flora of a healthy host. Indeed, the most densely populated microbial environment is the colon, thanks to its large surface area and nutrient availability[20–24]. Microbial communities play a pivotal role in host health and in maintaining various aspect of host homeostasis, including nutrition, immune function, metabolism, and defense against pathogens[25]. These communities vary within the regions of the gastrointestinal tract, and they can change in response to disease, or environmental modification, leading to interindividual variation[26,27]. Gut microbiota can ferment carbohydrates and indigestible oligosaccharides into short chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, which provide energy for the intestinal epithelium. Beneficial bacteria can interact with host’s immune cells and employ immunosuppressive effects, meanwhile certain harmful bacteria could promote intestinal damage via the

induction of inflammatory cytokines by the interaction between immune cells and their metabolites [28].

IBD patients exhibit distinct gut microbiota compared to healthy individuals. This disease is linked to reduced microbial diversity, and an imbalance in its composition[29]. A decrease in beneficial bacteria like *Clostridium*, *Bacteroides*, *Sutterella*, *Roseburia*, *Bifidobacterium*, and *Faecalibacterium prausnitzii* is typically involved, along with an increase in possibly harmful bacteria, including *Proteobacteria*, *Veillonellaceae*, *Pasteurellaceae*, *Fusobacterium*, and *Ruminococcus gnavus* [30,31].

THE ROLE OF DIET IN IBD MANAGEMENT: IMPACT, APPROACHES, AND RECOMMENDATIONS

Diet is widely recognized as a pivotal factor in the development and management of IBD[32]. Western lifestyle is promoting an increase in this chronic disease, and researchers predict its prevalence to rise in the coming years[33]. The modern Western diet, marked by increased caloric intake, low dietary fiber, and a shift from nutrient-rich foods to refined and highly processed alternatives, is a major contributor[34–36]. In contrast, Mediterranean societies report lower rates of diet-associated complications. The common diet in these areas is distinguished by high intake of fiber from vegetables, fruits and nuts rather than highly processed meats and industrialised goods[37,38]. Dietary fiber from vegetables, fruits, and cereals is a key nutrient that provides energy to gut cells and supports beneficial microbiota[32]. Fermentation of fiber by gut microbiota produces SCFAs such as acetate, propionate, and butyrate, which are crucial for metabolic balance, inflammatory responses, and maintaining gut barrier integrity. SCFAs exert their effect in combination with immune cells, they help maintain gut epithelium health, which is vital for an appropriately regulated relationship between the gut and the immune system[39]. Diets from industrialized countries disrupt this balance by lowering these beneficial microbiota and SCFAs production, possibly leading to gut permeability, inflammation, and autoimmune disorders. Fiber can be classified as soluble or insoluble, both of which benefit gut health: soluble fiber is easily fermented by gut bacteria, enhancing SCFAs production, whereas insoluble fiber improves digestion through the regulation of bowel movements and the alleviation from constipation[40]. The

progression from a pre-industrial dietary pattern to a western dietary pattern is associated with a higher incidence of IBD[41]. A characteristic of western diet includes low vitamin D intake, which can be obtain from food, supplements, or sun exposure. It was shown that IBD patients with a correction in vitamin D were less likely to require surgery, in comparison to those who remained vitamin D deficient[42,43]. Other effects of western diet include altered fat composition, with increased saturated fat, decreased monounsaturated fat, and imbalanced polyunsaturated fatty acids. High fat intake can alter gut microbiota composition, potentially leading to intestinal barrier dysfunction[44]. Among long-chain fatty acids, saturated, trans, and omega-6 polyunsaturated fatty acids possess pro-inflammatory properties, whereas oleic acid and omega-3 polyunsaturated fatty acids exert anti-inflammatory effects[45]. It was also shown that while high sodium intake may promote inflammation, dietary potassium has the opposite effect. Potassium seems to support immune tolerance and it might reduce CD risk[46]. Overall, the multifactorial components of the diet show plausible mechanisms that underscore the contribution of IBD development[41].

As previously mentioned, the Mediterranean diet may be helpful in the management of IBD because it involves a large intake of anti-inflammatory and nutrient-rich foods. The Mediterranean diet is widely regarded as the “gold standard” for health promotion, emphasizing unprocessed whole-plant foods, olive oil, dairy, moderate consumption of poultry and fish, and minimal red meat[47–49]. A meta-analysis showed that a high consumption of fruits and vegetables could reduce the risk in both CD and UC [50]. A high score on Mediterranean diet was recently found to be inversely associated with the risk and progression of IBD[51]. This diet was reported to lower calprotectin levels and modulate instestinal inflammation in IBD patients after pouch surgery[52], as well as a general reduction of intestinal permeability[53]. Wine and extra virgin olive oil could be consider as the main antioxidant ingredients in the Mediterranean diet. The consumption of moderate doses of wine could protect against dextran sodium sulphate-induced colitis in animal models, while extra virgin olive oil could reduce the inflammatory cascade because of its potential for antioxidant, anti-inflammatory, and immunomodulatory activities[54–56].

Moreover, the semivegetarian diet, described as largely plant-based with daily consumption of brown rice, miso soup, yogurt, vegetables, fruits, legumes, and potatoes with consumption of fish once a week or meat only once every 2 weeks, has been found to have a

positive influence on the progression of IBD as well. In a trial conducted by Chiba *et al*. the purpose was to encourage the consumption of dietary fiber with an aim to increase the presence of beneficial gut bacteria, concluding that this type of diet was highly effective in preventing relapse in CD[57]. Undeniably, the semivegetarian diet follow dietary patterns that are usually rich in dietary fiber, but low in protein. It was shown how the intake of vegetables and fruits seemed to reduce the risk of both CD and UC, and that this type of diet could assist as a protective factor against IBD[50,58]. Even if a vegetarian or semi vegetarian lifestyle may be beneficial, it could also lead to nutritional deficiencies and lower blood pressure if not carefully design in order to provide adequate nutrition[59,60].

In addition, strong evidence supports the efficacy of the low FODMAP diet in alleviating functional gastrointestinal symptoms[61,62]. FODMAP stands for Fermentable Oligosaccharide, Disaccharide, Monosaccharide, and Polyol, which are highly fermentable, but poorly absorbed carbohydrates and polyols. An increase in intestinal permeability, which was linked to the development of IBD, was casued by the rapid fermentation and passing of these subtances[63]. The low FODMAP diet consistis of eliminating food high in FODMAPs which can be fermated by the gut microbiota, resulting in gas, bloating, abdominal pain and changes in bowel habits. Patients are supervised by a dietitian, and they need to be strict with this elimination process for the first 4 to 6 weeks, after which they can gradually reintroduce foods high in fermentable carbohydrates to determine individual tolerance to specific FODMAPs[64,65]. This dietary approach has been proven to improve symptoms of irritable bowel syndrome in patients with IBD, to relieve gastrointestinal symptons in quiescent IBD patients, and in most IBD patients[66–69]. The use of the low FODMAP diet needs to be controlled and supervised by experts for different reasons: patients with IBD are often nutritionally compromised, this diet could affect food related quality of life, taking into consideration the high rates of anxiety and depression in IBD patients, and it could potentially reduce beneficial gut bacteria[66,70–72]. However current studies are focused on symptom relief, indeed more robust reaserch are needed.

Furthermore, exclusive enteral nutrition (EEN) is characterized by the replacement of all food with a nutritional supplement, a formula, usually for 6 to 8 weeks. It has also been shown to have an effect on the progression of IBD, indeed EEN is now consider as a first-line therapy in paediatric patients with CD[73]. It has been proven to be more effective in

paediatric patients that suffer from CD, with comparable effects on clinical disease activity, and higher effects in achieving mucosal remission and in reducing endoscopic and histologic scores in comparison to corticosteroids[74,75]. The situation seems to be different in adults because lower rates of efficacy have been observed, the main reason is thought to be a poor level of adherence[76,77]. Interestingly, the effects of formula composition didn't shown differences in efficacy, although most formulas are polymeric, and lactose and gluten-free, and lack fiber[78,79].

Finally, the Crohn's Disease Exclusion Diet (CDED) involves the consumption of a liquid formula as well as whole foods that includes fruits, vegetables, meats, and both simple and complex carbohydrates, but it eliminates some animal fats, certain types of meats, and it reduces exposure to food additives like emulsifiers and maltodextrins, as these dietary components can disrupt the intestinal mucus layer or alter the gut microbiota[80]. It was shown that CDED was effective in the induction of a rapid clinical response and remission in pediatric patients with active CD, as well as remission in adults with mild to moderate biologic naïve CD[81,82].

The Mediterranean, semivegetarian, low FODMAP, EEN, and CDED diets have shown promising results in either symptom alleviation or induction of remission in IBD, among other dietary approaches. Each one of these diets is characterized by certain considerations such as nutritional adequacy, impacts on quality of life, and their effects on gut microbiota. Dietary interventions should be tailored to the individual, considering nutritional needs and varying responses in IBD patients. Professional guidance is essential to ensure safe and effective implementation. In 2020 the International Organization for the Study of Inflammatory Bowel Diseases published some dietary recommendations which were developed according to the disease. A general advice for both UC and CD would be to incorporate moderate quantities of all macronutrients and to increase nutrients dense food, with high-fiber fruits and vegetables. Patients with IBD are also invited to limit emulsifiers, thickeners, processed foods, trans fats, and unpasteurised dairy. Delving into the details patients with CD are encouraged to restrict the intake of saturated fats, and for those with stricturing disease, to restrict insoluble fiber intake. Meanwhile, patients with UC are advised to restrict the consumption of red meat and myristic acid, like palm and coconut oils, and to increase n-3 fatty acids by consuming fish rather than supplements[83].

The recommended food pyramid for patients with IBD showed in *Figure 1* encourages a balanced, mindful approach to nutrition by highlighting plant-based consumption, such as fruits, vegetables, and legumes. It promotes a reduction in the intake of red and processed meat, additives, and unhealthy fats, with increased homemade meals to better control ingredients and food quality. Furthermore, it supports the addition of healthy fats and proteins in moderation to support general dietary well-being[41].

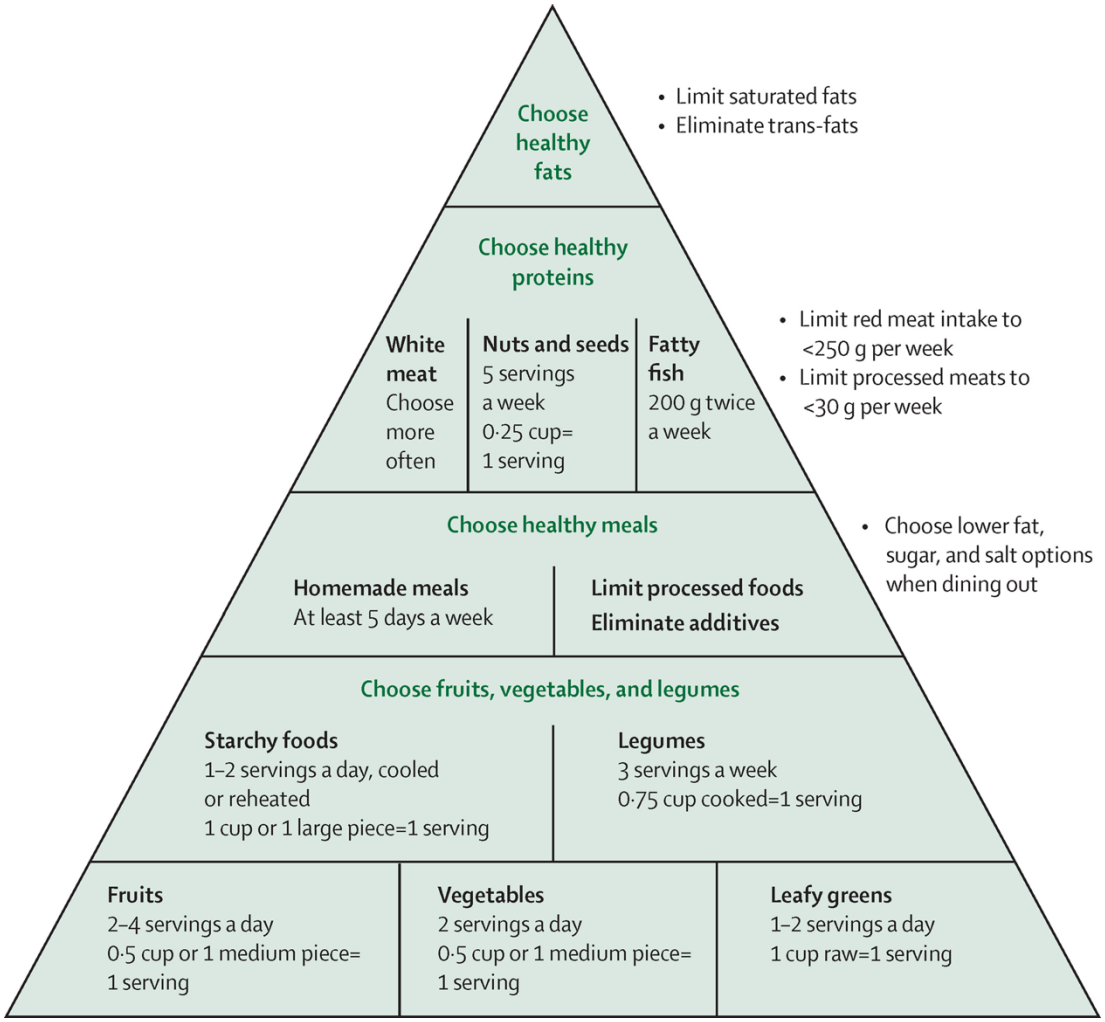

Figure 1: Recommended food pyramid for patients with IBD. Optimal intake and amount of dietary food groups for individuals with IBD [41].

METHODS FOR DIETARY ASSESSMENT AND THE USE OF FOOD SCORES IN RESEARCH

Dietary assessment is essential to understand the many complex relationships of diet, health, and disease, including in the context of IBD, in order to enable evidence-based practices that may improve overall well-being. Different method to assess diet exists, and usually in order to select a dietary assessment tool that is appropriate to a research question is a matter of compromise between their advantages and disadvantages. Current methods are available in various formats, such as paper or electronic, indeed they can be distinguished based on technology: conventional methods for dietary data collection, which include food records, food frequency questionnaires, 24-hour dietary recalls, and food records, and dietary assessment tool based on innovative technologies like photo-based dietary assesement tool and mobile apps[84].

Food Frequency Questionnaires (FFQ) are questionnaires in which the participant is presented with a list of foods and is required to say how often each is eaten in broad terms (i.e. x times per day/per week/per month, etc.). The foods that characterize the FFQ are usually chosen for the specific purposes of a study and may or may not assess total diet. These questionnaires may be either interviewer- or self-administered, where the self-administered ones require more careful preparation and pre-testing. FFQ can have some limitations, indeed they are not advisable in studies with small numbers of subjects, in studies where absolute intakes are required, and using an FFQ developed for one country in another country is not reccommended unless dietary habits are very similar[85].

The 24-hour dietary recall (24hDR) is a subjective, retrospective method that preferably requires an interview, but it can also be self-administered using computer programmes. This method consists in precisely recalling, describing, and quantifying the consumption of foods and beverages in the 24 hour before the moment of the assessement. The information need to be as precise as possible, describing the type of food, its characteristics, the quantity consumed, the preparation methods, the condiments, ect. This methods requires various instruments for reference, like household measures, drawings, and photographic models. In order to establish the usual intake a mimimum of 2 to 5 24hDRs are needed, and to capture seasonal variation it would be optimal to administered it in distinct times of the year. The 24-

hour dietary recall methods can have some limitations because it is based on memory, it depends on the interviewer ability to describe ingredients, food preparation, and dishes, and usually it tends to underestimate the dietary intake of the patient[86].

Another dietary assessment method could be food diaries, where patients are invited to record all food and beverages that they consume over three-day period, usually two working days and one weekend day. This method could be burdensome for both participants and researchers, inteed it is often time consuming, labour intensive, and it relies on participant literacy which may lead to underreporting[87].

The use of technology may be an interactive way for the patients to provided their dietary intakes, and it could be less time consuming as well. Photo-based dietary assesement tools require patients to take picture of their meal before and after eating in order to estimate portion sizes and food types. Nutrition applications for mobile devices allow real time recording for patients. Both these methods are shown to be valid, user-friendly, and they can assist with self-monitoring, possibly leading to a more realistic assessment[88,89].

In summary, each dietary assessment method has its strengths and limitations, hence, the choice of tool represents a trade-off between practicality, accuracy, and relevance for the research objectives. For the analysis conducted in this thesis FFQ were chosen as dietary assessment tool.

In order to evaluate diet quality of patients multiple dietary scores could be take into consideration. Different scores may be able to highlight various aspects, such as the general quality of the diet, nutrient diversity, or the possible inflammatory potential of the diet. They are typically used for the estimation of how well an individual food consumption aligns with recognised healthy dietary patterns, that could be presented on specific dietary guidelines. Some examples of dietary scores, among many others, include the Healthy Food Diversity (HFD) index, the Healthy Eating Index (HEI), and the Empirical Dietary Inflammatory Index (EDII), where they measure the diet adherence to the German dietary guidelines, the diet adherence to the American dietary guidelines, and the inflammatory potential of a diet based on foods that promote or reduce inflammation, respectively[90–93]. In reaserch, dietary scores might be valuable since they can provide a standardized way to assess diet quality, leading to comparison of diet quality across populations and to understanding possible

connection between diet and health outcomes[94]. A more detailed description of these dietary scores is presented in the methods, since they are used to assess diet quality of the patients that are taken into consideration in this thesis.

AIM OF THE THESIS

The goal of this study is the investigation of dietary habits in Irish patients that have been diagnosed with IBD, as well as the examination of how these habits may impact disease management and treatment outcomes. Identifying common dietary patterns is crucial to understanding the impact of specific foods, nutrients, and overall dietary approaches on disease activity and patient response to treatment. Additionally, the study seeks to determine the most accurate tool for assessing diet quality in IBD patients by comparing various dietary scoring methods.

METHODS

STUDY POPULATION, SAMPLE AND DATA COLLECTION

All patients had well-established diagnoses by conventional and investigative criteria[95]. The analysis presented in this thesis was conducted on the first 100 patients enrolled in an ongoing clinical study, AUGMENT. Of these, eight participants were excluded: four due to lack of consent, three because of substantial missing data in their food frequency questionnaires (FFQ), and one due to an unclassified diagnosis. Consequently, a total of 92 patients, including 55 with Crohn's disease (CD) and 37 with ulcerative colitis (UC), were recruited from Cork University Hospital (CUH) and Mercy University Hospital (MUH) (see *Table 1* for patients' characteristics).

The study was structured around three time points: baseline (V1) and two follow-up visits (V2 and V3). After enrollment and screening at V1, patients began biologic treatment, with a flexible start time averaging approximately 5 weeks post-V1. Biologics included TNF-alpha blockers (i.e., adalimumab and infliximab), integrin blockers (i.e., vedolizumab), IL-12 and IL-23 blockers (i.e., risankizumab and ustekinumab), S1P receptor modulators (i.e., ozanimodand), and JAK inhibitors (i.e., tofacitinib and upadacitinib), in accordance with standard treatment protocols. V2 occurred two weeks after treatment initiation, followed by V3 six weeks later. Biological samples collected at V1 included blood, stool, and biopsy tissue; V2 involved the collection of a stool sample, while V3 included both stool and blood samples (*Figure 2*).

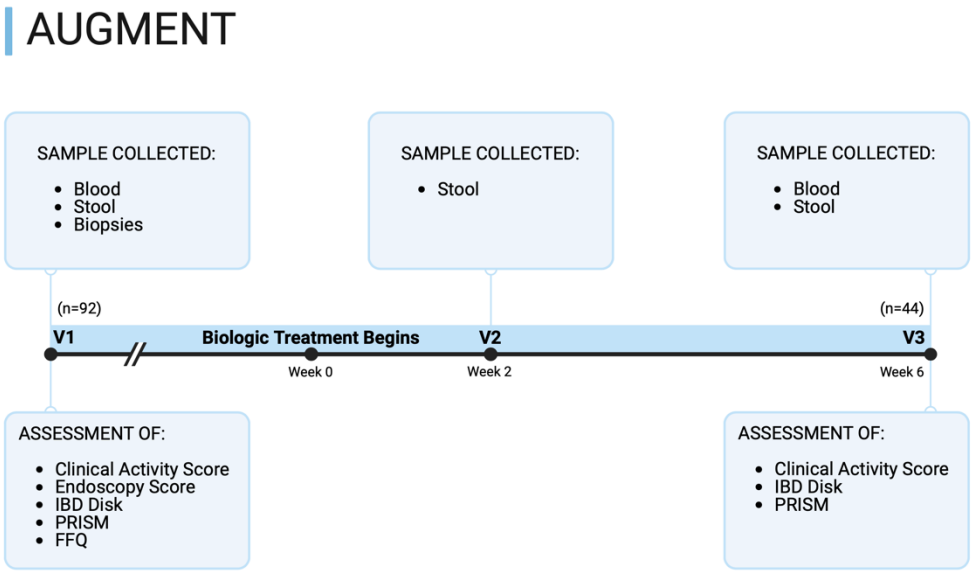

Figure 2: Study design AUGMENT.

Blood samples were collected to measure C-reactive protein (CRP) and albumin levels, while fecal samples were collected for fecal calprotectin (FCAL) measurement. Biopsies were obtained through colonoscopy to assess tissue from both inflamed and non-inflamed sites in the lower and upper gastrointestinal (GI) tract, including sections from the terminal ileum, caecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum.

Assessment of clinical activity occurred at V1 and at V3. Different criteria were applied to determine disease activity, including clinical assessment scores (CAS) and biomarkers such as fecal calprotectin (FCAL), C-reactive protein (CRP), albumin, and endoscopic scores. CAS measures included the Harvey-Bradshaw Index (HBI) for CD and the Simple Clinical Colitis Activity Index (SCCAI) for UC; disease was considered active with an HBI score of ≥5 or an SCCAI score of ≥3, and inactive with an HBI <5 or SCCAI ≤2. Disease severity was further categorized as remission (HBI <5 or SCCAI ≤2), mild (HBI >5 <7 or SCCAI >3 <5), moderate (HBI >8 <16 or SCCAI >6 <11), and severe (HBI >16 or SCCAI >12)[96–99]. Active disease was defined by a fecal calprotectin (FCAL) level of ≥250 µg/g, in line with established cutoff values[100,101]. Inactive disease was defined by CRP levels of ≤1 mg/dl, while elevated CRP levels ranged from >1 to ≤5 mg/dl, and active disease was indicated by CRP levels >5 mg/dl[102]. For albumin, levels <35 g/L classified disease activity as active, whereas levels ≥35 g/L indicated inactive disease[103]. Endoscopic disease activity was assessed during V1 and it was evaluated using the Mayo Endoscopic Score (MES) for UC and the Simple Endoscopic

Score for Crohn's Disease (SES-CD) for CD. MES or SES-CD scores <3 indicated inactive disease, while scores ≥3 indicated active disease. Endoscopic severity was categorized as remission (MES <3 or SES-CD <3), mild (MES >3 <5 or SES-CD >3 <6), moderate (MES >6 <10 or SES-CD >7 <15), and severe (MES >10 or SES-CD >16)[104,105].

During V1 long-term dietary habits were captured via a FFQ encompassing 149 food items. The FFQ included frequency options ranging from "never" to "6+ per day" (i.e. never, less than once per month, once per month, once per week, twice per week, 5 per week, once a day, 2 per day, 4 per day, 6+ per day), and portion sizes (i.e. medium serving, a cupful, size deck of cards, and teaspoon), enabling the identification of dietary patterns[106]. These were subsequently summarised into 21 broader food categories as well as into four validated dietary assessment scores: the Healthy Food Diversity (HFD) Index[90], the Healthy Eating Index (HEI)[91,92], the Empirical Dietary Inflammatory Index (EDII)[93], and a Simple Food Diversity Score.

The IBD-disk and the Pictorial Representation of Illness and Self Measure (PRISM) were utilized as part of the data collection for evaluating disease impact on patients. Their assessment occurred both at V1 and at V3. The IBD-disk is a visual tool designed for patients with IBD to evaluate their own health status. It is organized around 10 items that relate to the patient's everyday life. Patients score each item from 0 (absolutely disagree) to 10 (absolutely agree), based on how they feel. The 10 items are: abdominal pain, regulating defecation, interpersonal interactions, education and work, sleep, energy, emotions, body image, sexual function, and joint pain. They are presented as parts of a circle and once all items are scored, a graph is created by connecting the scores, in which closer proximity to the center reflects a better state of health. The PRISM is a two-dimensional pictorial method used to assess a patient's level of suffering. Patients indicate their burden by measuring the distance between a "self" circle and an "illness" circle, with a shorter distance implying a higher burden of suffering[107–109].

Treatment response was evaluated both through FCAL and clinical response measures across the three time points. Patients were classified as in remission if FCAL was <250 µg/g at both V1 and V3. Non-responders had FCAL >250 µg/g with less than a 100 µg/g decrease between V1 and V3, while responders had a FCAL decrease >100 µg/g, but still >250 µg/g at V3. Super-responders exhibited a FCAL decrease >100 µg/g with FCAL <250 µg/g at V3. Clinical

response was defined as remission if patients were in remission at both V1 and V3. Non-responders were those not in remission at V1, with a combined difference in clinical assessment scores (CAS) <3. Responders had a CAS difference ≥3 without remission at V3, while super-responders also had a CAS difference ≥3. Remission cases were reclassified based on CAS changes: those with a CAS difference ≥3 were responders, and those with a CAS difference <3 and HBI ≥3 or SCCAI ≥3 at V3 were classified as non-responders.

DATA HANDLING

Stool samples were processed at Mercy Hospital, where FCAL was extracted using Buhlmann Calex Cap kit. An Abbott Alinity C analyser was used for the analyses, applying the Particle Enhanced Turbidimetric Immunoassay (PETIA), with Buhlmann fCal Turbo Reagent kit. This method uses antibodies that bind to calprotectin increasing the turbidity of the sample, which provide a quantitative value for FCAL levels. Blood samples were processed at Cork University Hospital. A Beckman Coulter AU5832 analyser was used to measure CRP levels, via the Quantitative Turbidimetric Immunoassay method. The Beckman Coulter CRP latex reagent was used, containing a glycine buffer with anti-CRP antibody-coated latex particles (<0.5% w/v) and a preservative (<0.1% w/v). This reagent causes the sample's turbidity to increase proportionally to CRP concentration, providing a quantitative measurement of CRP levels. Albumin levels were also measured on the Beckman Coulter AU5832 analyser, using a Quantitative Photometric method. The Beckman Coulter Albumin reagent with bromocresol green dye was employed, which binds to albumin in the sample, producing a color change that allows for quantitative measurement of albumin concentration.

Data processing and statistical analyses were performed using *R* (v. 4.3.2) and *RStudio* (v. 2023.12.1.402), visualizations were obtained using: *ggplot2* (v. 3.5.1)[110], *ggpubr* (v. 0.6.0)[111], *rlang* (v. 1.1.4)[112], *patchwork* (v. 1.3.0)[113], and *pheatmap* (v. 1.0.12)[114], if not further specified basic R functions were used.

Dietary intake data from FFQ were entered in Castor database, a flexible data management platform that allows researchers to customize their own databases specifically for clinical trials, enabling efficient data collection, management, and analysis. Adjustments were manually made for patients who reported frequencies intake that didn't match the FFQ

options, in order to ensure accuracy in dietary frequency data, and reflect patients' actual dietary consumption. A script was developed to automate the process, including renaming columns taking into consideration specified variations. For example "cow milk" was assigned for any missing data for milk types, unless the patient stated otherwise (e.i. soy, almond, coconut, lactose-free, or goat milk), and in this case, for each milk types additional column were created where the frequencies were updated as per patient's reported intake. The data were converted into machine-readable monthly intake frequencies (e.i., "never=0", "<1/month=0.5", "1/month=1", "1.5/month=1.5", "2/month=2", "1/week=4", "1.5/week=6", "2/week=8", "3/week=12", "3.5/week=14", "5/week=20", "0.5/day=14", "1/day=28", "2/day=56", "3/day=84", "4/day=112", "6+/day=168", "missing=NA"). The *Naniar* (v. 1.1.0)[115] and *mice* (v. 3.16.0)[116] packages in R were used to manage missing data in the FFQ dataset. Multiple imputation methods were applied to ensure a comprehensive and unbiased reflection of patients' dietary intake, aiming to reduce the potential for bias introduced by missing information. Food frequency data were converted into gram-based intake via Aqua-Calc[117], an online tool that provided volume to weight conversions based on USDA data, and additional food items from USDA Branded Food Products Database. Using the EuroFIR database[118], macro- and micronutrient intakes per portion were calculated for each food item. EuroFIR AISBL includes validated bioactive compound information (eBASIS) and global food data (FoodEXplorer) from Europe, the USA, and Canada. Food items relevant to this study were downloaded primarily from the Irish food composition database, however, where data were unavailable, the United Kingdom database was used as a secondary source. For food items not included in the database, nutritional information was retrieved from individual item websites.

These final steps required assumptions at multiple levels. First, food items were considered as reported by participants, assuming accuracy in their responses. Next, broader food categories were created to organize food items. This process, though necessary, introduced some abstraction: for example, grains could be classified together or separated by type (i.e., whole vs. refined grains). Composite foods were deconstructed into component categories throught the USDA food equivalent database[119], thus some assumptions were necessary. Nutritional information for each item was obtained from the EuroFIR database, based on

standardized portion sizes we assumed participants consumed. It was also assumed that the database values accurately reflected the nutrient content of each food item.

Food intake was summarized into four different dietary scores, Healthy Food Diversity (HFD) index, Healthy Eating Index (HEI), Empirical Dietary Inflammatory Index (EDII), and a simple food diversity score. The HFD index assesses diet diversity, and the adherence to a healthy diet according to the German dietary guidelines (DGE). It was calculated by dividing food items into food groups, each assigned a proportional share based on their FFQ values (s_i). Each food group was given a health value (hv) reflecting its nutritional quality based on DGE recommendations. The index was then calculated as the product of one minus the sum of the squared proportions of the food groups and the health values (*eq. 1*). These calculations were done as described in earlier research[90].

$$HFD\ index = (1 - \sum {s_i}^2) \cdot hv \qquad (1)$$

The HEI is a measure to assess dietary quality, precisely the degree to which a set of foods aligns with dietary guidelines for Americans (DGA). It is characterized by 13 components that sum to a total of 100 points, the total score is the sum of the score of adequacy components (i.e. foods to eat more of for good health) and moderation components (i.e. foods to limit for good health). The HEI-2020 is the latest version which allows the assessment of alignment with the 2020-2025 DGA. Since no major changes occurred between the previous guidelines the HEI-2020 components and scoring standards are the same as the HEI-2015[91,92]. It was calculated following the R script for FFQ provided by the Division of Cancer Control and Population Sciences (DCCPS) of the National Institutes of Health (NIH)[120].

The EDII denotes the inflammatory potential of the diet based on circulating concentrations of inflammatory biomarkers. It is based on 18 food groups, 9 pro-inflammatory, having a positive association, and 9 anti-inflammatory, having an inverse association with the score. Each food group's daily frequency intake was multiplied by their specific weight. The calculations were done following the same model and using the same weights as previous research[93].

A simple food diversity score was calculated, based on the presence (+1) or absence (0) of each food item, to provide a simple measure of overall dietary diversity. Dietary diversity itself has been associated with various beneficial effects[121].

STATISTICAL ANALYSIS AND VISUALIZATION

Dietary intake differences were determined via permutational multivariate analysis of variance (PERMANOVA), through the *adonis2* function from the *vegan* package (v. 2.6-8)[122]. Dietary data were examined as food items, food categories, and nutrient intake. To visualise the overall dietary consumption patterns based on food items, categories, and nutrients, Principal Component Analysis (PCA) was used. Differences in specific dietary measures between diagnoses and inflammation at V1 and V3 were analysed using the Wilcoxon Rank Sum Test (or Mann-Whitney U Test) for two-group comparisons. Differences in dietary data across diagnostic extent (colonic, ileal, and ileocolonic for CD; distal UC, pancolitis, and proctitis for UC), inflammation at V1 and V3 (inactive, elevated, and active based on CRP levels) and treatment response categories based on clinical and FCAL response between V1 and V3 (non-responders, responders, super-responders, and remission) were evaluated using the Kruskal-Wallis Rank Sum Test for three-group and four-group comparisons. Boxplots illustrated group-level differences in specific dietary data. Spearman correlations were carried out to examine relationships between dietary intake differences and inflammation (V1, V3) or treatment response. Heatmaps visualized and clustered significant multiple correlations, while scatterplots pictured significant single correlations. A significance threshold of $p < 0.05$ was applied, with p-values adjusted for multiple comparisons using the Benjamini and Hochberg method[123].

RESULTS

STUDY POPULATION

In this analysis we tracked dietary patterns and inflammation markers over multiple time points to determine whether specific dietary habits impact inflammatory responses and treatment outcomes in IBD patients. The clinical study was thoroughly discussed with patients who had previously provided informed consent. It had a longitudinal study design with three time points: baseline (V1) and two follow-up visits (V2 and V3) as described before (*Figure 2*).

We collected data from 92 patients, including 55 with Crohn's disease (CD) and 37 with ulcerative colitis (UC), recruited from Cork University Hospital (CUH) and Mercy University Hospital (MUH) in Cork, Ireland, as part of a cohort study investigating dietary patterns and IBD. Among those with UC, 11 had pancolitis, 17 had distal UC, and 8 had proctitis; among those with CD, 12 had colonic, 17 had ileal, and 26 had ileocolonic CD. Both sexes were similarly represented (50 female and 42 male). Patients with the two diagnoses showed comparable BMI values (26.31 in UC and 25.65 in CD) and average ages (43.46 in UC and 42.2 in CD), with an age range of 20 to 73 years. The group of smokers included 3 patients with UC and 11 with CD, while 3 patients with UC and 16 with CD were vape users. See *Table 1* for subject characteristics.

This analysis included data from the ongoing AUGMENT clinical study, which investigates how dietary diversity and the microbiome influence immune therapy response in individuals with IBD. Since the study was still in progress and not all results were available at the time of writing, indeed within the timeframe of this thesis only 44 patients concluded the study, most results lost statistical significance after p-values were adjusted for multiple testing, unless stated otherwise.

Table 1:Subjects characteristics. n/a stands for not applicable.

Type of cohort		
	UC	CD
Number of subjects	37	55
Extensive UC/Pancolitis	11	n/a
Left sided UC/Distal UC	17	n/a
Ulcerative Proctitis	8	n/a
Colonic CD	n/a	12
Ileal CD	n/a	17
Ileocolonic CD	n/a	26
Age	43.46 +/- 13.66	42.2 +/- 13.52
Females	18	32
Males	19	23
BMI	26.31 +/- 4.93	25.65 +/- 5.15
Current smoking	3	11
Former smoking	19	20
Non-smoking	15	23
Current vaping	3	16
Former vaping	1	2
Non-vaping	33	36
Colonic Resection	0	6
Small Bowel Resection	0	5
Ileocolonic Resection	0	10
Peri-Anal drainage	0	3
Seton procedure	0	2
IBDD-V1	56.61 +/- 25.67	58.22 +/- 20.16
PRISM-V1	47.32 +/- 45.65	67.64 +/- 59.53
IBDD-V3	37.89 +/- 26.39	42.04 +/- 23.28
PRISM-V3	106.5 +/- 63.28	108.09 +/- 67.42

ASSESSING DIETARY DIFFERENCES IN ULCERATIVE COLITIS AND CROHN'S DISEASE

We first wanted to assess if dietary patterns differ between patients with different IBD subtypes and different disease extents. To achieve this, we compared the overall dietary composition, the consumption of individual food items or categories, nutrient intake, and overall diet diversity, quality, and inflammatory potential. The overall dietary composition, including food items, food categories, nutrients and dietary scores, exhibited no significant differences between diagnoses (PERMANOVA p>0.05) (*Supplementary tables S1; S2; S3; S4*).

When comparing the consumption of individual food items between patients diagnosed with UC and CD, 5 items showed significant differences (WILCOXON p<0.05). Patients with UC displayed a generally higher median intake and wider range of consumption for potato salad, vegetarian lasagne (remaining significant after multiple testing adjustment, padj<0.05), quiche, baked beans, and tinned vegetable soups (*Figure 3*).

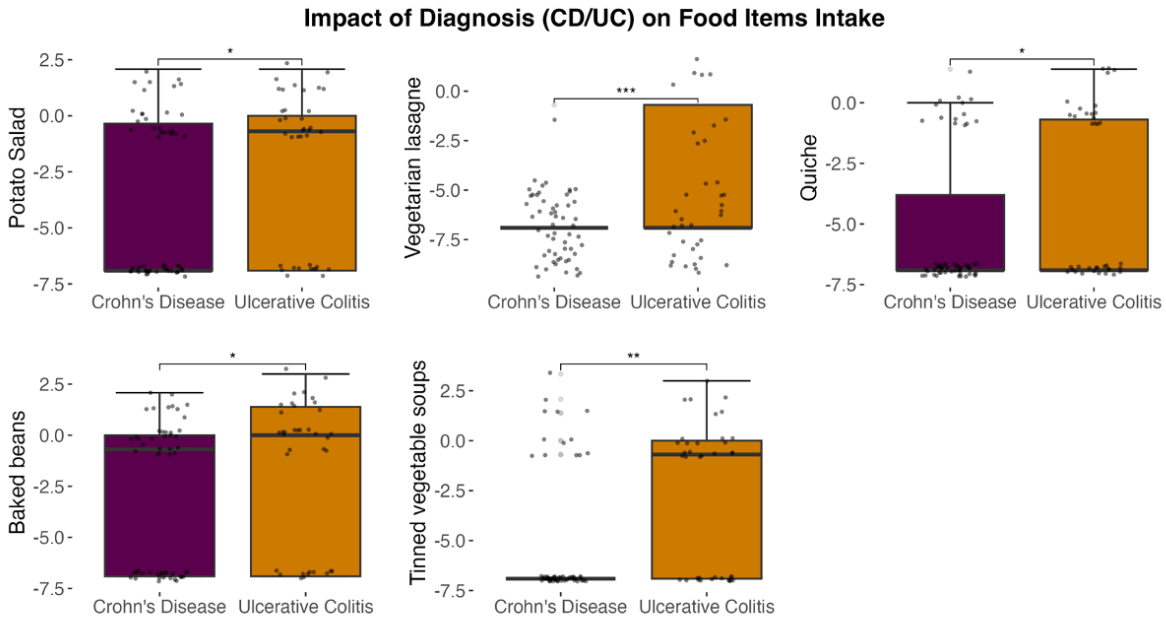

*Figure 3: Comparison of food items consumption between patients with different diagnosis (UC and CD). *p<0.05; **p<0.01; ***p<0.001.*

Comparisons of food categories, nutrients, and various dietary scores also exhibited no significant differences (WILCOXON p>0.05) (*Supplementary tables S5; S6; S7*).

ASSESSING DIETARY DIFFERENCES IN CROHN'S DISEASE SUBTYPES

The overall dietary composition showed no significant differences between patients that differ in CD extent (PERMANOVA p>0.05) (*Supplementary tables S1; S2; S3; S4*).

When comparing the consumption of individual food items among patients with varying extents of CD, 4 items showed significant differences (KRUSKAL p<0.05). Median intake of sugar-coated cereals and peanut butter was higher in colonic CD, while light margarine and grapes were more frequently consumed in ileal CD. Grapes consumption was also lower in colonic CD compared to ileocolonic CD (*Figure 4*).

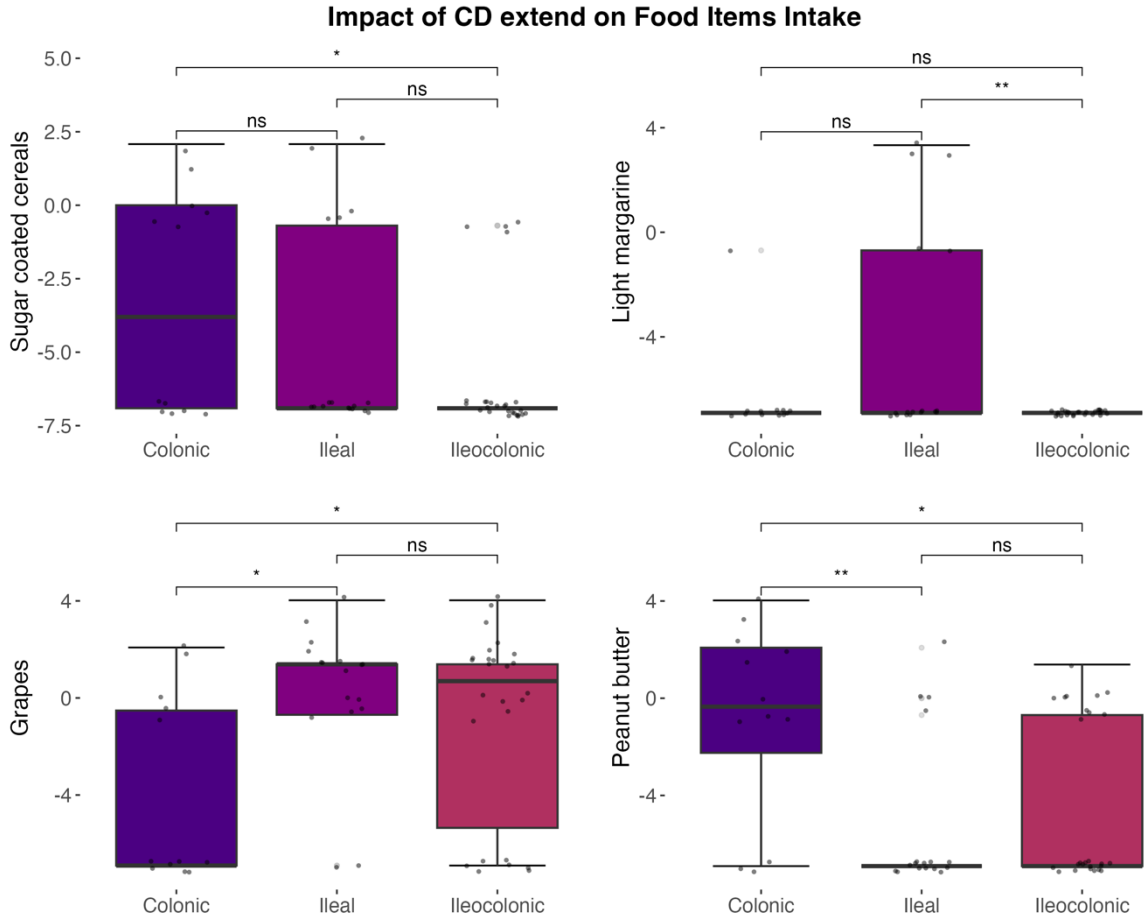

*Figure 4: Comparison of food items consumption between patients with different CD extent. ns p>0.05; *p<0.05; **p<0.01.*

Comparisons of food categories, nutrients, and various dietary scores also displayed no significant differences (WILCOXON p>0.05) (*Supplementary tables S8; S9; S10*).

ASSESSING DIETARY DIFFERENCES IN ULCERATIVE COLITIS SUBTYPES

When evaluating differences between the dietary composition across 21 food categories in UC patients, the first two axes of the PCA explained 74.5% of the variation, and showed a significant shift in dietary patterns across UC types (PERMANOVA p<0.05). A distinct shift along the second principal component was evident, moving from pancolitis over distal UC to proctitis, while a less pronounced shift was observed along the first principal component from pancolitis to distal UC to proctitis (*Figure 5a*).

In comparison, the dietary composition in terms of macro- and micronutrient intake among UC patients with differing disease extents showed a less distinct shift along the first principal component, ranging from pancolitis to distal UC and proctitis, which reached significance only under a more relaxed p-value cutoff (PERMANOVA p<0.1) (*Figure 5b*).

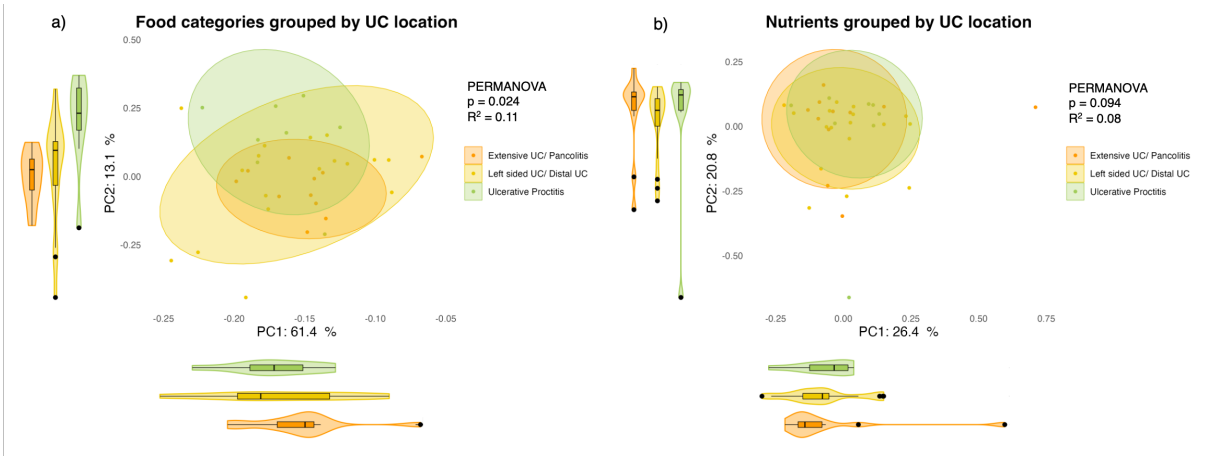

Figure 5: PCA of monthly food categories consumption in patients with UC grouped by UC type (a), PCA of nutrients intake in patients with UC grouped by UC type (b).

Taking into consideration the overall dietary composition with respect to food items and dietary scores revealed no significant differences between patients that differ in UC extent (PERMANOVA p>0.05) (*Supplementary tables S1; S4*).

When examining variation in the intake of individual food items between patients with differing types of UC, seven items show significant differences (KRUSKAL p<0.05). The median uptake of wholemeal pasta, cottage cheese, green salad, and herbal tea was higher in patients with proctitis. White bread consumption was higher in patients with distal UC than in proctitis patients, while leek intake was especially lower in patients with distal UC

compared to patients with pancolitis and proctitis. Fresh vegetable soup intake was notably lower in patients with pancolitis compared to distal UC and proctitis (*Figure 6a*).

We also found significant differences in diet quality, measured with HFD and HEI among patients with different types of UC (KRUSKAl p<0.05). These differences remained significant even after adjustment (padj<0.05), with higher scores observed in patients with proctitis (*Figure 6b*).

The comparisons of food categories and nutrients found no significant differences between patients with different UC extent (KRUSKAL p>0.05), (*Supplementary Tables S11; S12*).

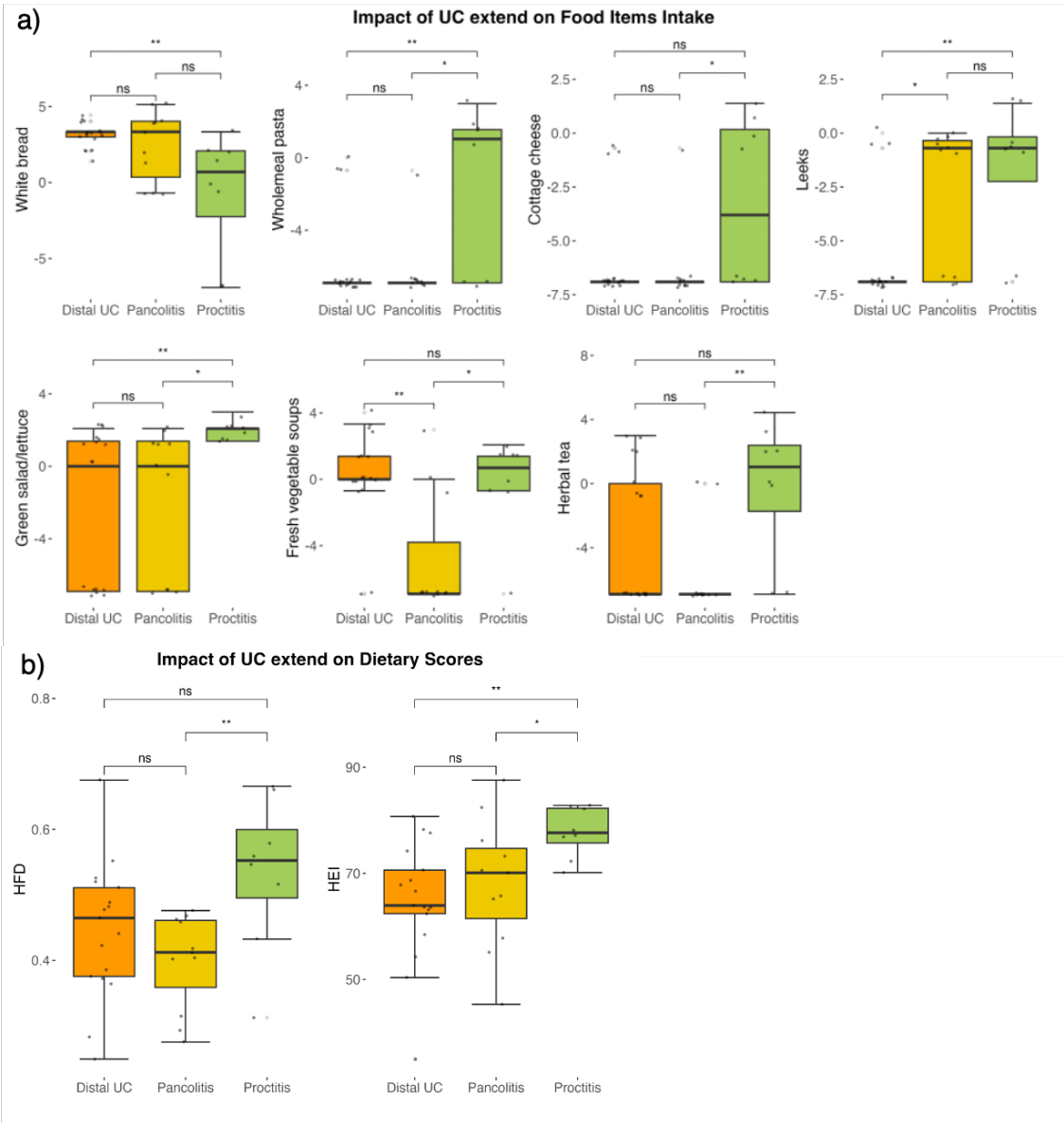

*Figure 6: Comparison of food items consumption between patients with different UC extent (a), comparison of dietary scores between patients with different UC extent (b). ns p>0.05; *p<0.05; **p<0.01.*

ASSESSING DIETARY DIFFERENCES BY DISEASE ACTIVITY AT BASELINE (V1) IN IBD PATIENTS

Next, we compared the diets of patients with active versus inactive disease at baseline, to explore potential dietary differences among patients with IBD in relation to disease activity. Disease activity status was determined using several criteria measured at V1, including, clinical assessment scores, FCAL levels, CRP levels, albumin levels and endoscopic scores. The first two axes of a PCA of dietary intake across 149 food items accounted 35.6% of the variation. Disease activity, as indicated by serum albumin levels explained 2% of the variation in dietary composition (PERMANOVA $p<0.05$; *Figure 7a*). When assessing dietary composition with respect to food category consumption, the first two axes of the PCA capture 75.6% of the variation. Disease activity, based on serum levels of CRP, contributed to 4% of the variation, but only with a relaxed p-value cutoff (PERMANOVA $p<0.1$; *Figure 7b*). In contrast, CAS explained only 2% of the variation, but achieved statistical significance (PERMANOVA $p<0.05$; *Figure 7c*). Finally, when examining the overall daily nutrient intake of patients, the first two axes of the PCA represented 43.4% of the variation. Here, disease activity measured by endoscopy accounted for 12% of the overall variation (PERMANOVA $p<0.05$; *Figure 7d*), while inflammation status, determined by CAS, explained 5% of the variance (PERMANOVA $p<0.05$; *Figure 7e*). These findings indicate an association between inflammation and patients' dietary patterns.

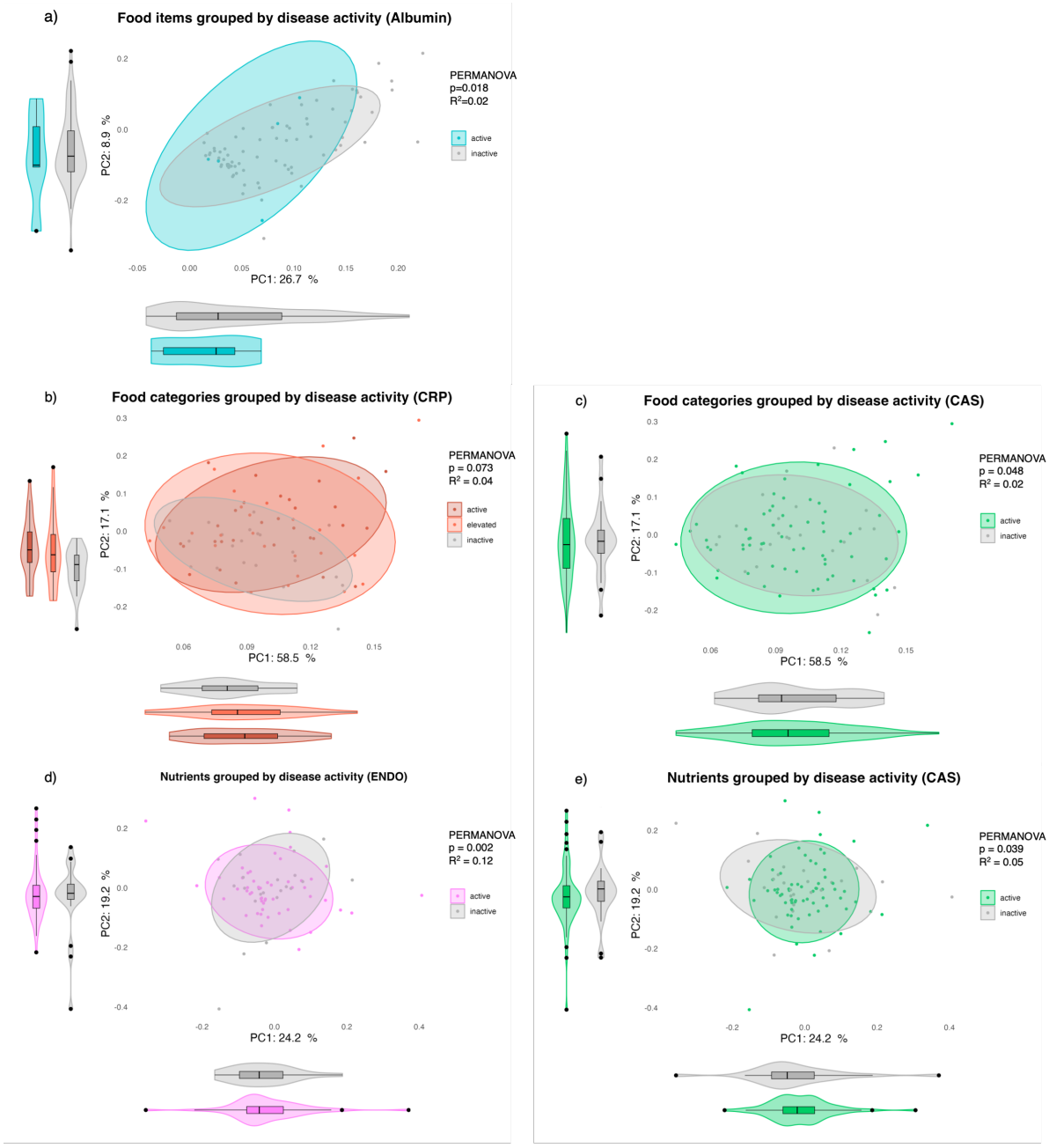

Figure 7: PCA of monthly intake of food items grouped by disease activity based on albumin at baseline (a), PCA of monthly intake of food categories grouped by disease activity based on CRP at baseline (b) and CAS at baseline(c) , PCA of nutrients grouped by disease activity based on endoscopic scores at baseline (d) and CAS at baseline (e).

FOOD ITEMS

Subsequently, we investigated the intake of specific food item among patients with varying disease activity in relation to the different inflammation markers and identified several significant differences.

For FCAL, ten items showed significant differences (WILCOXON $p<0.05$). The median consumption of white rice, white pasta, low-fat cheddar, melon, broccoli, and sweetcorn was higher in active patients, while the intake of white bread, sugar-coated cereals, cream, and vegetable oil spread was elevated for inactive patients (*Figure 8a*).

For CAS, six items exhibited significant differences (WILCOXON $p<0.05$). Patients with inactive disease more frequently consumed savory pies, dairy desserts, butter, cakes, and chocolates but had a lower milk pudding intake than patients with active disease (*Figure 8b*).

For albumin, eight items showed significant differences (WILCOXON $p<0.05$). The median intake of cheddar cheese, oranges, coleslaw, plain biscuits, spirits, and probiotic yogurts was higher among active patients, while light butter was more commonly consumed by inactive patients (*Figure 8c*).

For endoscopic scores, eight items revealed significant differences (WILCOXON $p<0.05$). The median consumption of white rice, low-fat cheddar cheese, broccoli, and herbal tea was higher in active disease. In contrast, crispbread, cream and vegetable oil spread, peanuts and nuts, and low-alcohol beer were more prevalent in the diet of patients with low inflammation (*Figure 8d*).

Eight food items showed significant differences in relation to CRP levels (KRUSKAL $p<0.05$). Patients with inactive disease had higher median intakes of wholemeal bread, wholemeal pasta, apples, frozen fruit, and ready meals, while light butter was more commonly consumed by active patients. Beetroot intake was elevated in patients with high CRP levels compared to those with active disease, whereas sweets and mints were consumed less frequently by inactive patients (*Figure 8e*).

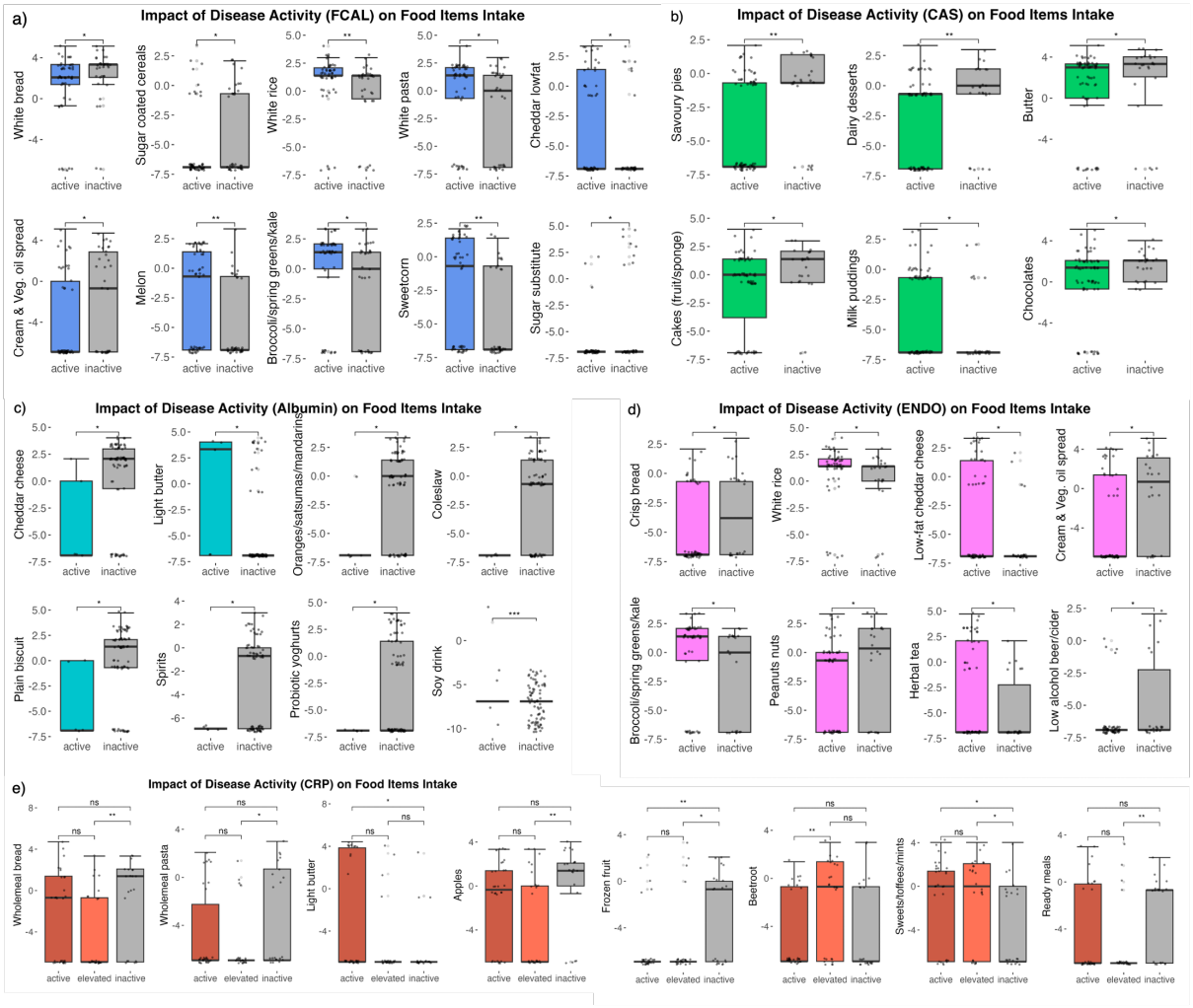

*Figure 8: Comparison of food items consumption in relation to disease activity based on FCAL (a), CAS (b), serum levels of albumin (c), endoscopic scores (d), and serum levels of CRP (e). ns p>0.05; *p<0.05; **p<0.01; ***p<0.001.*

Investigating the relationship between food frequencies and inflammation markers as numerical variables may provide a more consistent picture than categorizing patients into active and inactive disease groups. Therefore, we performed correlation analyses between the variables and clustered food items based on their correlation patterns with the inflammation markers. We found several significant associations (SPEARMAN CORRELATION $p<0.05$).

Higher consumption of items like meat-based lasagne, beer and cider, cheddar, roasted or fried potatoes, and oranges showed a positive association with albumin levels, suggesting that increased intake of these foods may be linked with higher albumin levels. In contrast, foods like blueberries, parsnips and turnips, and light butter were negatively associated with albumin.

White pasta, broccoli, light butter, white rice, low-fat cheddar, and sweetcorn displayed positive correlations with FCAL levels, indicating that their higher consumption aligns with elevated FCAL. On the other hand, cream and vegetable oil spread, leeks, crispbread, and beetroot showed a negative association with FCAL.

Endoscopic scores were positively correlated with the intake of garlic, semi-skimmed milk, melon, and broccoli, while cream and vegetable oil spread exhibited a negative association with endoscopic scores.

Clinical scores were positively correlated with peaches/plums and milk puddings, whereas foods such as butter, lamb, tinned meat cream soups, dairy desserts, apples, beef burgers, and mushrooms showed a negative association, potentially suggesting an association between these items and lower clinical scores.

Lastly, CRP levels were positively associated with the consumption of sugar and fizzy drinks, while cream and vegetable oil spread, pickles and chutney, and frozen fruit were negatively correlated, implying lower CRP levels with increased consumption of these items (*Figure 9*).

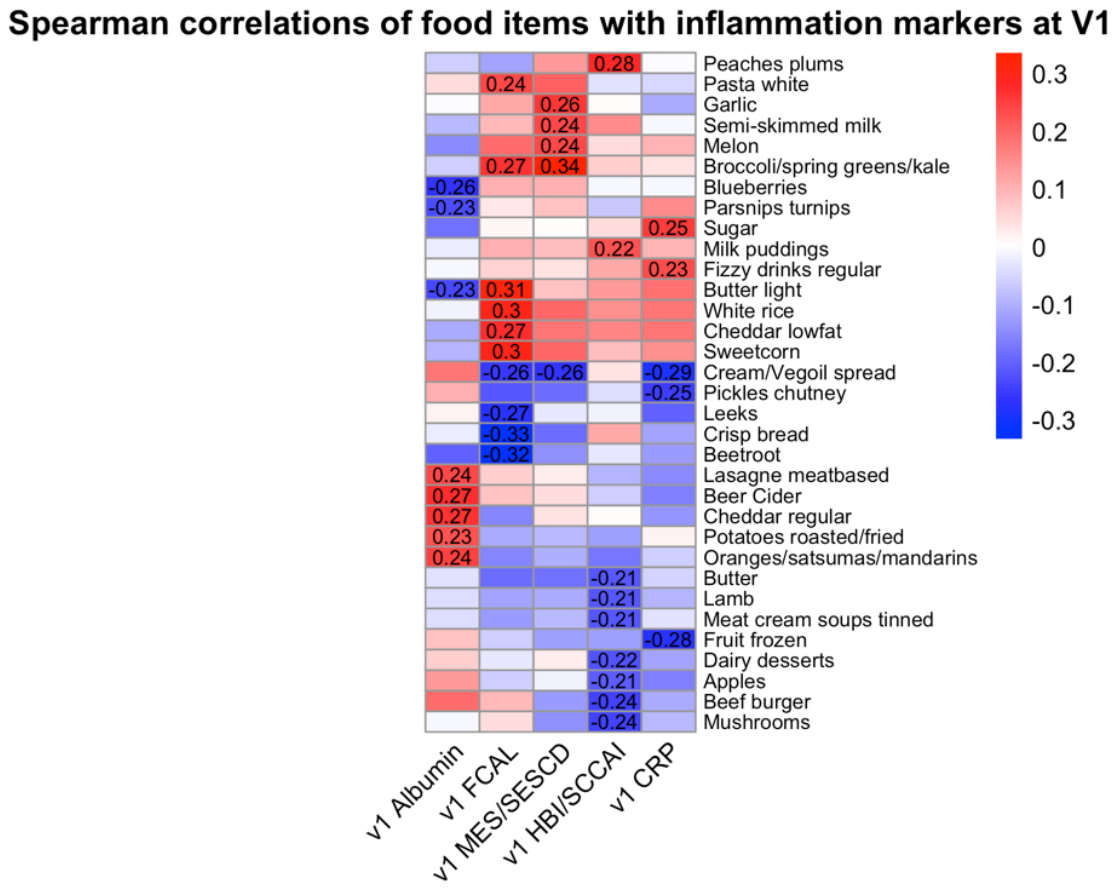

Figure 9: Heatmap of spearman correlations of food items with inflammation markers at baseline. Food items with at least one significant results are presented. rho is shown just in case p<0.05.

FOOD CATEGORIES

When comparing food categories consumption in relation to disease activity based on FCAL, albumin, and endoscopic scores, some categories showed significant differences.

For FCAL, three categories differed significantly (WILCOXON p<0.05). The median consumption of dairy and refined grains was higher for inactive patients, whereas low-fat dairy intake was higher in active patients (*Figure 10a*).

For albumin, alcohol and vegetables oils showed significant differences (WILCOXON p<0.05), with both consumed more by inactive patients (*Figure 10b*).

Concerning endoscopic scores the only category that showed a significant difference (WILCOXON p<0.05) was drink, which was higher in active patients (*Figure 10c*).

Comparisons of food categories in relation to disease activity based on CAS and CRP showed no significant differences (WILCOXON and KRUSKAL p>0.05) (*Supplementary tables S13; S14*).

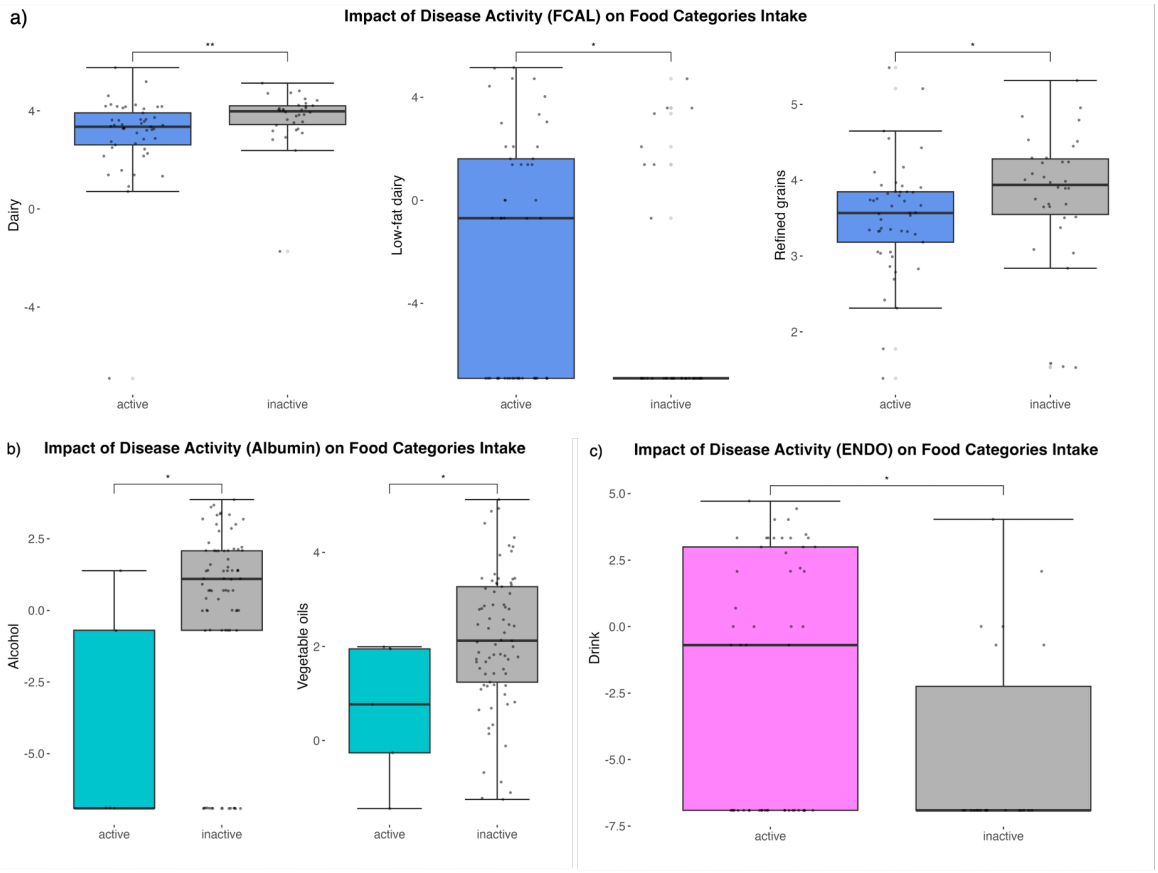

*Figure 10: Comparison of food categories consumption in relation to disease activity based on FCAL (a), serum levels of albumin (b), endoscopic scores (c). *p<0.05; **p<0.01.*

During correlations analyses between food categories and inflammation markers at V1, some associations stood out (SPEARMAN CORRELATION p<0.05).

The consumption of vegetable oils and processed meat was positively associated with albumin levels, indicating that the higher their intake the higher albumin levels will be.

While low-fat dairy showed a positive association with FCAL levels, vegetables oils, refined grains, dairy, and tea and coffee were negatively associated with FCAL.

CRP levels were positively correlated with high sugar foods, and negatively correlated with vegetable oils (*Figure 11*).

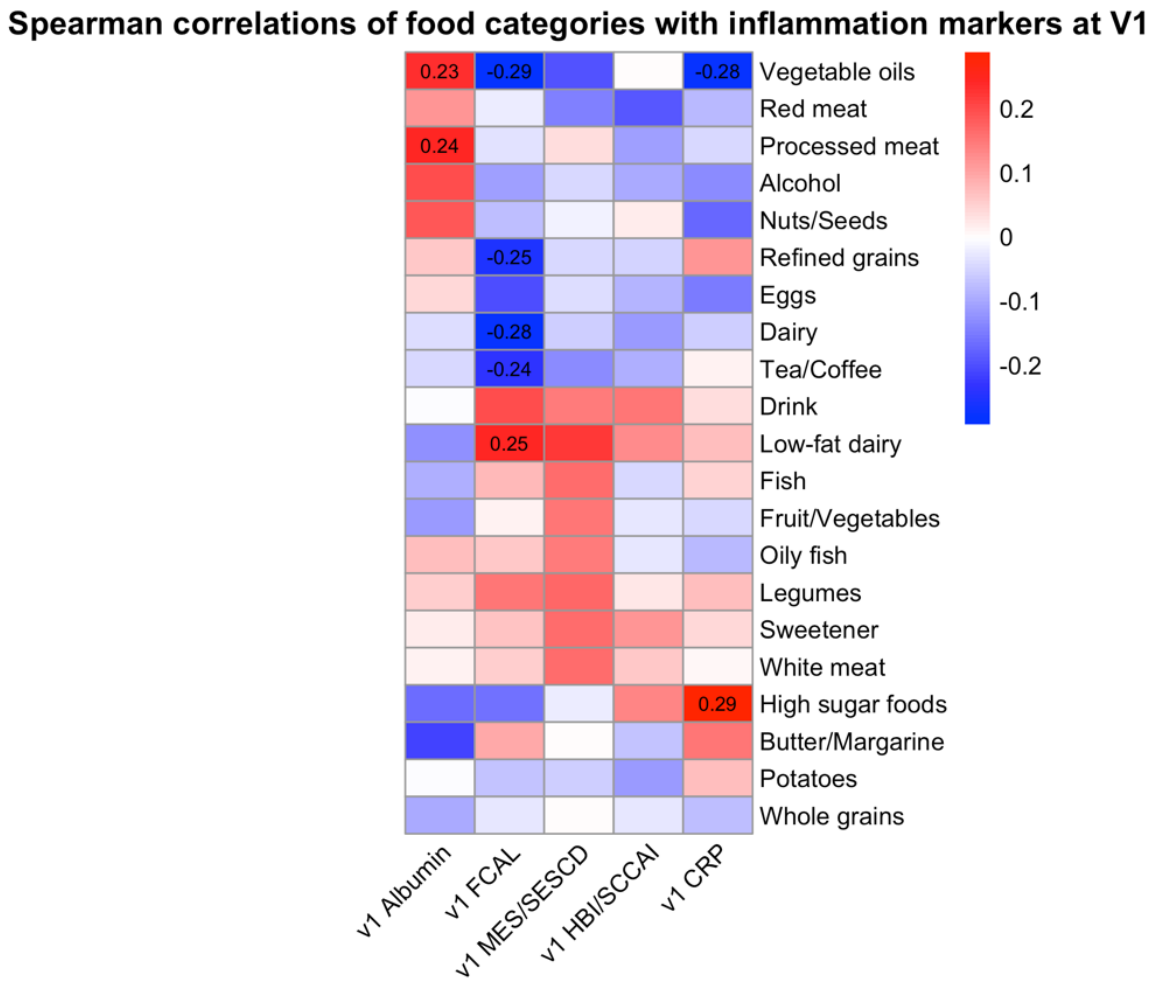

Figure 11: Heatmap of spearman correlations of food categories with inflammation markers at baseline. rho is shown just in case p<0.05.

NUTRIENTS

When comparing nutrients consumption in relation to disease activity based on albumin just alcohol showed a significant difference (WILCOXON p<0.05), beign consumed more by inactive patients (*Figure 12*).

While the comparisons of nutrients intake in relation to disease activity based on FCAL, CAS, CRP, and endoscopic scores showed no significant differences (WILCOXON and KRUSKAL p>0.05) (*Supplementary tables S15; S16; S17; S18)*.

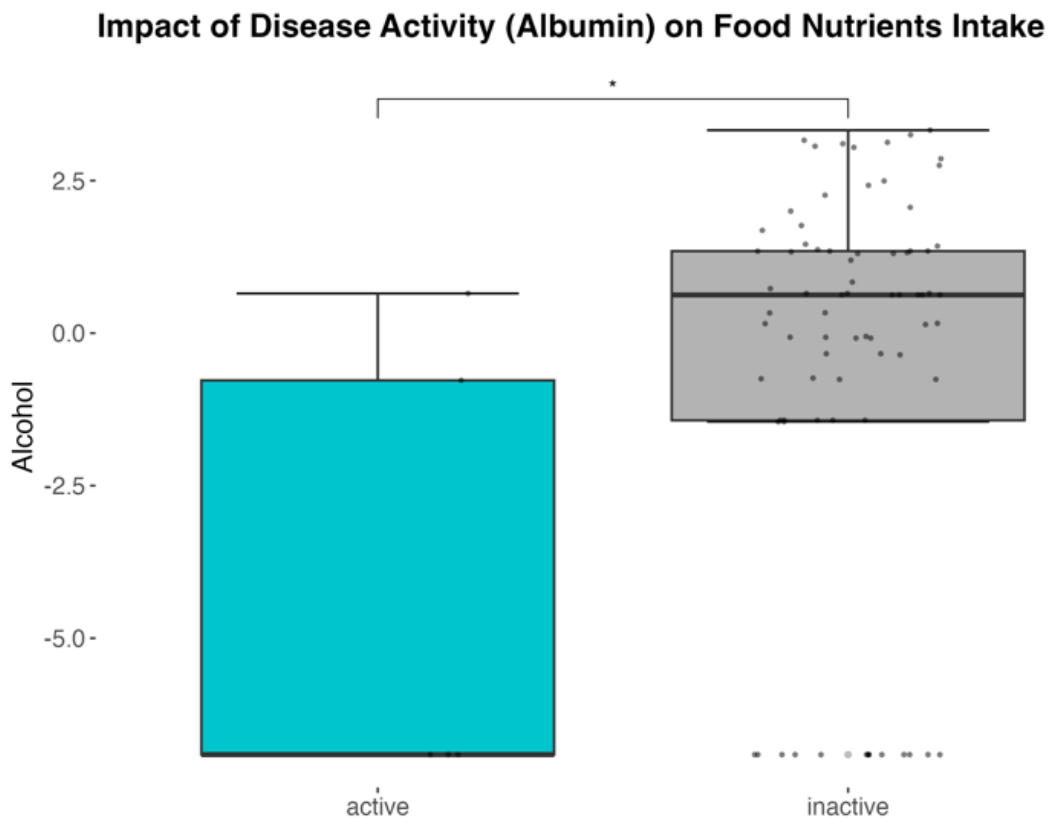

*Figure 12: Comparison of nutrients consumption in relation to disease activity based on serum levels of albumin. *p<0.05.*

During correlations analyses between nutrients and inflammation markers at V1, the only associations that stood out was between sugar and albumin levels (SPEARMAN CORRELATION $p<0.05$), which were negatively correlated, indicating that the higher its intake the lower albumin levels will be (*Figure 13*).

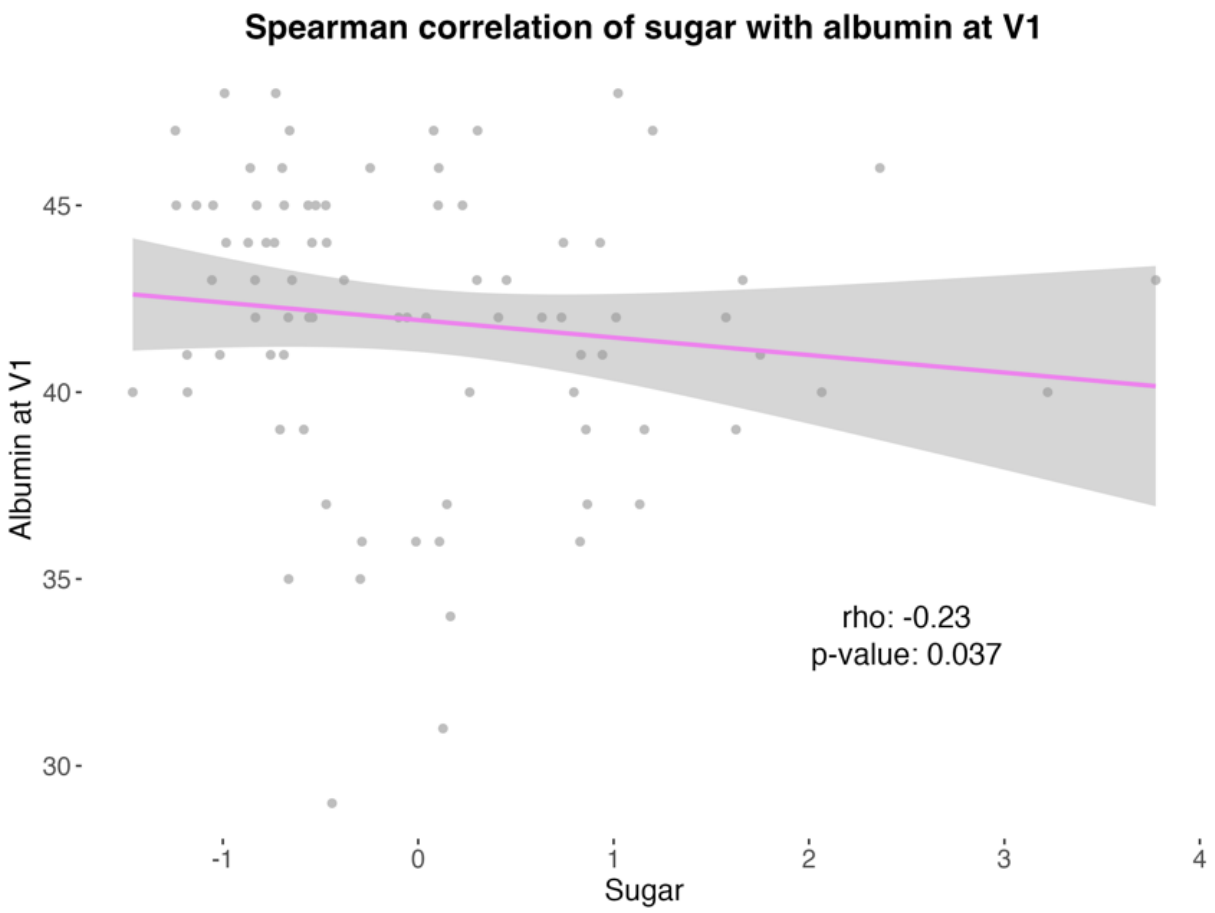

Figure 13: Spearman correlations of nutrients with inflammation markers at baseline.

DIETARY SCORES

When comparing dietary scores in relation to disease activity based on FCAL just EDII showed a significant difference (WILCOXON $p<0.05$), beign higher for inactive patients (*Figure 14*).

While the comparisons of dietary scores in relation to disease activity based on CAS, CRP, albumin, and endoscopic scores showed no significant differences (WILCOXON, KRUSKAL $p>0.05$) (*Supplementary tables S19; S20; S21; S22)*.

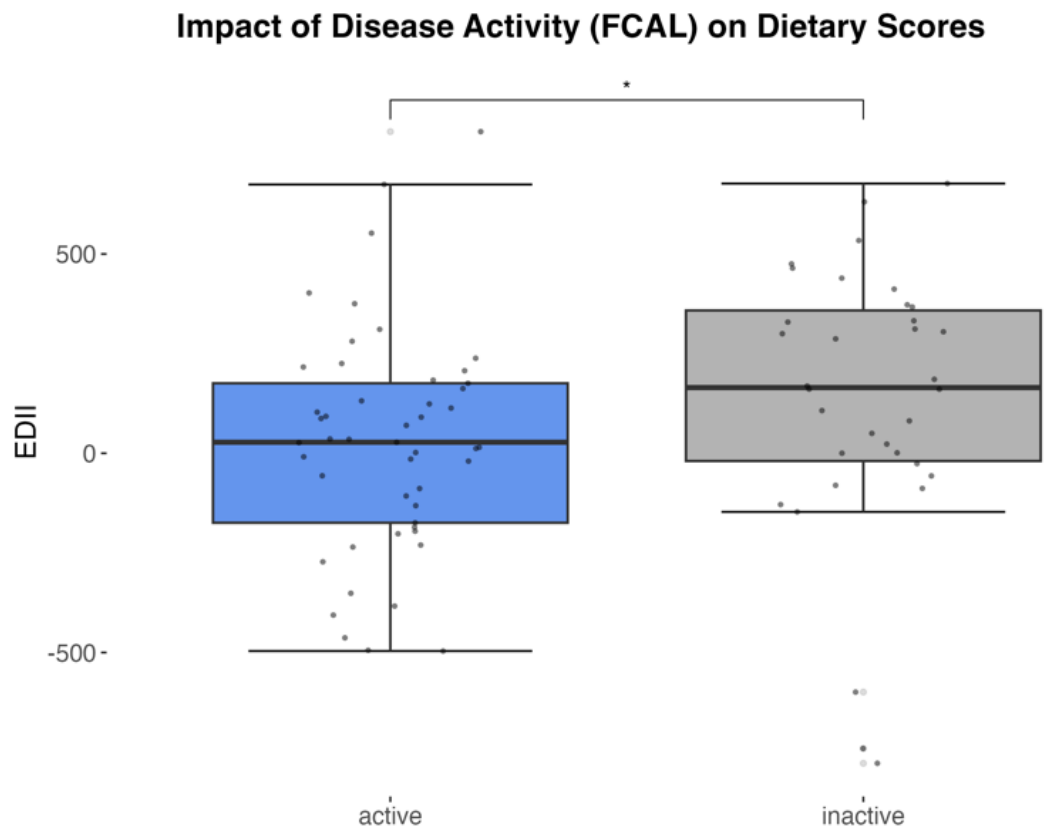

*Figure 14: Comparison of dietary scores in relation to disease activity based on FCAL. *p<0.05.*

During correlations analyses between dietary scores and inflammation markers at V1, the only associations that stood out was between EDII and FCAL levels (SPEARMAN CORRELATION $p<0.05$), which were negatively correlated, indicating that the higher the score is the lower FCAL levels will be (*Figure 15*).

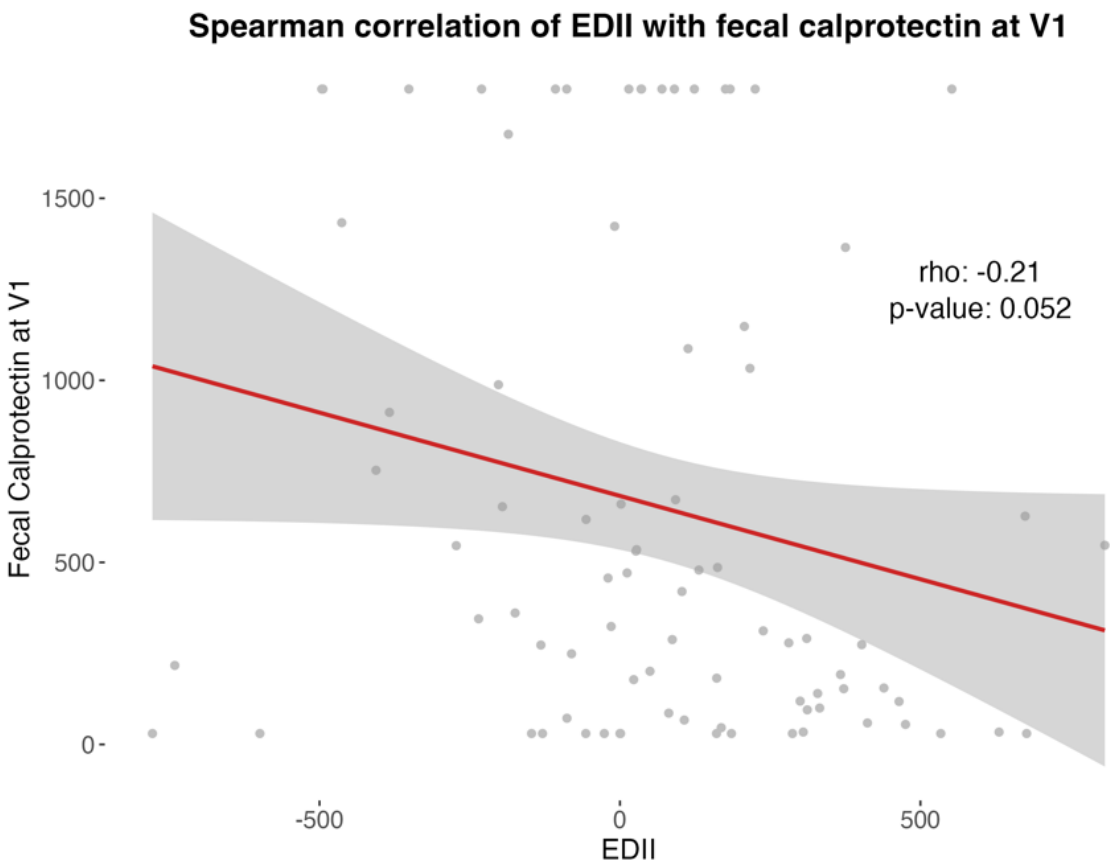

Figure 15: Spearman correlations of dietary scores with inflammation markers at baseline.

ASSESSING DIETARY DIFFERENCES BY DISEASE ACTIVITY AT V3 AND TREATMENT RESPONSE IN IBD PATIENTS

Next, we compared the diets of patients in different response categories (remission, non-responder, responder, super-responder), to explore potential dietary differences among patients with IBD in relation to treatment response. These comparisons were assessed through changes in FCAL levels and clinical response status throughout the study.

The first two axes of a PCA of dietary intake across 149 food items accounted 35.6% of the variation. Treatment response, as indicated by disease activity based on FCAL changes at V1, V2, and V3 explained 14% of the variation in dietary composition, but only with a relaxed p-value cutoff (PERMANOVA $p<0.1$; *Figure 16a*). When assessing dietary composition with respect to food category consumption, the first two axes of the PCA capture 75.6% of the variation. Treatment response, as indicated by disease activity based on FCAL changes at V1,

V2, and V3 explained 16% of the variation in dietary composition, considering a more relaxed p-value cutoff (PERMANOVA $p<0.1$; *Figure 16b*). In contrast, CAS explained only 5% of the variation, always taking into consideration a more relaxed p-value cutoff (PERMANOVA $p<0.1$; *Figure 16c*). Finally, when examining the overall daily nutrient intake of patients, the first two axes of the PCA represented 43.4% of the variation. Here, treatment response, as indicated by disease activity based on FCAL changes at V1, V2, and V3 explained 9% of the variation in dietary composition, but only with a relaxed p-value cutoff (PERMANOVA $p<0.1$; *Figure 16d*), while CAS explained 25% of the variation, achieving statistical significance (PERMANOVA $p<0.05$; *Figure 16e*). These findings indicate an association between treatment response and patients' dietary patterns.

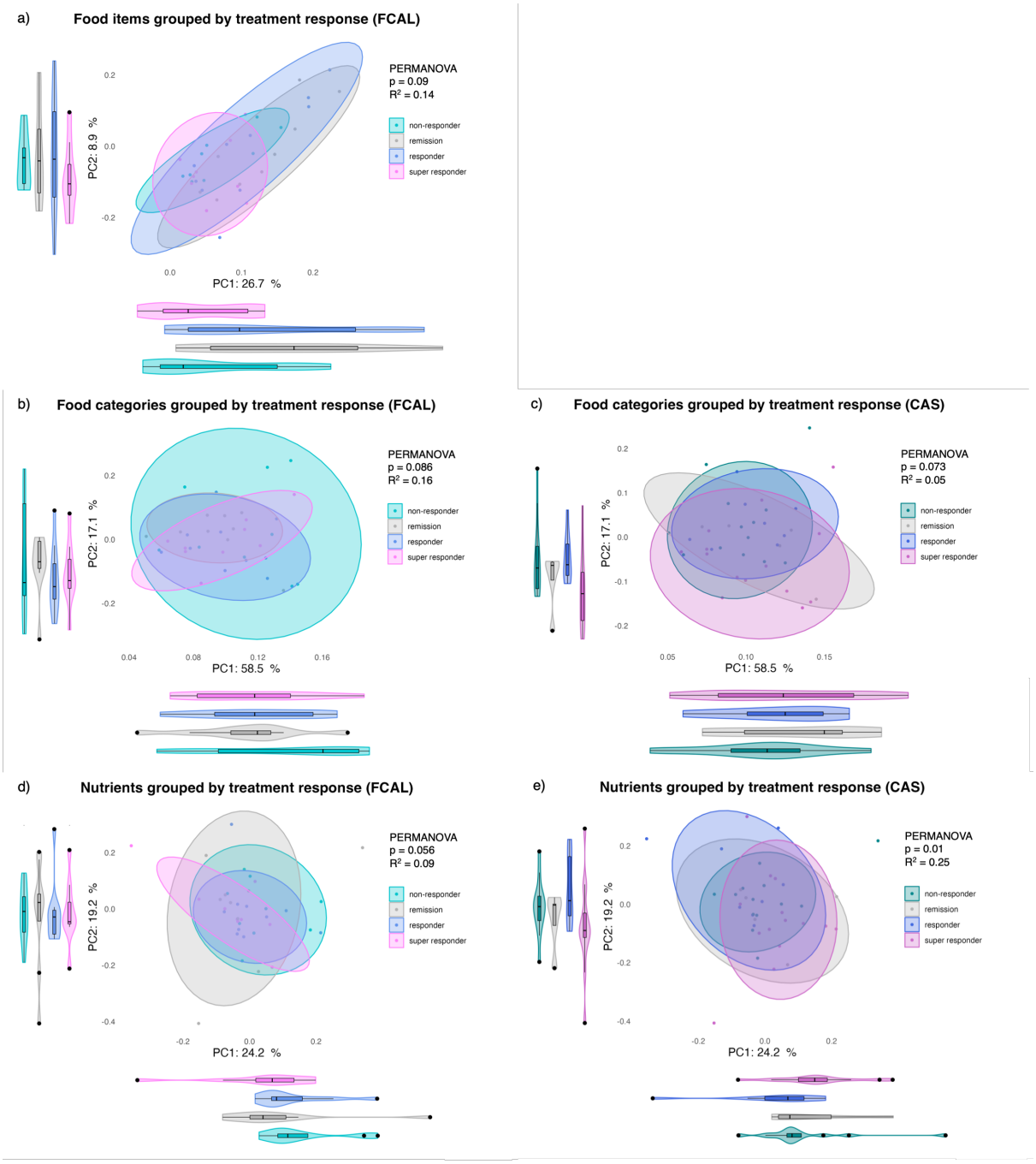

Figure 16: PCA of monthly intake of food items grouped by disease activity based on changes in FCAL in V1, V2, and V3 (a), PCA of monthly intake of food categories grouped by disease activity based on changes in FCAL in V1, V2, and V3 (b), and combined differences of HBI and SCCAI between V1 and V3 (c), PCA of nutrients intake grouped by disease activity based on changes in FCAL between V1 and V3 (d), and combined differences of HBI and SCCAI between V1 and V3 (e).

FOOD ITEMS

Afterwards, we evaluated the intake of specific food item among patients belonging into different response categories (remission, non-responder, responder, super-responder), in relation to treatment response based on clinical response and identified nine items showing significant differences (KRUSKAL $p<0.05$). Super responders had a higher median intake of brown bread and wholemeal pasta, while their consumption of white bread, sponge puddings, sweets and mints, and jam and honey was lower. Non-responders consumed more light salad cream, whereas melon intake was lower among them. Lastly, patients in remission showed a higher median intake of tinned meat cream soups, and a lower jam and honey consumption than responders (*Figure 17*).

In contrast, when examining individual food item consumption in relation to treatment response based on FCAL changes from V1 to V3, no significant differences were observed (*Supplementary table S23*).

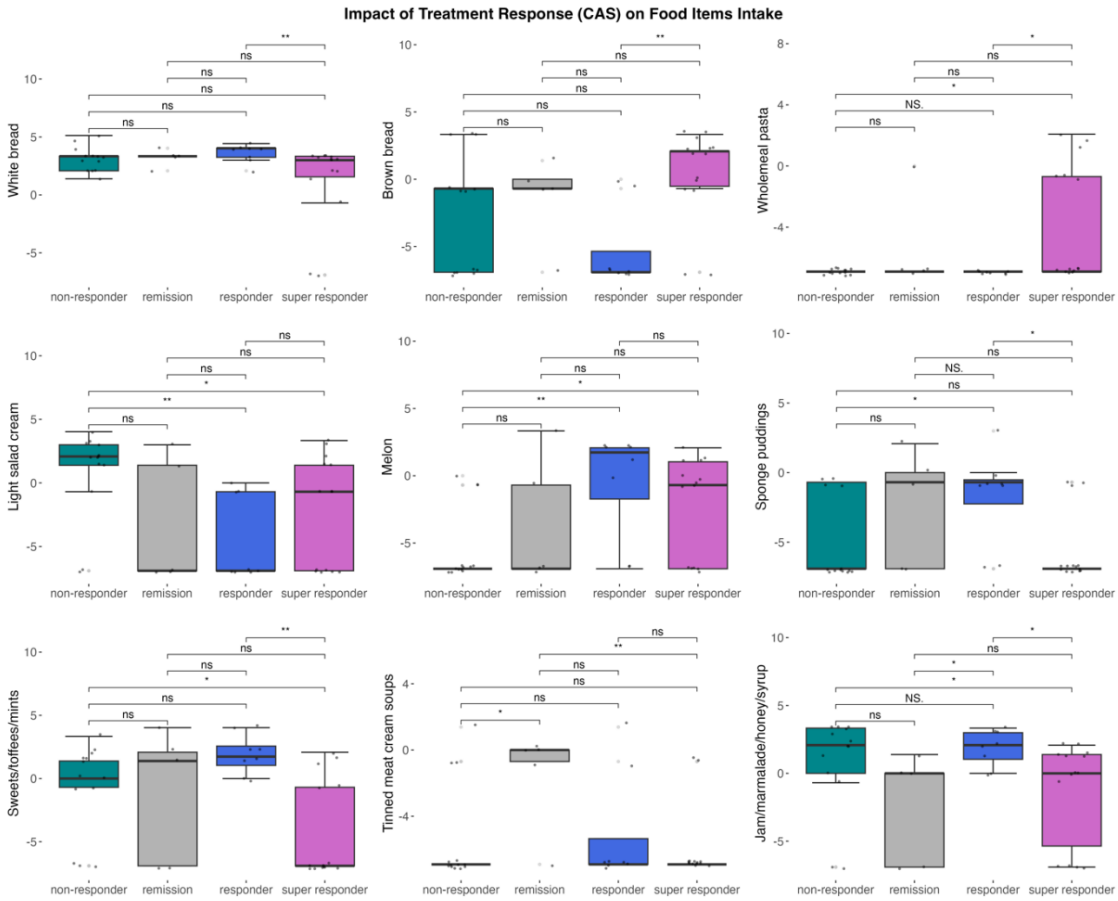

*Figure 17: Comparison of food items consumption in relation to treatment response based on clinical response. ns p>0.05; *p<0.05; **p<0.01.*

In correlation analyses between individual food items and inflammation markers at V3 and treatment response, several associations stood out (SPEARMAN CORRELATION $p<0.05$).

FCAL levels at V3 were negatively associated with the consumption of wheat-free bread, French dressings, and wholemeal bread, while they showed a positive association with dried lentils or beans, fizzy drinks, plain poultry, white rice, white pasta, margarine, and sweetcorn. CAS levels at the third visit were negatively linked with wholemeal pasta and marmite intake, while they showed a positive association with pizza, jam, light salad cream, and herbal tea consumption. CRP levels at V3 showed a negative association with apples, broccoli, and pork intake, while a positive one with beetroot and sugar consumption. Albumin levels at V3 were positively linked with the consumption of sugar-coated cereals, cream, and oranges.

While examining changes in FCAL levels between V1 and V3, wholemeal bread consumption was positively correlated, whereas steak and butter intake were negatively correlated. Differences in FCAL levels between V1 and V2 were positively associated with high-fiber cereals, instant coffee, low-fat cheddar, probiotic yoghurts, wholemeal bread, and light butter, while butter, parsnips, and shellfish showed negative associations. The consumption of canned fruit, white fish, parsnips, breaded fish, sweets and mints, bacon, and white pasta was positively associated with changes in FCAL between V2 and V3.

Changes in albumin levels between V1 and V3 were positively associated with the consumption of canned fruit, sponge puddings, milk puddings, pancakes, pizza, and spirits.

Differences in CAS between V1 and V3 showed a positive association with the intake of melon, brown bread, wholemeal pasta, peaches, and plums, and a negative association with roasted or fried potatoes and light salad cream.

Finally, the consumption of coleslaw, beetroot, spirits, pickles, and chutney was negatively associated with changes in CRP levels between V1 and V3 (*Figure 18*).

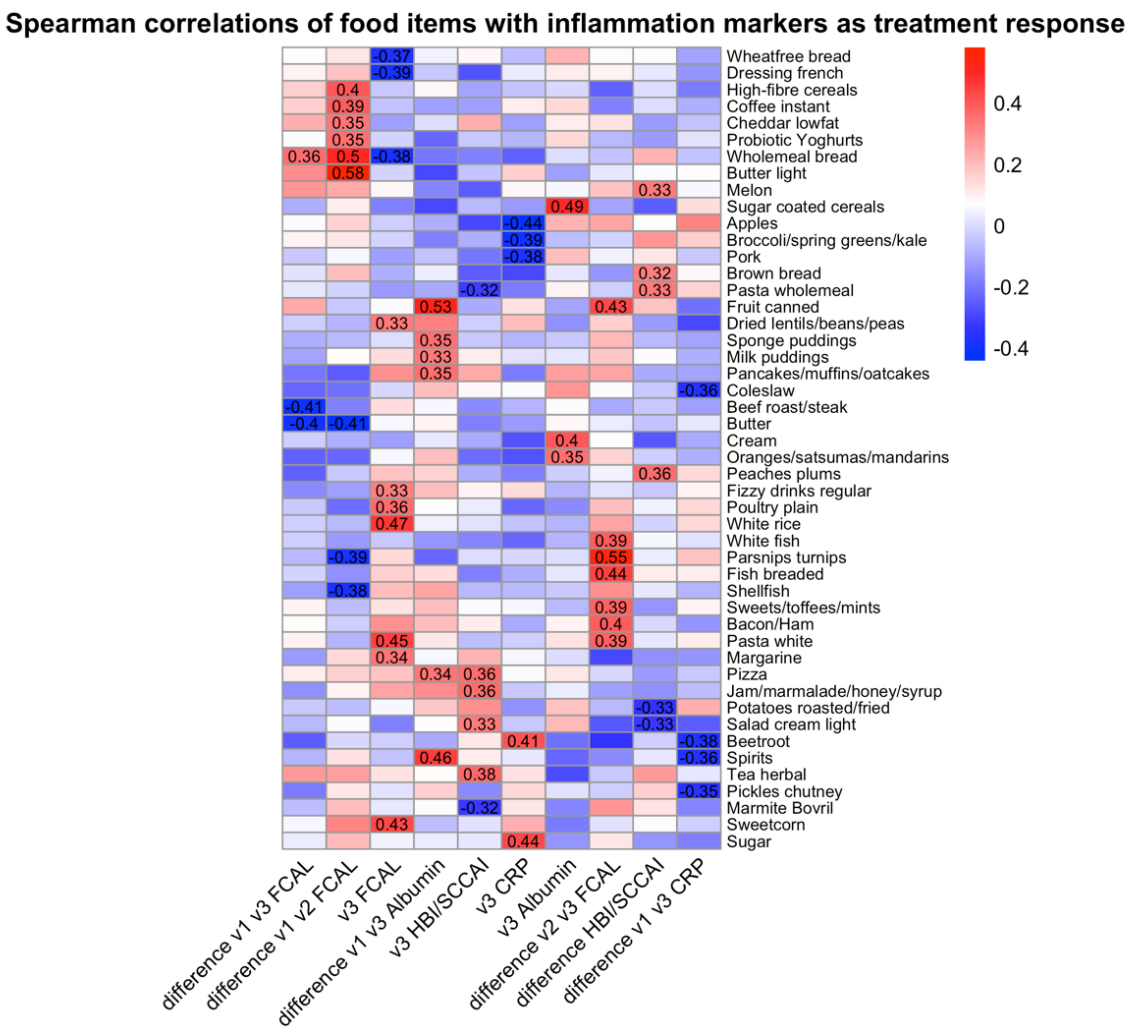

Figure 18: Heatmap of spearman correlations of food items with inflammation markers as treatment response and at V3. Food items with at least one significant results are presented. rho is shown just in case p<0.05.

FOOD CATEGORIES

When comparing food category consumption in relation to treatment response, based on both clinical response and FCAL changes from V1 to V3, no significant differences were observed (*Supplementary tables S24; S25*).

In terms of correlations with inflammation markers at V3 and treatment response, a few associations stood out (SPEARMAN CORRELATION, p<0.05).

The drink category was positively associated with changes in FCAL between V1 and V2, changes in FCAL between V1 and V3, and CAS scores at V3. Dairy consumption, on the other hand, was negatively associated with changes in FCAL between V1 and V3, as well as between V2 and V3.

Differences in CAS between V1 and V3, albumin levels at V3, and differences in FCAL between V2 and V3 showed positive association with whole grains, processed meat, and fish, respectively (*Figure 19*).

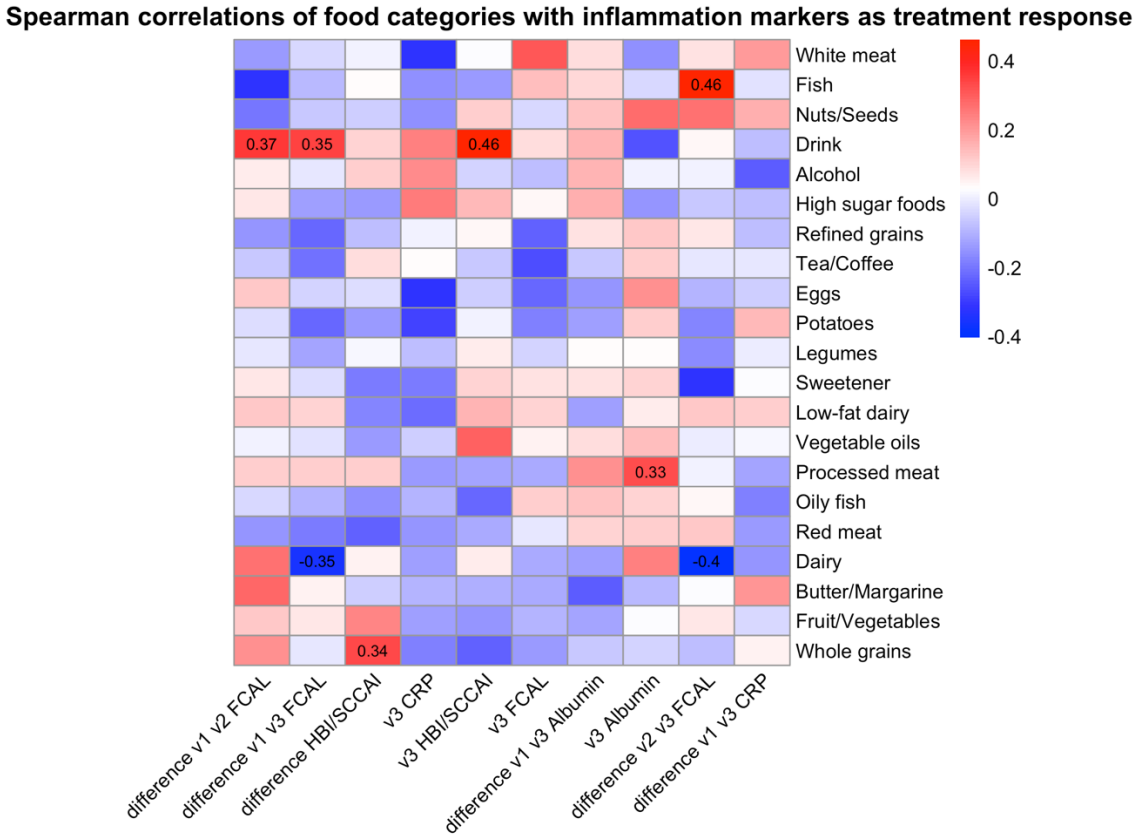

Figure 19: Heatmap of spearman correlations of food categories with inflammation markers as treatment response and at V3. rho is shown just in case p<0.05.

NUTRIENTS

For nutrient intake, the results were similar: no significant differences were found in relation to treatment response based on clinical response or FCAL changes from V1 to V3 (*Supplementary table S26; S27*).

However, in correlation analyses with inflammation markers at V3, only protein intake showed a notable association: it was negatively correlated with CRP levels at V3 (SPEARMAN CORRELATION $p<0.05$), suggesting that as protein consumption increases, CRP levels tend to decrease (*Figure 20*).

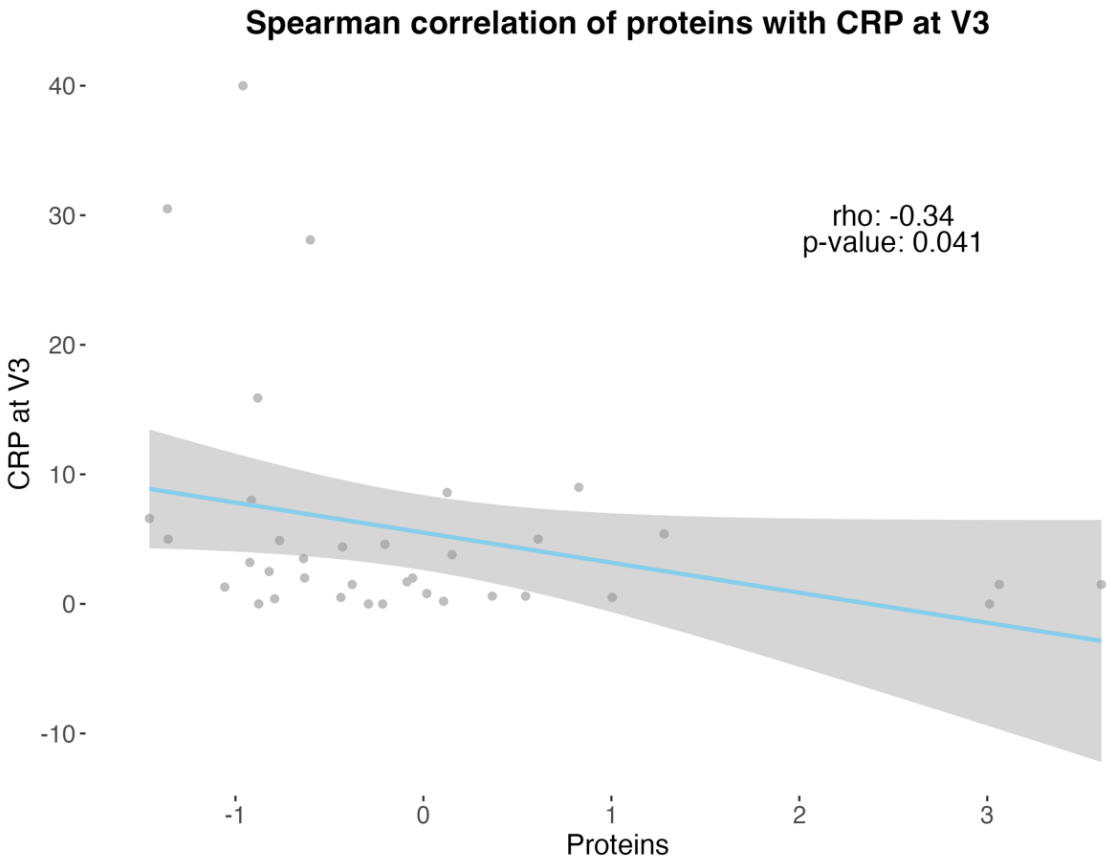

Figure 20: Spearman correlations of nutrients with inflammation markers as treatment response and at V3.

DIETARY SCORES

When comparing dietary scores in relation to treatment response based on clinical response, HFD and HEI scores showed significant differences (KRUSKAL $p<0.05$). In both

cases, super responders manifested higher scores, suggesting they followed a more diverse and healthier diet (*Figure 21a*).

In contrast, when comparing dietary scores in relation to treatment response based on FCAL changes from V1 to V3, only EDII showed a significant difference (KRUSKAL p<0.05). Patients in remission had higher EDII score, indicating a more pro-inflammatory diet (*Figure 21b*).

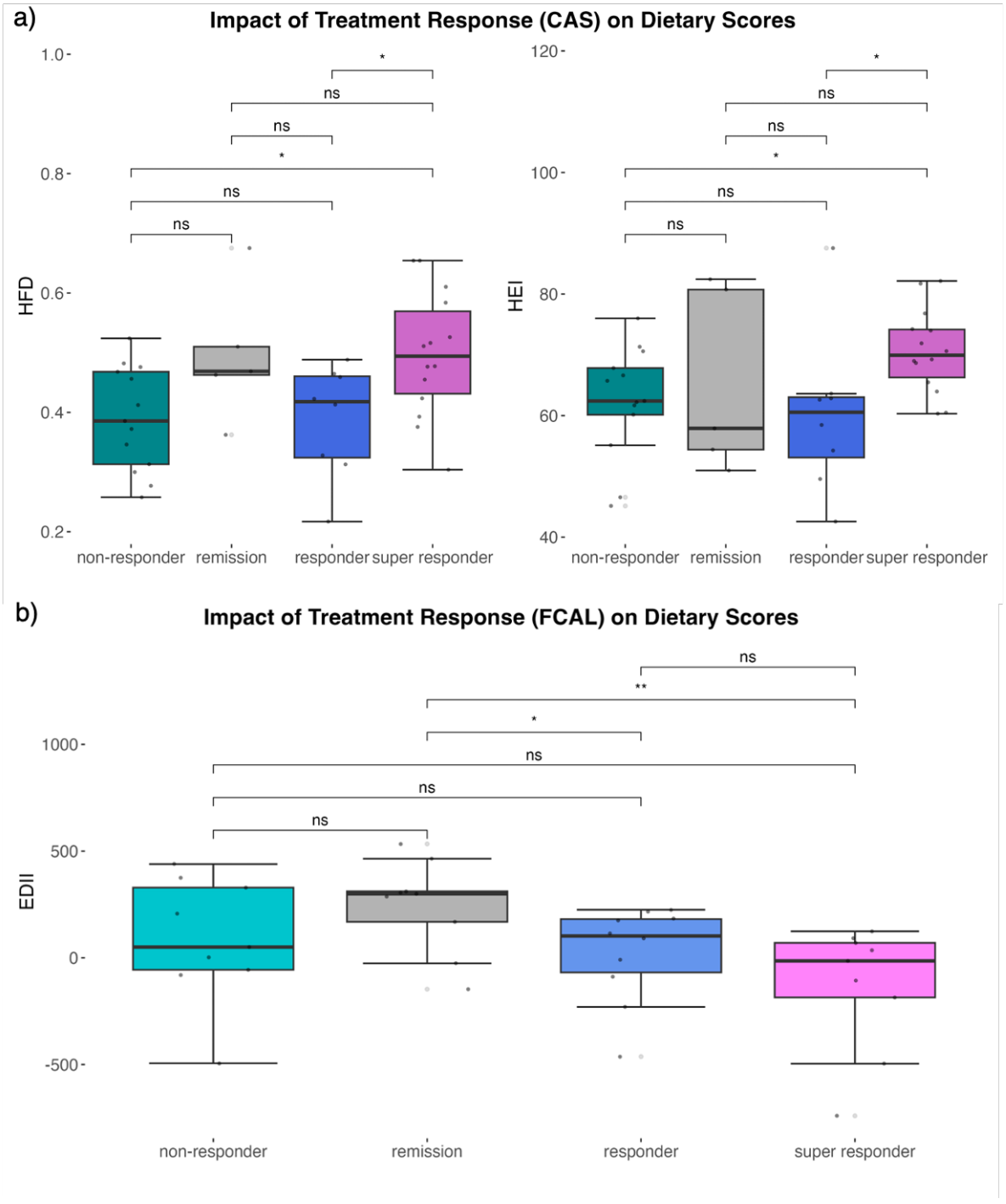

*Figure 21: Comparison of dietary scores in relation to treatment response based on clinical response (a), comparison of dietary scores in relation to treatment response based on FCAL levels between V1 and V3 (b). ns p>0.05; *p<0.05; **p<0.01.*

When examining correlations with inflammation markers at V3 and treatment response, some associations stood out (SPEARMAN CORRELATION, $p<0.05$).

EDII score was negatively correlated with differences in CRP levels between V1 and V3, and differences in FCAL levels between V1 and V2. While HFD was negatively linked with CAS levels at V3, but it showed a positive correlation with the differences in CAS between V1 and V3. These results suggest that higher inflammation score (EDII) lead to lower response, while having a better quality diet (HFD) is related to a bigger reduction within inflammation (*Figure 22*).

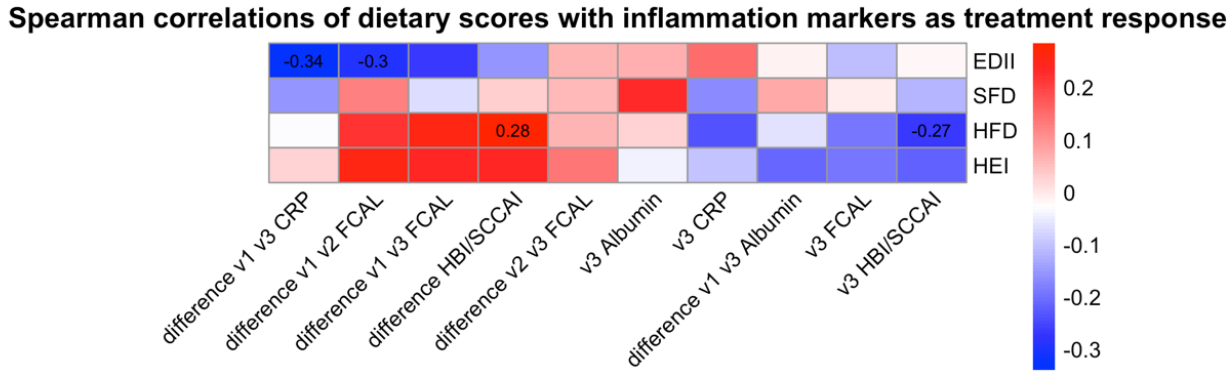

Figure 22: Heatmap of spearman correlations of dietary scores with inflammation markers as treatment response and at V3. rho is shown just in case p<0.05.

DISCUSSION

Inflammatory Bowel Disease (IBD) is a chronic condition with a high prevalence worldwide. It affects millions of people causing significant psychosocial and economic burdens[1,2,9,14–18]. The two main subtypes are Ulcerative Colitis (UC) and Crohn's Disease (CD), which differ in manifestation, severity and complications[1,2]. IBD treatments have unquestionably improved over the years, however the multifactorial etiology of this disease poses challenges in understading its progression and management[8]. Diet, among other factors, has emerged as a pivotal regulator of gut health and inflammation, linking Western dietary patterns with increased IBD risk and progression, and other dietary intervention like mediterranean, semi vegetarian, low FODMAP, exclusive enteral nutrition, and Crohn's disease exclusion diets have shown promising results in mitigating symptoms and promoting remission[32–38,47,57,61,73,80].

Considering the growing evidence on the role of diet in IBD management, this thesis' goal was to explore dietary patterns and how they associate with treatment outcomes and disease activity in Irish patients diagnosed with IBD, further investigating which dietary score best reflects diet quality and its association with IBD activity and treatment response. This analysis included data from the ongoing AUGMENT clinical study. Since the study was still in progress and not all results were available at the time, most results lost statistical significance after p-values were adjusted for multiple testing, indicating potential false positive in the results.

Considering dietary differences in patients with UC and CD, no significant differences were seen in the overall dietary composition. However patients with UC were found to consume more of some specific food items, such as potato salad and vegetarian lasagna, which remained significant even after adjustment for multiple comparisons (*Figure 3*). It is possible that these specific foods reflect cultural or symptomatic dietary choices rather than patterns driven by the disease. Not many studies specifically compare certain food items across these diagnoses, on the other hand it has been shown that food choices may be influenced by symptoms, which can vary between UC and CD. Indeed certain dietary choices in patients with UC may be influenced by the differences in disease location and its symptoms[4]. This

analysis suggests that possible dietary differences among patients with UC and CD could be determined by individual or regional habits, rather than disease pathology.

While no significant dietary differences were observed among patients with CD subtypes, some differences were noted across patients with UC subtypes, specifically when analyzing the overall dietary composition in relation to food categories (*Figure 5*). The captured variation reflects dietary differences among patients with different UC extents. Patients who were diagnosed with proctitis showed a higher consumption of wholemeal pasta, cottage cheese, green salad, herbal tea, leeks, and fresh vegetable soup. In contrast, patients diagnosed with pancolitis consumed fewer, and showed a higher intake of leeks and green salad (*Figure 6a*). Furthermore, dietary scores like HFD and HEI, which indicate greater diversity and healthier diets, were significantly higher in patients with proctitis, even after adjusting for multiple testing (*Figure 6b*). Proctitis is often associated with milder symptoms than pancolitis, possibly allowing more diverse and fiber-rich dietary choices. Indeed patients that have been diagnosed with acute forms of UC, like pancolitis may tend to avoid this type of dietary choice due to symptoms aggravation[4]. These associations among UC extent show how a customize diet could be needed on disease extent.

Remarkable dietary differences were observed between patients with active and inactive disease at baseline, comprising individual food items, food categories, nutrients, and dietary scores. Patients with active disease tended to consume more foods such as white rice, white pasta, low-fat cheddar, broccoli, milk puddings, and herbal tea, potentially exhibiting dietary choices driven by symptoms, also favoring low-fat and easily digestible options. In contrast, patients with inactive disease had higher intakes of foods such as wholemeal bread, wholemeal pasta, nuts, plain biscuits, and certain fruits, implying greater dietary diversity and higher intake of fiber-rich foods intake (*Figure 8*). While food categories and nutrients displayed fewer significant differences. We can still see that patients with active disease tend to choose low-fat dairy, whereas patients with inactive disease showed sligtly higher consumption of refined grains, vegetable oils, and alcohol (*Figure 10, Figure 12*). Some correlations between inflammation markers and dietary components were found, providing additional understanding into probable mechanisms that links diet and disease activity. The consumption of refined grains like white pasta and white rice, regular fizzy drinks, low-fat dairy, and high sugar foods was positively associated with higher levels of FCAL, CRP, and

clinical or endoscopic scores, implying a possible link to inflammation. In contrast, fruits and vegetables like apples, oranges, leeks, frozen fruits, and mushroom, beef burger, lamb, and butter are linked to lower levels of FCAL, CRP, endoscopic and clinical scores, or higher levels of albumin, indicating lower inflammation (*Figure 9*). It is possible to notice some patterns which show that refined grains could be linked to higher inflammation, while high fiber food may be associated with lower inflammation. Interestingly, the EDII, that captures the inflammatory potential of the diet, was found to be higher in patients with inactive disease (*Figure 14*). This result contrasts with expectations, as we would anticipate the EDII to be higher in patients with active disease, given its focus on dietary inflammation. Additionally, the EDII was aligned with lower FCAL levels, contrary to the expectation that a higher EDII would correspond with elevated FCAL levels, indicative of increased inflammation. These unexpected findings suggest that the EDII may reflect broader dietary patterns associated with long-term disease stability rather than acute inflammation control (*Figure 15*). These findings align with prior research indicating that dietary patterns can influence inflammation and disease progression. It has been suggested that high-fiber and low-fat diets are associated with better outcomes, while high sugar and processed food may worsen the progression of the disease [34–38]. On the other hand some correlations show contrary results, reflecting the complexity of dietary impacts on gut inflammation, likely influenced by individual disease states and microbiota composition. Active disease states may force patients to ingest specific foods due to tolerability or symptom alleviation, and simple foods like white rice and broccoli, which are more common in patients with active disease, could be beneficial or just be easier to digest during flare-ups. Overall, these findings underline the importance of diet in the managemenet of IBD, strengthening the necessity of customized dietary interventions considering individual patient tolerances and disease states as well.

Treatment response in patients with IBD showed limited variation considering food categories and nutrient across responses groups, while significant tendencies were seen among individual food items, and dietary scores, specifically for super responders and remission groups. Super responders, who are characterized by significant clinical improvement, showed to have an higher consumption of brown bread, and wholemeal pasta, while consuming less white bread, and processed sweets, sush as jam, honey, and mints (*Figure 17*). This suggests that diets rich in whole grains, and lower in processed sugars

may be beneficial favoring better treatment outcomes. Furthermore, dietary scores contextualized these findings as well, as higher HFD and HEI scores in super responders underline the possible benefits of dietary diversity and overall diet quality (*Figure 21a*). In contrast, patients that showed to be in remission had higher EDII score, which is indicative of pro-inflammatory diet, potentially reflecting broader dietary patterns that allow for disease stability (*Figure 21b*). Correlations with inflammatory markers displayed additional dietary influences. For instance the consumption of non-refined grains like wholemeal bread, brown bread, and whole meal pasta, light butter, white fish, highe-fiber cereals, legumes, fruits and vegetables like melon, oranges, peaches, sweetcorn, and parsnips, and non-alcoholic drinks was positively correlated with reduction in inflammation markers, suggesting a higher treatment response, therefore an anti inflammatory effects. While the intake of dressing like French dressing, and light salad cream, and beef, butter, spirits, chutney, marmite, and dairy products was negatively correlated with a reduction in inflammatory markers over time, indicating lower treatment response (*Figure 18, Figure 19*). It was noticed that CRP levels at V3 were negatively associated with protein-rich foods, suggesting an anti inflammatory effect (*Figure 20*). Reinforcing the potential role of inflammatory foods in poorer outcomes. Finally, dietary scores like EDII showed to be negatively correlated with FCAL changes over time indicating that higher inflammation can lead to lower response, while HFD was positively correlated with the difference in clinical scores, indicating that a better quality diet can be related to higher responses (*Figure 22*). These findings align with prior studies which link quality of diet with inflammation and treatment efficacy in patients with IBD. Previous research has shown how diets rich in whole grains, fiber, and healthy fats, like the Mediterranean diet, can support intestinal health and reduce inflammation. On the other hand, diets rich in refined sugars, processed foods, and saturated fats, like the Western diet, are associated with elevated inflammatory markers and worse clinical outcomes [32,34–38,124]. The fact that a higher HFD aligned with a better response underscore that a diverse diet can support gut microbiota diversity, which is crucial in IBD management. As mentioned, super responder showed a higher consumption of whole grains and a lower intake of processed foods, which may actively contribute to amplify treatment response via the modulation of gut inflammation and the promotion of a healthier microbiota. Conversely, non responders may be inclined toward processed or refined foods due to symptom-driven dietary choices. Patients in remission showed a higher EDII, which could indicate that pro-inflammatory

dietary patterns may be less impactful when the disease is stable. Additionally, the associations between dietary components and certain inflammation marker could also suggest that dietary choices may be linked to specific inflammatory pathways, influencing treatment response in various ways. These findings underline the complicated interaction between diet and treatment response in IBD, reinforcing the importance of dietary interventions that focus on diverse, minimally processed, and wholegrain rich foods to enhance clinical response and reduce inflammation. Dietary scoring systems like HFD and HEI could be helpful for guiding personalized nutrition strategies in IBD care.

The proposed analysis provides important insights concerning the relationship between dietary patterns, disease activity, and treatment response in Irish patients diagnosed with IBD, highlighting the pivotal role of diet in the management of this disease. The findings underscore some dietary differences between active and inactive disease states, UC extent, and treatment response groups, pointing out the possible benefits of diets that are characterized by diversity, whole grain and high fiber foods, and the adverse effects of processed and refined foods. As for dietary scores, HFD and HEI seem to be promising tools to assess diet quality. These results align with prior research, underscoring the need of personalized dietary intervention in order to improve disease management and treatment outcomes.

A consideration need to be made, while looking at the daily calories intake among the different BMI categories they didn't align with the expectations, patient who belonged in overweight or obesity categories were expected to have a higher caloric intake, while in this case they appeared to eat less, therefore they probably report less of what they actually eat (*Supplementary Figure 1*). This could be due to bias, like body image issue and the possibility to feel judged, or to the fact that symptom severity may contribute to a reduced food intake. This highlights a limitation of FFQ in capturing accurate dietary data, particularly in populations prone to reporting bias, leading to possible inaccuracies in the results.

This analysis has several limitations. The preliminary nature of it, meaning that not all the data from the AUGMENT clinical study were available, potentially limited the statistical power of the findings. Indeed many results lost significance after the adjustment for multiple testing, increasing the risk of false positives. Additionally, the FFQ used to assess patients' dietary intake could be exposed to reporting bias, specifically in overweight and obese

patients, leading to possible inaccuracies. Finally, the variability in individual disease states, different symptoms, and microbiota composition can complicate the interpretation of the possible findings.

Future research should validate these results once the AUGMENT clinical study is complete, including the role of gut microbiota in the observed dietary effects. Further improvements of dietary scores like HFD and HEI could be helpful in the development of personalized nutritional interventions for patients diagnosed with IBD.

CONCLUSION

The proposed analysis provides important insights concerning the relationship between dietary patterns, disease activity, and treatment response in Irish patients diagnosed with IBD, highlighting the pivotal role of diet in the management of this disease. Preliminary findings suggest that patients which have different disease extent, activity states, and treatment responses exhibit noticeable dietary choices and nutrient profile, possibly reflecting symptom driven adaptations or potential effects on inflammation and clinical outcomes. Higher dietary scores like HFD and HEI, which indicate greater dietary diversity and adherence to healthier dietary patterns, were linked to better treatment outcomes, underscoring the importance of diet quality in IBD care.

However, since this analysis is based on data from an ongoing clinical study, the results should be carefully interpreted and validated once the study is complete. Future studies should focus on improving dietary scoring systems and investigate the mechanism between dietary patterns, gut health, and therapeutic efficacy to develop personalized nutritional strategies for IBD management.

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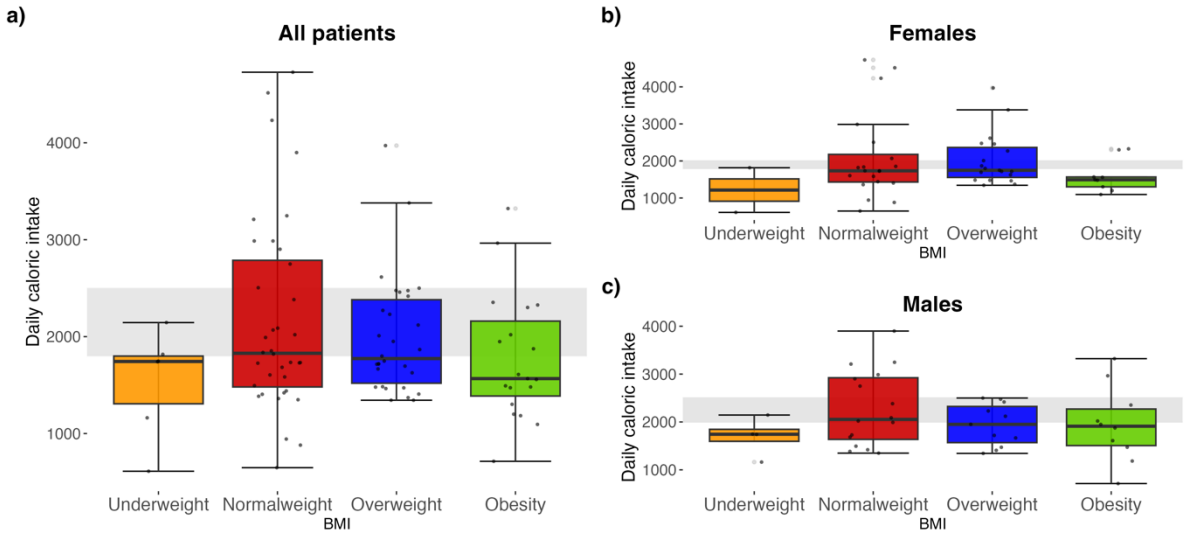
Finally, I am deeply grateful to my family for their unconditional support in every decision I make.

SUPPLEMENTARY FIGURES



Supplementary Figure 1: Comparison of daily caloric intake within BMI categories. (a) Comparison of daily caloric intake within BMI categories in all patients. (b) Comparison of daily caloric intake within BMI categories just in females. (c) Comparison of daily caloric intake within BMI categories just in males. The grey interval represents the recommended daily caloric intake.

SUPPLEMENTARY TABLES

PERMANOVA - FOOD ITEMS

	Df	SumOfSqs	R2	F	Pr(>F)	padj
dx_ren_dx	1	0.032770681	0.008131088	0.737797003	0.8421	0.943888889
dx_ren_crohns_dis_location	2	0.061309293	0.02406246	0.641049179	0.9876	0.9876
dx_ren_ulc_col_extent	2	0.090294468	0.064736259	1.142082415	0.2251	0.643142857
pat_sex	1	0.063764658	0.015821339	1.446810969	0.0774	0.4485
v1_lab_faecal_calprotectin	1	0.046953948	0.012635087	1.036538775	0.3866	0.7732
combined_CAS	1	0.052663137	0.01306682	1.191584027	0.2222	0.643142857
combined_ENDO	1	0.038660845	0.011558332	0.853624738	0.6501	0.943888889
v1_lab_activity_150	1	0.042012404	0.01130534	0.926203611	0.5454	0.943888889
v1_lab_activity	1	0.033189624	0.008931172	0.729944153	0.8495	0.943888889
v1_clin_activity_b	1	0.036107612	0.00895905	0.813603601	0.7199	0.943888889
v1_endo_activity_b	1	0.048060325	0.01436847	1.064189114	0.3455	0.7732
v1_crp_activity	2	0.083746716	0.024759898	0.926680802	0.5986	0.943888889
v1_albumin_activity	1	0.08623431	0.023680441	1.940384453	0.0175	0.295
fcal_responder_100_2	3	0.180399807	0.135444837	1.253313545	0.0897	0.4485
fcal_responder_103_2	3	0.140919842	0.08595124	1.034368931	0.377	0.7732
clinical_response2	3	0.115828585	0.065757854	0.844635673	0.7824	0.943888889
diff_v1_v3_fcal	1	0.055319956	0.033741301	1.2221836	0.2075	0.643142857
diff_v1_v2_fcal	1	0.080516183	0.05177415	1.692633303	0.0295	0.295
diff_v2_v3_fcal	1	0.0264547	0.01897507	0.541578444	0.957	0.9876
diff_hbi_sccai	1	0.031703091	0.017998383	0.696473946	0.8135	0.943888889

S 1: PERMANOVA based on dietary composition data, using food items as input variables.

PERMANOVA - FOOD CATEGORIES

	Df	SumOfSqs	R2	F	Pr(>F)	padj
dx_ren_dx	1	0.029586436	0.006258168	0.566782164	0.7603	0.840210526
dx_ren_crohns_dis_location	2	0.071765423	0.02355289	0.627146241	0.7982	0.840210526
dx_ren_ulc_col_extent	2	0.173930102	0.108897774	2.0163941	0.0241	0.3428
pat_sex	1	0.071683657	0.015162637	1.385647398	0.1954	0.466888889
v1_lab_faecal_calprotectin	1	0.062982979	0.014813679	1.217950345	0.271	0.492727273
combined_CAS	1	0.114588386	0.024237911	2.235598226	0.0479	0.3428
combined_ENDO	1	0.081631827	0.020365934	1.51762092	0.1638	0.466888889
v1_lab_activity_150	1	0.054483281	0.012814539	1.05145153	0.3586	0.551692308
v1_lab_activity	1	0.070895121	0.016674625	1.37354805	0.2101	0.466888889
v1_clin_activity_b	1	0.019613097	0.004148592	0.374928737	0.9264	0.9264
v1_endo_activity_b	1	0.027940885	0.006970838	0.512443301	0.7943	0.840210526
v1_crp_activity	2	0.171052005	0.043933058	1.677243033	0.0732	0.3428
v1_albumin_activity	1	0.09226251	0.021956089	1.795918431	0.1071	0.357
fcal_responder_100_2	3	0.20948903	0.160935815	1.534431506	0.0857	0.3428
fcal_responder_103_2	3	0.163458495	0.09473697	1.151164504	0.3002	0.500333333
clinical_response2	3	0.159816978	0.091912916	1.214591655	0.2389	0.4778
diff_v1_v3_fcal	1	0.046467	0.026931257	0.968681812	0.425	0.607142857
diff_v1_v2_fcal	1	0.035944217	0.022485452	0.713082997	0.6194	0.825866667
diff_v2_v3_fcal	1	0.026726526	0.018669547	0.532692456	0.7846	0.840210526
diff_hbi_sccai	1	0.086459472	0.049724018	1.988383074	0.0733	0.3428

S 2: PERMANOVA based on dietary composition data, using food categories as input variables.

PERMANOVA - NUTRIENTS

	Df	SumOfSqs	R2	F	Pr(>F)	padj
dx_ren_dx	1	35.42664381	0.006782422	0.614586357	0.8868	0.9816
dx_ren_crohns_dis_location	2	102.8459995	0.01989009	0.527637088	0.8825	0.9816
dx_ren_ulc_col_extent	2	1.439735701	0.083977203	1.512652143	0.0935	0.374
pat_sex	1	62.39609654	0.011945717	1.088112797	0.4035	0.796142857
v1_lab_faecal_calprotectin	1	0.256930407	4.94E-05	0.003997718	0.9816	0.9816
combined_CAS	1	266.086623	0.050942216	4.830896	0.0389	0.259333333
combined_ENDO	1	633.093042	0.121522127	10.0982797	0.0024	0.48
v1_lab_activity_150	1	30.23420811	0.005807494	0.473154832	0.5573	0.796142857
v1_lab_activity	1	47.34554614	0.0090943	0.743398996	0.5377	0.796142857
v1_clin_activity_b	1	25.5532974	0.004892172	0.442460096	0.3472	0.796142857
v1_endo_activity_b	1	32.54237986	0.006246506	0.458861186	0.4431	0.796142857
v1_crp_activity	2	98.73300146	0.018981155	0.706216981	0.9519	0.9816
v1_albumin_activity	1	4.155214191	0.000798094	0.063898554	0.5418	0.796142857
fcal_responder_100_2	3	693.5563191	0.137289009	1.273093866	0.2011	0.616285714
fcal_responder_103_2	3	448.2608307	0.087894716	1.060011265	0.0555	0.2775
clinical_response2	3	241.5437741	0.047255902	0.595197417	0.8856	0.9816
diff_v1_v3_fcal	1	140.5811343	0.027565065	0.992125267	0.3641	0.796142857
diff_v1_v2_fcal	1	297.3098154	0.058388353	1.922277573	0.2157	0.616285714
diff_v2_v3_fcal	1	17.42843312	0.003441401	0.096691981	0.7401	0.9816
diff_hbi_sccai	1	1270.244406	0.248512079	12.56634834	0.0097	0.97

S 3: PERMANOVA based on dietary composition data, using nutrients as input variables.

PERMANOVA - DIETARY SCORES

	Df	SumOfSqs	R2	F	Pr(>F)	padj
dx_ren_dx	1	1.927746922	0.000998271	0.089934154	0.793	0.9867
dx_ren_crohns_dis_location	2	1.0797252	0.001395002	0.036320726	0.9717	0.9867
dx_ren_ulc_col_extent	2	71.56496905	0.06204531	1.091468095	0.393	0.731818182
pat_sex	1	18.31600604	0.009484821	0.861807992	0.4025	0.731818182
v1_lab_faecal_calprotectin	1	21.98865458	0.01153942	0.945604713	0.3559	0.731818182
combined_CAS	1	59.85470929	0.03099536	2.878812262	0.0885	0.731818182
combined_ENDO	1	10.21094626	0.005332984	0.391395116	0.5356	0.854769231
v1_lab_activity_150	1	0.673325818	0.000353354	0.028631828	0.8957	0.9867
v1_lab_activity	1	6.619406613	0.003473796	0.282358367	0.6461	0.923
v1_clin_activity_b	1	44.8666755	0.023233907	2.140790604	0.1334	0.731818182
v1_endo_activity_b	1	11.35779277	0.00593196	0.435617139	0.5556	0.854769231
v1_crp_activity	2	63.01029118	0.03312861	1.250625745	0.3056	0.731818182
v1_albumin_activity	1	0.011248987	5.90E-06	0.000472267	0.9867	0.9867
fcal_responder_100_2	3	178.7033304	0.147948031	1.389098665	0.2635	0.731818182
fcal_responder_103_2	3	62.11823282	0.050022185	0.579217777	0.8046	0.9867
clinical_response2	3	231.3583211	0.189762129	2.810465464	0.0277	0.554
diff_v1_v3_fcal	1	63.77003777	0.051352341	1.894625365	0.1929	0.731818182
diff_v1_v2_fcal	1	71.51361605	0.057660449	1.896846967	0.1957	0.731818182
diff_v2_v3_fcal	1	0.412539158	0.000333875	0.009351629	0.8982	0.9867
diff_hbi_sccai	1	31.63382672	0.025946343	1.012224554	0.2745	0.731818182

S 4: PERMANOVA based on dietary composition data, using dietary scores as input variables.

WILCOXON - FOOD CATEGORIES - UC vs CD

	statistic	pvalue	padjust
alcohol	1147.5	0.29930834	0.804255101
butter_margarine	1196	0.156371243	0.804255101
dairy	937	0.524108127	0.804255101
drink	973.5	0.706647514	0.927474862
eggs	1005.5	0.927036909	0.980941577
fish	912	0.402854187	0.804255101
fruit_vegetables	1014	0.980941577	0.980941577
high_sugar_foods	1101	0.508667386	0.804255101
legumes	843	0.165807015	0.804255101
lowfat_dairy	1101	0.467737535	0.804255101
nuts_seeds	906.5	0.378322033	0.804255101
oily_fish	951	0.585144396	0.819202154
potatoes	900.5	0.353570216	0.804255101
processed_meat	1035	0.892319723	0.980941577
red_meat	1039.5	0.864059255	0.980941577
refined_grains	821	0.118591512	0.804255101
sweetener	864	0.195819903	0.804255101
tea_coffee	1095.5	0.536170067	0.804255101
vegetable_oils	1109	0.468687216	0.804255101
white_meat	1022	0.97458644	0.980941577
whole_grains	870	0.241290261	0.804255101

S 5: Wilcoxon test comparing food categories intake between patients with UC and CD.

WILCOXON - NUTRIENTS - UC vs CD

	statistic	pvalue	padjust
energy_total_kcal	946	0.571828738	0.723642858
protein_total_g	952	0.604749	0.723642858
fat_total_g	911	0.398636435	0.723642858
fatty_acids_total_saturated_g	905	0.372480881	0.723642858
fatty_acids_total_monounsaturated_g	976	0.744064507	0.826738342
fatty_acids_total_polyunsaturated_g	1001	0.898619754	0.898619754
cholesterol_mg	952	0.604749	0.723642858
carbohydrate_g	927	0.473587695	0.723642858
sugars_total_g	996	0.867197549	0.897100913
starch_total_g	841	0.161077619	0.723642858
non_starch_polysaccharides_g	917	0.425868099	0.723642858
fibre_total_dietary_g	872	0.248250573	0.723642858
salt_g	848	0.178393894	0.723642858
sodium_mg	848	0.178393894	0.723642858
potassium_mg	989	0.82356743	0.882393675
calcium_mg	870	0.241785876	0.723642858
phosphorus_mg	951	0.599203565	0.723642858
magnesium_mg	949	0.58818242	0.723642858
iron_total_mg	869	0.238598337	0.723642858
zinc_mg	881	0.278833445	0.723642858
retinol_ug	873	0.251527876	0.723642858
thiamin_mg	871	0.245003263	0.723642858
riboflavin_mg	892	0.319564804	0.723642858
vitamin_B_6_total_mg	897	0.339305448	0.723642858
vitamin_B_12_ug	898	0.343345515	0.723642858
vitamin_D_ug	906	0.376764715	0.723642858

S 6: Wilcoxon test comparing nutrients intake between patients with UC and CD.

WILCOXON - DIETARY SCORES - UC vs CD

	statistic	pvalue	padjust
HFD	991	0.83598382	0.83598382
SFD	895.5	0.333153711	0.719622937
HEI	902	0.359811468	0.719622937
EDII	954	0.615908317	0.821211089

S 7: Wilcoxon test comparing dietary scores between patients with UC and CD.

KRUSKAL - FOOD CATEGORIES - CD TYPES

	statistic	pvalue	padjust
alcohol	22.09788123	0.279411973	0.558403047
butter_margarine	54	0.474403013	0.558403047
dairy	54	0.474403013	0.558403047
drink	12.30938824	0.340842513	0.558403047
eggs	54	0.435954664	0.558403047
fish	36.76503609	0.341984218	0.558403047
fruit_vegetables	54	0.474403013	0.558403047
high_sugar_foods	54	0.474403013	0.558403047
legumes	39.75088001	0.570156476	0.5986643
lowfat_dairy	11.03034652	0.608275293	0.608275293
nuts_seeds	37.91015912	0.217729476	0.558403047
oily_fish	4.893882159	0.298360174	0.558403047
potatoes	51.98807665	0.435190359	0.558403047
processed_meat	54	0.435954664	0.558403047
red_meat	52.94646098	0.398900503	0.558403047
refined_grains	54	0.474403013	0.558403047
sweetener	18.8544739	0.063756293	0.558403047
tea_coffee	24.71151214	0.478631183	0.558403047
vegetable_oils	54	0.474403013	0.558403047
white_meat	43.06328874	0.55430722	0.5986643
whole_grains	44.86771409	0.275088525	0.558403047

S 8: Kruskal test comparing food categories intake between patients with different CD extent.

KRUSKAL - NUTRIENTS - CD TYPES

	statistic	pvalue	padjust
energy_total_kcal	0.097238056	0.952543953	0.988532208
protein_total_g	0.056051302	0.972363425	0.988532208
fat_total_g	0.030340248	0.984944363	0.988532208
fatty_acids_total_saturated_g	0.313396897	0.854961835	0.988532208
fatty_acids_total_monounsaturated_g	0.351557266	0.838803646	0.988532208
fatty_acids_total_polyunsaturated_g	0.280927896	0.868954992	0.988532208
cholesterol_mg	1.101394194	0.576547761	0.988532208
carbohydrate_g	0.041167656	0.979626573	0.988532208
sugars_total_g	0.513151554	0.773696364	0.988532208
starch_total_g	1.088452724	0.580290545	0.988532208
non_starch_polysaccharides_g	0.222906505	0.894533208	0.988532208
fibre_total_dietary_g	0.151613093	0.92699552	0.988532208
salt_g	0.583845566	0.746826201	0.988532208
sodium_mg	0.583845566	0.746826201	0.988532208
potassium_mg	0.129338309	0.937377539	0.988532208
calcium_mg	0.02466651	0.987742488	0.988532208
phosphorus_mg	0.023068108	0.988532208	0.988532208
magnesium_mg	0.043165658	0.978648414	0.988532208
iron_total_mg	0.624225774	0.731898902	0.988532208
zinc_mg	0.137512488	0.933554212	0.988532208
retinol_ug	0.421145031	0.810120307	0.988532208
thiamin_mg	0.072307105	0.964492182	0.988532208
riboflavin_mg	0.298316389	0.86143283	0.988532208
vitamin_B_6_total_mg	0.240142211	0.886857374	0.988532208
vitamin_B_12_ug	0.493040783	0.781515425	0.988532208
vitamin_D_ug	1.06269172	0.587813323	0.988532208

S 9: Kruskal test comparing nutrients intake between patients with different CD extent.

KRUSKAL - DIETARY SCORES - CD TYPES

	statistic	pvalue	padjust
HFD	0.832050303	0.659663679	0.999241401
SFD	0.001517774	0.999241401	0.999241401
HEI	0.301569019	0.860033008	0.999241401
EDII	0.043165658	0.978648414	0.999241401

S 10: Kruskal test comparing dietary scores between patients with different CD extent.

KRUSKAL - FOOD CATEGORIES - UC TYPES

	statistic	pvalue	padjust
alcohol	9.959016291	0.765173657	0.781089546
butter_margarine	35	0.468202724	0.656962978
dairy	35	0.468202724	0.656962978
drink	16.66738906	0.118106361	0.656962978
eggs	35	0.420403904	0.656962978
fish	24.65745614	0.593652014	0.663653869
fruit_vegetables	35	0.468202724	0.656962978
high_sugar_foods	35	0.468202724	0.656962978
legumes	31.30394737	0.600448739	0.663653869
lowfat_dairy	9.234053885	0.415955655	0.656962978
nuts_seeds	24.44232456	0.436550509	0.656962978
oily_fish	1.752887902	0.781089546	0.781089546
potatoes	33.96842105	0.46925927	0.656962978
processed_meat	35	0.468202724	0.656962978
red_meat	31.30394737	0.551687324	0.663653869
refined_grains	35	0.468202724	0.656962978
sweetener	7.937813283	0.439568217	0.656962978
tea_coffee	27.58276316	0.189923847	0.656962978
vegetable_oils	35	0.468202724	0.656962978
white_meat	32.32368421	0.450772311	0.656962978
whole_grains	30.26842105	0.503467178	0.660800671

S 11: Kruskal test comparing food categories intake between patients with different UC extent.

KRUSKAL - NUTRIENTS - UC TYPES

	statistic	pvalue	padjust
energy_total_kcal	0.651750012	0.721895414	0.973390949
protein_total_g	2.828895072	0.243059858	0.973390949
fat_total_g	1.405260876	0.495280783	0.973390949
fatty_acids_total_saturated_g	1.812521077	0.404032266	0.973390949
fatty_acids_total_monounsaturated_g	1.497832057	0.472878862	0.973390949
fatty_acids_total_polyunsaturated_g	2.189189189	0.334675259	0.973390949
cholesterol_mg	0.564941947	0.753918525	0.973390949
carbohydrate_g	0.227411235	0.89252066	0.973390949
sugars_total_g	0.184052368	0.912081267	0.973390949
starch_total_g	0.21266922	0.899123742	0.973390949
non_starch_polysaccharides_g	0.295924267	0.862463773	0.973390949
fibre_total_dietary_g	0.558028617	0.756529078	0.973390949
salt_g	1.596202486	0.450182941	0.973390949
sodium_mg	1.596202486	0.450182941	0.973390949
potassium_mg	0.151966806	0.926831589	0.973390949
calcium_mg	3.769108012	0.151896789	0.973390949
phosphorus_mg	1.059040324	0.588887473	0.973390949
magnesium_mg	0.121742063	0.940944584	0.973390949
iron_total_mg	0.419780074	0.810673385	0.973390949
zinc_mg	0.823360794	0.662535991	0.973390949
retinol_ug	2.221467457	0.329317243	0.973390949
thiamin_mg	0.031284627	0.984479392	0.984479392
riboflavin_mg	0.152189623	0.926728338	0.973390949
vitamin_B_6_total_mg	0.203039938	0.903463138	0.973390949
vitamin_B_12_ug	3.045593053	0.218101108	0.973390949
vitamin_D_ug	0.839548104	0.657195295	0.973390949

S 12: Kruskal test comparing nutrients intake between patients with different UC extent.

WILCOXON - FOOD CATEGORIES - CAS - INFLAMMATION V1

	statistic	pvalue	padjust
alcohol	657	0.111799025	0.493388363
butter_margarine	656	0.112145969	0.493388363
dairy	706	0.250236361	0.493388363
drink	956.5	0.258441523	0.493388363
eggs	692.5	0.204698533	0.493388363
fish	703	0.239306087	0.493388363
fruit_vegetables	843	0.964996423	0.964996423
high_sugar_foods	782	0.629287346	0.734168571
legumes	927	0.434626827	0.70208949
lowfat_dairy	971	0.199639998	0.493388363
nuts_seeds	907.5	0.541359583	0.734168571
oily_fish	789.5	0.664986935	0.73498556
potatoes	776.5	0.59540949	0.734168571
processed_meat	664	0.128907715	0.493388363
red_meat	647	0.095375928	0.493388363
refined_grains	698	0.222468376	0.493388363
sweetener	933	0.375994078	0.657989636
tea_coffee	700.5	0.229769291	0.493388363
vegetable_oils	763	0.516020747	0.734168571
white_meat	902.5	0.571254675	0.734168571
whole_grains	868	0.792099897	0.831704891

S 13: Wilcoxon test comparing food categories intake between active and inactive patients, with disease activity determined by clinical assessment scores at baseline.

KRUSKAL - FOOD CATEGORIES - CRP - INFLAMMATION V1

	statistic	pvalue	padjust
alcohol	18.58996835	0.773488288	0.794846597
butter_margarine	75	0.478281308	0.618858152
dairy	75	0.478281308	0.618858152
drink	13.49016548	0.488341854	0.618858152
eggs	74.12084399	0.441396015	0.618858152
fish	39.14380377	0.717413567	0.792930785
fruit_vegetables	75	0.478281308	0.618858152
high_sugar_foods	75	0.478281308	0.618858152
legumes	67.30314656	0.364745216	0.618858152
lowfat_dairy	14.7397	0.543779548	0.634409473
nuts_seeds	43.03638689	0.426679121	0.618858152
oily_fish	5.072941099	0.279894834	0.618858152
potatoes	74.12084399	0.441396015	0.618858152
processed_meat	74.12084399	0.441396015	0.618858152
red_meat	74.12084399	0.408856146	0.618858152
refined_grains	75	0.478281308	0.618858152
sweetener	11.37112816	0.412715304	0.618858152
tea_coffee	27.96729028	0.794846597	0.794846597
vegetable_oils	75	0.478281308	0.618858152
white_meat	57.30842633	0.500980408	0.618858152
whole_grains	57.33600713	0.283920781	0.618858152

S 14: Wilcoxon test comparing food categories intake between active and inactive patients, with disease activity determined by CRP at baseline.

WILCOXON - NUTRIENTS - FCAL - INFLAMMATION V1

	statistic	pvalue	padjust
energy_total_kcal	672	0.137817448	0.680785085
protein_total_g	781	0.635231482	0.778120393
fat_total_g	685	0.172922357	0.680785085
fatty_acids_total_saturated_g	701	0.22469084	0.680785085
fatty_acids_total_monounsaturated_g	679	0.155976808	0.680785085
fatty_acids_total_polyunsaturated_g	711	0.262136569	0.680785085
cholesterol_mg	744	0.414573459	0.731600221
carbohydrate_g	692	0.194367767	0.680785085
sugars_total_g	706	0.242912556	0.680785085
starch_total_g	708	0.250481164	0.680785085
non_starch_polysaccharides_g	831	0.988980838	0.988980838
fibre_total_dietary_g	815	0.871986957	0.902055472
salt_g	702	0.228255668	0.680785085
sodium_mg	702	0.228255668	0.680785085
potassium_mg	763	0.521910987	0.778120393
calcium_mg	727	0.330497341	0.708208587
phosphorus_mg	737	0.378541111	0.731600221
magnesium_mg	806	0.807215206	0.896905784
iron_total_mg	883	0.64843366	0.778120393
zinc_mg	777	0.609171515	0.778120393
retinol_ug	686	0.17587409	0.680785085
thiamin_mg	719	0.29500687	0.680785085
riboflavin_mg	772	0.577276309	0.778120393
vitamin_B_6_total_mg	798	0.750703777	0.866196665
vitamin_B_12_ug	782	0.641818579	0.778120393
vitamin_D_ug	895	0.570991819	0.778120393

S 15: Wilcoxon test comparing nutrients intake between active and inactive patients, with disease activity determined by FCAL at baseline.

WILCOXON - NUTRIENTS - CAS - INFLAMMATION V1

	statistic	pvalue	padjust
energy_total_kcal	657	0.114142561	0.570550019
protein_total_g	713	0.276446324	0.570550019
fat_total_g	711	0.26877374	0.570550019
fatty_acids_total_saturated_g	727	0.334314302	0.570550019
fatty_acids_total_monounsaturated_g	696	0.215884971	0.570550019
fatty_acids_total_polyunsaturated_g	691	0.200042971	0.570550019
cholesterol_mg	676	0.157631371	0.570550019
carbohydrate_g	694	0.209443036	0.570550019
sugars_total_g	742	0.404389954	0.577699934
starch_total_g	742	0.404389954	0.577699934
non_starch_polysaccharides_g	844	0.958001637	0.991036177
fibre_total_dietary_g	816	0.853766228	0.91474953
salt_g	733	0.361348345	0.570550019
sodium_mg	733	0.361348345	0.570550019
potassium_mg	759	0.493596913	0.643822061
calcium_mg	836	0.992997127	0.992997127
phosphorus_mg	733	0.361348345	0.570550019
magnesium_mg	758	0.48807359	0.643822061
iron_total_mg	786	0.654425654	0.785310785
zinc_mg	706	0.250236361	0.570550019
retinol_ug	733	0.361348345	0.570550019
thiamin_mg	712	0.272591562	0.570550019
riboflavin_mg	725	0.325600479	0.570550019
vitamin_B_6_total_mg	712	0.272591562	0.570550019
vitamin_B_12_ug	709	0.26124866	0.570550019
vitamin_D_ug	706	0.250236361	0.570550019

S 16: Wilcoxon test comparing nutrients intake between active and inactive patients, with disease activity determined by clinical assessment scores at baseline.

KRUSKAL - NUTRIENTS - CRP - INFLAMMATION V1

	statistic	pvalue	padjust
energy_total_kcal	0.020150376	0.989975397	0.994035047
protein_total_g	0.596283566	0.742196101	0.994035047
fat_total_g	0.917843961	0.631964549	0.994035047
fatty_acids_total_saturated_g	1.575875403	0.454781725	0.994035047
fatty_acids_total_monounsaturated_g	0.602874719	0.739754163	0.994035047
fatty_acids_total_polyunsaturated_g	0.541835758	0.762679126	0.994035047
cholesterol_mg	1.806538424	0.405242668	0.994035047
carbohydrate_g	0.108602676	0.947146652	0.994035047
sugars_total_g	0.4033942	0.817342464	0.994035047
starch_total_g	0.500308564	0.778680638	0.994035047
non_starch_polysaccharides_g	0.13897471	0.93287193	0.994035047
fibre_total_dietary_g	0.110571233	0.946214855	0.994035047
salt_g	0.644894053	0.724374303	0.994035047
sodium_mg	0.644894053	0.724374303	0.994035047
potassium_mg	0.011965628	0.994035047	0.994035047
calcium_mg	1.774479055	0.411790923	0.994035047
phosphorus_mg	0.041367054	0.97952891	0.994035047
magnesium_mg	0.332580803	0.846800287	0.994035047
iron_total_mg	0.630733327	0.729521336	0.994035047
zinc_mg	0.436476907	0.803933718	0.994035047
retinol_ug	0.397738502	0.819657056	0.994035047
thiamin_mg	0.368053901	0.831913383	0.994035047
riboflavin_mg	0.267206328	0.874937203	0.994035047
vitamin_B_6_total_mg	1.138252124	0.566019889	0.994035047
vitamin_B_12_ug	0.667479738	0.716240074	0.994035047
vitamin_D_ug	1.454658725	0.483197714	0.994035047

S 17: Wilcoxon test comparing nutrients intake between active and inactive patients, with disease activity determined by CRP at baseline.

WILCOXON - NUTRIENTS - ENDO - INFLAMMATION V1

	statistic	pvalue	padjust
energy_total_kcal	570	0.884347436	0.976791164
protein_total_g	593	0.911973318	0.976791164
fat_total_g	534	0.572491413	0.976791164
fatty_acids_total_saturated_g	537	0.596475569	0.976791164
fatty_acids_total_monounsaturated_g	492	0.292280141	0.976791164
fatty_acids_total_polyunsaturated_g	507	0.379628835	0.976791164
cholesterol_mg	498	0.325453993	0.976791164
carbohydrate_g	614	0.722647126	0.976791164
sugars_total_g	605	0.802439053	0.976791164
starch_total_g	648	0.452908293	0.976791164
non_starch_polysaccharides_g	644	0.481415342	0.976791164
fibre_total_dietary_g	633	0.564599702	0.976791164
salt_g	588	0.958237289	0.976791164
sodium_mg	588	0.958237289	0.976791164
potassium_mg	589	0.948968201	0.976791164
calcium_mg	557	0.766665726	0.976791164
phosphorus_mg	550	0.705284362	0.976791164
magnesium_mg	567	0.856861471	0.976791164
iron_total_mg	608	0.775565811	0.976791164
zinc_mg	556	0.75779632	0.976791164
retinol_ug	472	0.198488677	0.976791164
thiamin_mg	604	0.81145071	0.976791164
riboflavin_mg	540	0.62090713	0.976791164
vitamin_B_6_total_mg	553	0.731383029	0.976791164
vitamin_B_12_ug	548	0.688073748	0.976791164
vitamin_D_ug	665	0.342925176	0.976791164

S 18: Wilcoxon test comparing nutrients intake between active and inactive patients, with disease activity determined by endoscopic scores at baseline.

WILCOXON - DIETARY SCORES - CAS - INFLAMMATION V1

	statistic	pvalue	padjust
HFD	827	0.930060182	0.930060182
SFD	736	0.375218096	0.930060182
HEI	868	0.792313688	0.930060182
EDII	756	0.477127695	0.930060182

S 19: Wilcoxon test comparing dietary scores between active and inactive patients, with disease activity determined by clinical assessment scores at baseline.

KRUSKAL - DIETARY SCORES - CRP - INFLAMMATION V1

	statistic	pvalue	padjust
HFD	2.931867982	0.230862268	0.307816357
SFD	0.875574823	0.645462986	0.645462986
HEI	4.477732643	0.106579263	0.213158525
EDII	5.065837321	0.079426862	0.213158525

S 20: Wilcoxon test comparing dietary scores between active and inactive patients, with disease activity determined by CRP at baseline.

WILCOXON - DIETARY SCORES - ALBUMIN - INFLAMMATION V1

	statistic	pvalue	padjust
HFD	209	0.756517799	0.984539124
SFD	280	0.09169548	0.18339096
HEI	194	0.984539124	0.984539124
EDII	293	0.052640951	0.18339096

S 21: Wilcoxon test comparing dietary scores between active and inactive patients, with disease activity determined by albumin at baseline.

WILCOXON - DIETARY SCORES - ENDO - INFLAMMATION V1

	statistic	pvalue	padjust
HFD	611	0.748958686	0.902751178
SFD	610.5	0.753286864	0.902751178
HEI	571	0.893542142	0.902751178
EDII	594	0.902751178	0.902751178

S 22: Wilcoxon test comparing dietary scores between active and inactive patients, with disease activity determined by endoscopic scores at baseline.

KRUSKAL - FOOD ITEMS - FCAL (V1-V3)

	statistic	pvalue	padjust
Beef roast/steak	6.823635004	0.077736706	0.918990667
Beef stew	4.352202729	0.225858435	0.918990667
Beef burger	3.111065679	0.374816009	0.918990667
Pork	0.742304757	0.863211163	0.9813011
Lamb	4.076630435	0.253307435	0.918990667
Poultry plain	7.426724937	0.059471396	0.918990667
Poultry breaded	2.105348259	0.550831532	0.918990667
Bacon/Ham	3.435773773	0.329188077	0.918990667
Processed meat	2.231318408	0.525805994	0.918990667
Savoury pies	5.417028571	0.143686314	0.918990667
Organ meat	3.486520376	0.322514596	0.918990667
Fish breaded	0.905243446	0.824162264	0.977209336
White fish	1.102880658	0.776378727	0.973786071
Oily fish	1.072669221	0.783675599	0.973786071
Shellfish	5.484160757	0.139589055	0.918990667
White bread	4.397923875	0.221577969	0.918990667
Brown bread	1.62448355	0.653851169	0.970726764
Wholemeal bread	4.34345679	0.22668587	0.918990667
Wheatfree bread	6.502962963	0.089545725	0.918990667
Cream crackers	3.759337017	0.288651478	0.918990667
Crisp bread	1.949130526	0.583031694	0.918990667
Pancakes/muffins/oatcakes	3.906424911	0.271747448	0.918990667
Scone white	3.902981099	0.272132791	0.918990667
Scone brown	0.867088074	0.833362058	0.97772399
Non-eady to eat cereals	2.488948864	0.477291582	0.918990667
High-fibre cereals	1.358494559	0.715292012	0.973786071
Low-fibre cereals	1.410185185	0.703149014	0.973786071
Muesli	3.031448355	0.386801828	0.918990667
Sugar coated cereals	1.324867725	0.72323663	0.973786071
Potatoes boiled/baked	2.186471306	0.534618016	0.918990667
Potatoes mashed	5.636621787	0.13069168	0.918990667
Potatoes roasted/fried	1.873348519	0.599104993	0.918990667
Potato Salad	2.246271611	0.522891902	0.918990667
White rice	3.647063253	0.302183395	0.918990667
Brown rice	1.352633127	0.716674358	0.973786071
Pasta white	5.654131491	0.129705041	0.918990667
Pasta wholemeal	1.963973577	0.579917693	0.918990667
Lasagne meatbased	2.684713461	0.442831335	0.918990667
Lasagne vegetarian	2.501075269	0.47509679	0.918990667
Pizza	1.033484505	0.793150432	0.973786071
Cream	2.356139652	0.501851428	0.918990667

S 23: Kruskal-Wallis test comparing food items intake among patients categorized as in remission, non-responders, responders, and super-responders. Treatment response was determined by differences in FCAL levels between V1 and V3.

Yoghurt fullfat	1.057672634	0.787300627	0.973786071
Dairy desserts	0.089727463	0.993041006	1
Cheddar regular	2.696054591	0.440898192	0.918990667
Cheddar lowfat	2.209382507	0.530102675	0.918990667
Cottage cheese	2.507744108	0.473893175	0.918990667
Eggs	7.577617945	0.055597299	0.918990667
Quiche	2.750151105	0.431771806	0.918990667
Salad cream light	0.808227513	0.847498126	0.978893184
Salad cream regular	5.637468672	0.130643796	0.918990667
Dressing french	5.741046832	0.124911489	0.918990667
Dressing other	0.422348485	0.935588095	0.988671108
Butter	6.488315554	0.09012445	0.918990667
Butter light	3.654499089	0.301269964	0.918990667
Margarine	1.819944035	0.610604537	0.918990667
Margarine light	0.024836601	0.998966707	1
Margarine cholesterol lowering	1.043809524	0.790652994	0.973786071
Cream/Vegoil spread	1.917733799	0.58965566	0.918990667
Olive oil spread	0.509705285	0.916754088	0.986146484
Apples	0.465063061	0.926497061	0.986146484
Pears	1.971913316	0.578256618	0.918990667
Oranges/satsumas/mandarins	3.100999611	0.376313647	0.918990667
Grapefruit	2.011764706	0.56996849	0.918990667
Bananas	0.244169042	0.970162321	1
Grapes	1.075680466	0.78294792	0.973786071
Melon	4.523602394	0.210194645	0.918990667
Peaches plums	3.544991736	0.314973554	0.918990667
Apricots	0.7575	0.859603073	0.9813011
Strawberries/raspberries/kiwi	3.517528342	0.318495859	0.918990667
Blueberries	6.27748244	0.098863458	0.918990667
Fruit canned	2.761382114	0.429896626	0.918990667
Dried fruit	1.85	0.604115283	0.918990667
Fruit frozen	3.970729476	0.264642214	0.918990667
Carrots	0.631291307	0.889233049	0.981449809
Spinach	6.434221256	0.092293066	0.918990667
Broccoli/spring greens/kale	3.311309824	0.346071627	0.918990667
Brussel sprouts	0.819163714	0.844878048	0.978893184
Cabbage	2.432025334	0.48770096	0.918990667
Peas	1.977132075	0.577166569	0.918990667
Beans broad/runner/green	3.429473684	0.330025	0.918990667
Courgettes	2.269806763	0.518329794	0.918990667
Cauliflower	4.090709825	0.251834234	0.918990667
Parsnips turnips	2.104970128	0.550907927	0.918990667
Leeks	2.26245121	0.519752398	0.918990667
Onions	2.241447941	0.523830626	0.918990667

S 23 continued 1

Garlic	3.225730267	0.35811409	0.918990667
Mushrooms	2.933003551	0.402070473	0.918990667
Sweet peppers	7.750790816	0.051452909	0.918990667
Green salad/lettuce	4.865760041	0.181894926	0.918990667
Cucumber celery	0.962825376	0.810246072	0.977209336
Tomatoes	5.943651692	0.114384108	0.918990667
Sweetcorn	4.630688432	0.200925226	0.918990667
Beetroot	3.280954733	0.3503022	0.918990667
Coleslaw	3.853316614	0.277745126	0.918990667
Baked beans	4.094573643	0.25143131	0.918990667
Dried lentils/beans/peas	5.032129343	0.169459537	0.918990667
Soyproducts	3.981572128	0.263460895	0.918990667
Chocolate biscuits	0.061147741	0.99605146	1
Plain biscuit	2.261263235	0.519982433	0.918990667
Cakes	3.571851852	0.311562047	0.918990667
Buns pastries	1.377203984	0.710886836	0.973786071
Fruit pies/tarts/crumbles	0.079169971	0.994214139	1
Sponge puddings	1.037212911	0.792248542	0.973786071
Milk puddings	0.464675622	0.926580589	0.986146484
Ice cream	1.05047081	0.789042027	0.973786071
Chocolates	0.674258777	0.879241185	0.9813011
Sweets/toffees/mints	1.046755556	0.789940495	0.973786071
Sugar	2.351615509	0.502704921	0.918990667
Sugar substitute	3.496318863	0.321239866	0.918990667
Crisps	1.577402825	0.664524362	0.970726764
Peanuts nuts	2.289717156	0.514493689	0.918990667
Vegetable soups fresh	2.368928345	0.499444808	0.918990667
Vegetable soups tinned	1.828806584	0.608686453	0.918990667
Meat cream soups fresh	0.347215055	0.950917173	0.997793372
Meat cream soups tinned	5.856093979	0.118825373	0.918990667
Sauces white brown	1.591038389	0.661423508	0.970726764
Sauces tomato	2.736784606	0.434012287	0.918990667
Sauces curry	0.896116262	0.826364942	0.977209336
Pickles chutney	2.537302977	0.468587304	0.918990667
Marmite Bovril	0.571169355	0.902999587	0.986146484
Jam/marmalade/honey/syrup	2.008172725	0.570712159	0.918990667
Peanut butter	1.430705882	0.698353149	0.973786071
Tea black	6.340148835	0.09618436	0.918990667
Tea herbal	3.515303668	0.318782704	0.918990667
Semi-skimmed milk	3.113320826	0.374481187	0.918990667
Coffee instant	0.660245184	0.882512398	0.9813011
Coffee ground	2.881373303	0.410279001	0.918990667
Coffee decaf	1.016216216	0.797328193	0.973786071
Coffee whitener	2.172839506	0.537317936	0.918990667

S 23 continued 2

Hot Chocolate	2.538015771	0.468459941	0.918990667
Horlicks Ovaltine	2.172839506	0.537317936	0.918990667
Wine	2.683085881	0.443109329	0.918990667
Beer Cider	3.635939086	0.303554517	0.918990667
Low alcohol beer/cider	6.4	0.09369079	0.918990667
Port/Sherry/Vermouth/Liqueur	0.675016835	0.879063909	0.9813011
Spirits	1.46184739	0.691103506	0.973786071
Fizzy drink diet	7.013428488	0.07147099	0.918990667
Fizzy drinks regular	1.052105927	0.788646628	0.973786071
Pure fruit drinks	0.528030399	0.912691484	0.986146484
Fruit squash	1.102459129	0.776480473	0.973786071
Probiotic Yoghurts	1.037274368	0.792233676	0.973786071
Ready meal varies	1.859152881	0.602147968	0.918990667
Takeaway varies	0.913611111	0.822141954	0.977209336
Milk (cow)	2.27740113	0.51686407	0.918990667
Soy drink	3.111111111	0.374809261	0.918990667
Almond drink	3.111111111	0.374809261	0.918990667
Coconut drink	3.111111111	0.374809261	0.918990667
Milk (lactose free)	NA	NA	NA
Milk (goat)	NA	NA	NA

S 23 continued 3

KRUSKAL - FOOD CATEGORIES - CLINICAL RESPONSE

	statistic	pvalue	padjust
alcohol	15.67170513	0.547215613	0.683713877
butter_margarine	39	0.469878198	0.683713877
dairy	39	0.469878198	0.683713877
drink	15.27446119	0.226769039	0.683713877
eggs	36.18724967	0.553482662	0.683713877
fish	23.18891856	0.80741443	0.847785151
fruit_vegetables	39	0.469878198	0.683713877
high_sugar_foods	39	0.469878198	0.683713877
legumes	37.54773031	0.309809383	0.683713877
lowfat_dairy	15.7342158	0.151288354	0.683713877
nuts_seeds	16.87166222	0.854083761	0.854083761
oily_fish	1.682040701	0.793977311	0.847785151
potatoes	38.03070761	0.422249567	0.683713877
processed_meat	36.18724967	0.553482662	0.683713877
red_meat	39	0.469878198	0.683713877
refined_grains	39	0.469878198	0.683713877
sweetener	6.490748776	0.483751389	0.683713877
tea_coffee	23.89973298	0.467342808	0.683713877
vegetable_oils	39	0.469878198	0.683713877
white_meat	30.0771028	0.704620952	0.822057777
whole_grains	29.77069426	0.477441658	0.683713877

S 24: Kruskal-Wallis test comparing food categories intake among patients categorized as in remission, non-responders, responders, and super-responders. Treatment response was determined by clinical response.

KRUSKAL - FOOD CATEGORIES - FCAL (V1-V3)

	statistic	pvalue	padjust
alcohol	15.01952977	0.523208597	0.732140336
butter_margarine	36	0.46864767	0.702971504
dairy	36	0.46864767	0.702971504
drink	12.21683732	0.347567002	0.702971504
eggs	32.43230944	0.592685034	0.732140336
fish	21.09518392	0.737034063	0.767986984
fruit_vegetables	36	0.46864767	0.702971504
high_sugar_foods	36	0.46864767	0.702971504
legumes	27.58930603	0.64227885	0.749325325
lowfat_dairy	7.191750876	0.707226977	0.767986984
nuts_seeds	18.90443686	0.591270405	0.732140336
oily_fish	4.041788246	0.400379966	0.702971504
potatoes	36	0.46864767	0.702971504
processed_meat	36	0.46864767	0.702971504
red_meat	36	0.46864767	0.702971504
refined_grains	36	0.46864767	0.702971504
sweetener	4.101742176	0.767986984	0.767986984
tea_coffee	22.19681456	0.448194973	0.702971504
vegetable_oils	36	0.46864767	0.702971504
white_meat	34.44254835	0.39861779	0.702971504
whole_grains	27.97080015	0.309199256	0.702971504

S 25: Kruskal-Wallis test comparing food categories intake among patients categorized as in remission, non-responders, responders, and super-responders. Treatment response was determined by differences in FCAL levels between V1 and V3.

KRUSKAL - NUTRIENTS - CLINICAL RESPONSE

	statistic	pvalue	padjust
energy_total_kcal	1.968845484	0.578898056	0.963111887
protein_total_g	2.265444251	0.519173175	0.963111887
fat_total_g	4.01022246	0.260362403	0.963111887
fatty_acids_total_saturated_g	4.160083758	0.244688766	0.963111887
fatty_acids_total_monounsaturated_g	4.234333959	0.237246807	0.963111887
fatty_acids_total_polyunsaturated_g	1.969394264	0.578783278	0.963111887
cholesterol_mg	2.56695591	0.463312074	0.963111887
carbohydrate_g	1.410496516	0.703076145	0.963111887
sugars_total_g	0.783489681	0.853411871	0.963111887
starch_total_g	1.256148486	0.739571434	0.963111887
non_starch_polysaccharides_g	1.092213884	0.778954008	0.963111887
fibre_total_dietary_g	1.262452426	0.738067831	0.963111887
salt_g	5.219525596	0.156410319	0.963111887
sodium_mg	5.219525596	0.156410319	0.963111887
potassium_mg	0.387748593	0.942761558	0.963111887
calcium_mg	2.905336371	0.406451901	0.963111887
phosphorus_mg	1.526540472	0.676158489	0.963111887
magnesium_mg	0.283442107	0.963111887	0.963111887
iron_total_mg	0.389356741	0.942432261	0.963111887
zinc_mg	0.971616859	0.808119378	0.963111887
retinol_ug	2.51760989	0.472116987	0.963111887
thiamin_mg	0.76999531	0.856629464	0.963111887
riboflavin_mg	0.681677834	0.87750481	0.963111887
vitamin_B_6_total_mg	0.915100509	0.821782264	0.963111887
vitamin_B_12_ug	2.792211203	0.424783697	0.963111887
vitamin_D_ug	5.350203699	0.147877721	0.963111887

S 26: Kruskal-Wallis test comparing nutrients intake among patients categorized as in remission, non-responders, responders, and super-responders. Treatment response was determined by clinical response.

KRUSKAL - NUTRIENTS - FCAL (V1-V3)

	statistic	pvalue	padjust
energy_total_kcal	2.047889995	0.562526687	0.976262102
protein_total_g	0.591275486	0.898426715	0.976262102
fat_total_g	2.308582266	0.510878767	0.976262102
fatty_acids_total_saturated_g	2.641631105	0.450237776	0.976262102
fatty_acids_total_monounsaturated_g	2.744807966	0.432666277	0.976262102
fatty_acids_total_polyunsaturated_g	2.459080133	0.482731629	0.976262102
cholesterol_mg	0.902418208	0.824844201	0.976262102
carbohydrate_g	3.79886202	0.284018525	0.976262102
sugars_total_g	2.489900427	0.477119068	0.976262102
starch_total_g	2.641156946	0.450319845	0.976262102
non_starch_polysaccharides_g	0.453200569	0.929045946	0.976262102
fibre_total_dietary_g	0.767283073	0.857275402	0.976262102
salt_g	3.735893789	0.29143133	0.976262102
sodium_mg	3.735893789	0.29143133	0.976262102
potassium_mg	0.904599336	0.824317744	0.976262102
calcium_mg	0.513987672	0.915807809	0.976262102
phosphorus_mg	1.090943575	0.779260778	0.976262102
magnesium_mg	0.623613087	0.891006054	0.976262102
iron_total_mg	0.754480797	0.860320701	0.976262102
zinc_mg	0.595542911	0.89745196	0.976262102
retinol_ug	5.948885728	0.114123701	0.976262102
thiamin_mg	0.208155524	0.976262102	0.976262102
riboflavin_mg	1.566998578	0.666895601	0.976262102
vitamin_B_6_total_mg	0.951730678	0.812929396	0.976262102
vitamin_B_12_ug	1.664864865	0.644773179	0.976262102
vitamin_D_ug	2.544902798	0.467230769	0.976262102

S 27: Kruskal-Wallis test comparing nutrients intake among patients categorized as in remission, non-responders, responders, and super-responders. Treatment response was determined by differences in FCAL levels between V1 and V3.

BIBLIOGRAPHY

1. Torres, J., Mehandru, S., Colombel, J. F. & Peyrin-Biroulet, L. Crohn's disease. *The Lancet* vol. 389 1741–1755 Preprint at https://doi.org/10.1016/S0140-6736(16)31711-1 (2017).

2. Ungaro, R., Mehandru, S., Allen, P. B., Peyrin-Biroulet, L. & Colombel, J. F. Ulcerative colitis. *The Lancet* vol. 389 1756–1770 Preprint at https://doi.org/10.1016/S0140-6736(16)32126-2 (2017).

3. Actis, G. C., Pellicano, R., Fagoonee, S. & Ribaldone, D. G. History of inflammatory bowel diseases. *Journal of Clinical Medicine* vol. 8 Preprint at https://doi.org/10.3390/jcm8111970 (2019).

4. Inflammatory bowel disease- definition, epidemiology, etiologic aspects, and immunogenetic studies.

5. Campbell, J., Borody, T. J. & Leis, S. The many faces of Crohn's Disease: Latest concepts in etiology. *Open Journal of Internal Medicine* **02**, 107–115 (2012).

6. Crohn, B. B., Ginzburg, L., And, G. D. & Oppenheimer, D. *A Pathologic and Clinical Entity*.

7. Gonzalez, C. G. *et al.* Location-specific signatures of Crohn's disease at a multi-omics scale. *Microbiome* **10**, (2022).

8. Zhang, Y. Z. & Li, Y. Y. Inflammatory bowel disease: Pathogenesis. *World J Gastroenterol* **20**, 91–99 (2014).

9. Alatab, S. *et al.* The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* **5**, 17–30 (2020).

10. Molodecky, N. A. *et al.* Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* **142**, (2012).

11. Kaplan, G. G. The global burden of IBD: From 2015 to 2025. *Nature Reviews Gastroenterology and Hepatology* vol. 12 720–727 Preprint at https://doi.org/10.1038/nrgastro.2015.150 (2015).

12. Ng, S. C. *et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet* **390**, 2769–2778 (2017).

13. Sairenji, T., Collins, K. L. & Evans, D. V. An Update on Inflammatory Bowel Disease. *Primary Care - Clinics in Office Practice* vol. 44 673–692 Preprint at https://doi.org/10.1016/j.pop.2017.07.010 (2017).

14. Knowles, S. R. *et al.* Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses - Part i. *Inflammatory Bowel Diseases* vol. 24 742–751 Preprint at https://doi.org/10.1093/ibd/izx100 (2018).

15. Gomez, D. A., Ahmad-Waqar, M., Brookes, M. J. & Kumar, A. IBD-related mental health disorders: Where do we go from here? *Frontline Gastroenterology* vol. 14 512–520 Preprint at https://doi.org/10.1136/flgastro-2023-102403 (2023).

16. Barnes, E. L. Treating IBD? Don't Forget that Mental Health Matters. *Digestive Diseases and Sciences* vol. 67 4321–4323 Preprint at https://doi.org/10.1007/s10620-022-07510-y (2022).

17. Bernstein, C. N. Addressing Mental Health in Persons with IBD. *J Can Assoc Gastroenterol* **1**, 97–98 (2018).

18. Zhao, M., Gönczi, L., Lakatos, P. L. & Burisch, J. The Burden of Inflammatory Bowel Disease in Europe in 2020. *Journal of Crohn's and Colitis* vol. 15 1573–1587 Preprint at https://doi.org/10.1093/ecco-jcc/jjab029 (2021).

19. Qiu, P. *et al.* The Gut Microbiota in Inflammatory Bowel Disease. *Frontiers in Cellular and Infection Microbiology* vol. 12 Preprint at https://doi.org/10.3389/fcimb.2022.733992 (2022).

20. Mukhopadhya, I. *et al.* The fungal microbiota of de-novo paediatric inflammatory bowel disease. *Microbes Infect* **17**, 304–310 (2015).

21. Turnbaugh, P. J. *et al.* The Human Microbiome Project. *Nature* vol. 449 804–810 Preprint at https://doi.org/10.1038/nature06244 (2007).

22. Lopetuso, L. R., Ianiro, G., Scaldaferri, F., Cammarota, G. & Gasbarrini, A. Gut Virome and Inflammatory Bowel Disease. *Inflammatory Bowel Diseases* vol. 22 1708–1712 Preprint at https://doi.org/10.1097/MIB.0000000000000807 (2016).

23. Kostic, A. D., Xavier, R. J. & Gevers, D. The microbiome in inflammatory bowel disease: Current status and the future ahead. *Gastroenterology* **146**, 1489–1499 (2014).

24. Sender, R., Fuchs, S. & Milo, R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biol* **14**, (2016).

25. Thursby, E. & Juge, N. Introduction to the human gut microbiota. *Biochemical Journal* vol. 474 1823–1836 Preprint at https://doi.org/10.1042/BCJ20160510 (2017).

26. Johnson, A. J. *et al.* Daily Sampling Reveals Personalized Diet-Microbiome Associations in Humans. *Cell Host Microbe* **25**, 789-802.e5 (2019).

27. Flores, G. E. *et al.* Temporal variability is a personalized feature of the human microbiome. *Genome Biol* **15**, 531 (2014).

28. Ramakrishna, B. S. Role of the gut microbiota in human nutrition and metabolism. *Journal of Gastroenterology and Hepatology (Australia)* **28**, 9–17 (2013).

29. Halfvarson, J. *et al.* Dynamics of the human gut microbiome in inflammatory bowel disease. *Nat Microbiol* **2**, (2017).

30. Pittayanon, R. *et al.* Differences in Gut Microbiota in Patients With vs Without Inflammatory Bowel Diseases: A Systematic Review. *Gastroenterology* **158**, 930-946.e1 (2020).

31. Abdel-Rahman, L. I. H. & Morgan, X. C. Searching for a Consensus Among Inflammatory Bowel Disease Studies: A Systematic Meta-Analysis. *Inflamm Bowel Dis* **29**, 125–139 (2023).

32. Richards, J. L., Yap, Y. A., McLeod, K. H., MacKay, C. R. & Marinõ, E. Dietary metabolites and the gut microbiota: An alternative approach to control inflammatory and

autoimmune diseases. *Clinical and Translational Immunology* vol. 5 Preprint at https://doi.org/10.1038/cti.2016.29 (2016).

33. Windsor, J. W. & Kaplan, G. G. Evolving Epidemiology of IBD. *Current Gastroenterology Reports* vol. 21 Preprint at https://doi.org/10.1007/s11894-019-0705-6 (2019).

34. Ferenc, K., Jarmakiewicz-Czaja, S. & Filip, R. Components of the Fiber Diet in the Prevention and Treatment of IBD—An Update. *Nutrients* vol. 15 Preprint at https://doi.org/10.3390/nu15010162 (2023).

35. King, D. E., Mainous, A. G. & Lambourne, C. A. Trends in Dietary Fiber Intake in the United States, 1999-2008. *J Acad Nutr Diet* **112**, 642–648 (2012).

36. Picco, M. F. Dietary Intake and Risk of Developing Inflammatory Bowel Disease: A Systematic Review of the Literature. *Yearbook of Medicine* **2011**, 449–450 (2011).

37. Khalili, H. *et al.* Adherence to a Mediterranean diet is associated with a lower risk of later-onset Crohn's disease: Results from two large prospective cohort studies. *Gut* **69**, 1637–1644 (2020).

38. Estruch, R. *et al.* Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *New England Journal of Medicine* **378**, (2018).

39. Tan, J. *et al.* The Role of Short-Chain Fatty Acids in Health and Disease. in *Advances in Immunology* vol. 121 91–119 (Academic Press Inc., 2014).

40. O'Grady, J., O'Connor, E. M. & Shanahan, F. Review article: dietary fibre in the era of microbiome science. *Alimentary Pharmacology and Therapeutics* vol. 49 506–515 Preprint at https://doi.org/10.1111/apt.15129 (2019).

41. Sasson, A. N. *et al.* The role of precision nutrition in the modulation of microbial composition and function in people with inflammatory bowel disease. *The Lancet Gastroenterology and Hepatology* vol. 6 754–769 Preprint at https://doi.org/10.1016/S2468-1253(21)00097-2 (2021).

42. Ananthakrishnan, A. N. *et al.* Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. *Inflamm Bowel Dis* **19**, 1921–1927 (2013).

43. Spiro, A. & Buttriss, J. L. Vitamin D: An overview of vitamin D status and intake in Europe. *Nutrition Bulletin* vol. 39 322–350 Preprint at https://doi.org/10.1111/nbu.12108 (2014).

44. Rohr, M. W., Narasimhulu, C. A., Rudeski-Rohr, T. A. & Parthasarathy, S. Negative Effects of a High-Fat Diet on Intestinal Permeability: A Review. *Advances in Nutrition* vol. 11 77–91 Preprint at https://doi.org/10.1093/advances/nmz061 (2020).

45. Yan, D. *et al.* Fatty acids and lipid mediators in inflammatory bowel disease: from mechanism to treatment. *Frontiers in Immunology* vol. 14 Preprint at https://doi.org/10.3389/fimmu.2023.1286667 (2023).

46. Khalili, H. *et al.* Identification and characterization of a novel association between dietary potassium and risk of Crohn's disease and ulcerative colitis. *Front Immunol* **7**, (2016).

47. Muralidharan, J. *et al.* Effect on gut microbiota of a 1-y lifestyle intervention with Mediterranean diet compared with energy-reduced Mediterranean diet and physical activity promotion: PREDIMED-Plus Study. *American Journal of Clinical Nutrition* **114**, 1148–1158 (2021).

48. Meslier, V. *et al.* Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. *Gut* **69**, 1258–1268 (2020).

49. Ghosh, T. S. *et al.* Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: The NU-AGE 1-year dietary intervention across five European countries. *Gut* **69**, 1218–1228 (2020).

50. Li, F., Liu, X., Wang, W. & Zhang, D. Consumption of vegetables and fruit and the risk of inflammatory bowel disease: A meta-analysis. *European Journal of Gastroenterology and Hepatology* vol. 27 623–630 Preprint at https://doi.org/10.1097/MEG.0000000000000330 (2015).

51. Tian, Z. *et al.* Index-Based Dietary Patterns and Inflammatory Bowel Disease: A Systematic Review of Observational Studies. *Advances in Nutrition* vol. 12 2288–2300 Preprint at https://doi.org/10.1093/advances/nmab069 (2021).

52. Godny, L. *et al.* Adherence to the Mediterranean diet is associated with decreased fecal calprotectin in patients with ulcerative colitis after pouch surgery. *Eur J Nutr* **59**, 3183–3190 (2020).

53. Molendijk, I., Van Der Marel, S. & Maljaars, P. W. J. Towards a food pharmacy: Immunologic modulation through diet. *Nutrients* vol. 11 Preprint at https://doi.org/10.3390/nu11061239 (2019).

54. Covas, M. I., De La Torre, R. & Fitó, M. Virgin olive oil: A key food for cardiovascular risk protection. *British Journal of Nutrition* **113**, S19–S28 (2015).

55. Larrosa, M. *et al.* Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model. *J Agric Food Chem* **57**, 2211–2220 (2009).

56. Singh, U. P. *et al.* Resveratrol (Trans-3,5,4′-trihydroxystilbene) induces silent mating type information regulation-1 and down-regulates nuclear transcription factor-κB activation to abrogate dextran sulfate sodium-induced colitis. *Journal of Pharmacology and Experimental Therapeutics* **332**, 829–839 (2010).

57. Chiba, M. *et al.* Lifestyle-related disease in Crohn's disease: Relapse prevention by a semi-vegetarian diet. *World J Gastroenterol* **16**, 2484–2495 (2010).

58. Amarapurkar, A. D. *et al.* Risk factors for inflammatory bowel disease: A prospective multi-center study. *Indian Journal of Gastroenterology* **37**, 189–195 (2018).

59. Haider, L. M., Schwingshackl, L., Hoffmann, G. & Ekmekcioglu, C. The effect of vegetarian diets on iron status in adults: A systematic review and meta-analysis. *Crit Rev Food Sci Nutr* **58**, 1359–1374 (2018).

60. Yokoyama, Y. *et al.* Vegetarian diets and blood pressure ameta-analysis. *JAMA Intern Med* **174**, 577–587 (2014).

61. Halmos, E. P. A low FODMAP diet in patients with Crohn's disease. *Journal of Gastroenterology and Hepatology (Australia)* **31**, 14–15 (2016).

62. Gibson, P. R. Use of the low-FODMAP diet in inflammatory bowel disease. *Journal of Gastroenterology and Hepatology (Australia)* vol. 32 40–42 Preprint at https://doi.org/10.1111/jgh.13695 (2017).

63. Shepherd, S. J. & Gibson, P. R. Fructose Malabsorption and Symptoms of Irritable Bowel Syndrome: Guidelines for Effective Dietary Management. *J Am Diet Assoc* **106**, 1631–1639 (2006).

64. Rao, S. S. C., Yu, S. & Fedewa, A. Systematic review: Dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. *Aliment Pharmacol Ther* **41**, 1256–1270 (2015).

65. Barrett, J. S. How to institute the low-FODMAP diet. *Journal of Gastroenterology and Hepatology (Australia)* vol. 32 8–10 Preprint at https://doi.org/10.1111/jgh.13686 (2017).

66. Cox, S. R. *et al.* Effects of Low FODMAP Diet on Symptoms, Fecal Microbiome, and Markers of Inflammation in Patients With Quiescent Inflammatory Bowel Disease in a Randomized Trial. *Gastroenterology* **158**, 176-188.e7 (2020).

67. Zhan, Y. le, Zhan, Y. an & Dai, S. xue. Is a low FODMAP diet beneficial for patients with inflammatory bowel disease? A meta-analysis and systematic review. *Clinical Nutrition* **37**, 123–129 (2018).

68. Prince, A. C. *et al.* Fermentable carbohydrate restriction (Low FODMAP Diet) in clinical practice improves functional gastrointestinal symptoms in patients with inflammatory bowel disease. *Inflamm Bowel Dis* **22**, 1129–1136 (2016).

69. Gearry, R. B. *et al.* Reduction of dietary poorly absorbed short-chain carbohydrates (FODMAPs) improves abdominal symptoms in patients with inflammatory bowel disease-a pilot study. *J Crohns Colitis* **3**, 8–14 (2009).

70. Knowles, S., Andrews, J. M. & Porter, A. Predictors of impaired mental health and support seeking in adults with inflammatory bowel disease. *Gastroenterology Nursing* **41**, 38–46 (2018).

71. Halmos, E. P. *et al.* Consistent prebiotic effect on gut microbiota with altered fodmap intake in patients with crohn s disease: A randomised, controlled cross-over trial of well-defined diets. *Clin Transl Gastroenterol* **7**, (2016).

72. O'Keeffe, M. *et al.* Long-term impact of the low-FODMAP diet on gastrointestinal symptoms, dietary intake, patient acceptability, and healthcare utilization in irritable bowel syndrome. *Neurogastroenterology and Motility* **30**, (2018).

73. Ruemmele, F. M. *et al.* Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis* **8**, 1179–1207 (2014).

74. Borrelli, O. *et al.* Polymeric Diet Alone Versus Corticosteroids in the Treatment of Active Pediatric Crohn's Disease: A Randomized Controlled Open-Label Trial. *Clinical Gastroenterology and Hepatology* **4**, 744–753 (2006).

75. Yu, Y., Chen, K. C. & Chen, J. Exclusive enteral nutrition versus corticosteroids for treatment of pediatric Crohn's disease: a meta-analysis. *World Journal of Pediatrics* **15**, 26–36 (2019).

76. Wall, C. L., Day, A. S. & Gearry, R. B. Use of exclusive enteral nutrition in adults with Crohn's disease: A review. *World Journal of Gastroenterology* vol. 19 7652–7660 Preprint at https://doi.org/10.3748/wjg.v19.i43.7652 (2013).

77. Narula, N. *et al.* Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* vol. 2018 Preprint at https://doi.org/10.1002/14651858.CD000542.pub3 (2018).

78. Zachos, M., Tondeur, M. & Griffiths, A. M. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* Preprint at https://doi.org/10.1002/14651858.CD000542.pub2 (2007).

79. Logan, M. *et al.* Analysis of 61 exclusive enteral nutrition formulas used in the management of active Crohn's disease—new insights into dietary disease triggers. *Aliment Pharmacol Ther* **51**, 935–947 (2020).

80. Boneh, R. S. *et al.* Dietary therapy with the Crohn's disease exclusion diet is a successful strategy for induction of Remission in children and adults failing biological therapy. *J Crohns Colitis* **11**, 1205–1212 (2017).

81. Yanai, H. *et al.* The Crohn's disease exclusion diet for induction and maintenance of remission in adults with mild-to-moderate Crohn's disease (CDED-AD): an open-label, pilot, randomised trial. *Lancet Gastroenterol Hepatol* **7**, 49–59 (2022).

82. Sigall Boneh, R. *et al.* Dietary Therapies Induce Rapid Response and Remission in Pediatric Patients With Active Crohn's Disease. *Clinical Gastroenterology and Hepatology* **19**, 752–759 (2021).

83. Levine, A. *et al.* Dietary Guidance From the International Organization for the Study of Inflammatory Bowel Diseases. *Clinical Gastroenterology and Hepatology* vol. 18 1381–1392 Preprint at https://doi.org/10.1016/j.cgh.2020.01.046 (2020).

84. Khazen, W., Jeanne, J. F., Demaretz, L., Schäfer, F. & Fagherazzi, G. Rethinking the use of mobile apps for dietary assessment in medical research. *Journal of Medical Internet Research* vol. 22 Preprint at https://doi.org/10.2196/15619 (2020).

85. Cade, J., Thompson, R., Burley, V. & Warm, D. Development, validation and utilisation of food-frequency questionnaires – a review. *Public Health Nutr* **5**, 567–587 (2002).

86. Castell, G. S., Serra-Majem, L. & Ribas-Barba, L. ¿Qué y cuánto comemos? Método de recuerdo 24 horas. *Nutr Hosp* **31**, 46–48 (2015).

87. Fuller, N. R. *et al.* Comparison of an electronic versus traditional food diary for assessing dietary intake—A validation study. *Obes Res Clin Pract* **11**, 647–654 (2017).

88. Budiningsari, D. & Syahrian, F. Validity of a digital photo-based dietary assessment tool: Development and initial evaluation. *Nutr Health* (2024) doi:10.1177/02601060241239095.

89. Lieffers, J. R. L. & Hanning, R. M. Dietary assessment and self-monitoring: With nutrition applications for mobile devices. *Canadian Journal of Dietetic Practice and Research* vol. 73 Preprint at https://doi.org/10.3148/73.3.2012.e253 (2012).

90. Drescher, L. S., Thiele, S. & Mensink, G. B. M. *The Journal of Nutrition Nutrient Requirements and Optimal Nutrition A New Index to Measure Healthy Food Diversity Better Reflects a Healthy Diet Than Traditional Measures 1,2*. *J. Nutr* vol. 137 (2007).

91. Kirkpatrick, S. I. *et al.* Applications of the Healthy Eating Index for Surveillance, Epidemiology, and Intervention Research: Considerations and Caveats. *J Acad Nutr Diet* **118**, 1603–1621 (2018).

92. Krebs-Smith, S. M. *et al.* Update of the Healthy Eating Index: HEI-2015. *J Acad Nutr Diet* **118**, 1591–1602 (2018).

93. Tabung, F. K. *et al.* Development and validation of an empirical dietary inflammatory index. *Journal of Nutrition* **146**, 1560–1570 (2016).

94. Petersen, K. S. & Kris-Etherton, P. M. Diet quality assessment and the relationship between diet quality and cardiovascular disease risk. *Nutrients* vol. 13 Preprint at https://doi.org/10.3390/nu13124305 (2021).

95. *Fast Facts: Inflammatory Bowel Disease*. (S Karger AG, 2021).

96. HARVEY J M BRADSHAW Bristol Royal Infirmary, R. F. & Hospital, F. *Methods and Devices A SIMPLE INDEX OF CROHN'S-DISEASE ACTIVITY*.

97. Vermeire, S., Schreiber, S., Sandborn, W. J., Dubois, C. & Rutgeerts, P. Correlation Between the Crohn's Disease Activity and Harvey-Bradshaw Indices in Assessing Crohn's Disease Severity. *Clinical Gastroenterology and Hepatology* **8**, 357–363 (2010).

98. Higgins, P. D. R. *et al.* The quantitative validation of non-endoscopic disease activity indices in ulcerative colitis. *Aliment Pharmacol Ther* **25**, 333–342 (2007).

99. Zittan, E. *et al.* Development of the Harvey-Bradshaw Index-pro (HBI-PRO) Score to Assess Endoscopic Disease Activity in Crohn's Disease. *J Crohns Colitis* **11**, 543–548 (2017).

100. Lin, J. F. *et al.* Meta-analysis: Fecal calprotectin for assessment of inflammatory bowel disease activity. *Inflamm Bowel Dis* **20**, 1407–1415 (2014).

101. Mowat, C. *et al.* Faecal haemoglobin and faecal calprotectin as indicators of bowel disease in patients presenting to primary care with bowel symptoms. *Gut* **65**, 1463–1469 (2016).

102. Mosli, M. H. *et al.* C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: A systematic review and meta-analysis. *American Journal of Gastroenterology* vol. 110 802–819 Preprint at https://doi.org/10.1038/ajg.2015.120 (2015).

103. Khan, N., Patel, D., Shah, Y., Trivedi, C. & Yang, Y. X. Albumin as a prognostic marker for ulcerative colitis. *World J Gastroenterol* **23**, 8008–8016 (2017).

104. Higgins, P. D. R., Schwartz, M., Mapili, J. & Zimmermann, E. M. Is endoscopy necessary for the measurement of disease activity in ulcerative colitis? *American Journal of Gastroenterology* **100**, 355–361 (2005).

105. Sipponen, T., Nuutinen, H., Turunen, U. & Färkkilä, M. Endoscopic evaluation of Crohn's disease activity: Comparison of the CDEIS and the SES-CD. *Inflamm Bowel Dis* **16**, 2131–2136 (2010).

106. Harrington, J. *et al.* Sociodemographic, health and lifestyle predictors of poor diets. *Public Health Nutr* **14**, 2166–2175 (2011).

107. Ghosh, S. *et al.* A Global, Prospective, Observational Study Measuring Disease Burden and Suffering in Patients with Ulcerative Colitis, Using the Pictorial Representation of Illness and Self-measure Tool. *J Crohns Colitis* **15**, 228–237 (2021).

108. Tadbiri, S. *et al.* The IBD-disk Is a Reliable Tool to Assess the Daily-life Burden of Patients with Inflammatory Bowel Disease. *J Crohns Colitis* **15**, 766–773 (2021).

109. Ghosh, S. *et al.* Development of the IBD Disk: A Visual Self-Administered Tool for Assessing Disability in Inflammatory Bowel Diseases. *Inflamm Bowel Dis* **23**, 333–340 (2017).

110. Hadley Wickham. *Ggplot2: Elegant Graphics for Data Analysis*. (Springer-Verlag New York, 2016).

111. Alboukadel Kassambara. *Ggpubr: 'ggplot2' Based Publication Ready Plots*. https://rpkgs.datanovia.com/ggpubr/ (2023).

112. Lionel Henry & Hadley Wickham. *Rlang: Functions for Base Types and Core R and 'Tidyverse' Features*. https://rlang.r-lib.org (2024).

113. Thomas Lin Pedersen. patchwork: The Composer of Plots. (2024).

114. Raivo Kolde. pheatmap: Pretty Heatmaps. Preprint at https://doi.org/10.32614/CRAN.package.pheatmap (2019).

115. Nicholas Tierney & Dianne Cook. Expanding Tidy Data Principles to Facilitate Missing Data Exploration, Visualization and Assessment of Imputations. *J Stat Softw* **105**, 1–31 (2023).

116. Stef {van Buuren} & Karin Groothuis-Oudshoorn. {mice}: Multivariate Imputation by Chained Equations in R. *J Stat Softw* **45**, 1–67 (2011).

117. Aqua-Calc. https://www.aqua-calc.com.

118. EuroFIR AISBL. https://www.eurofir.org.

119. Food Patterns Equivalents Database. https://www.ars.usda.gov/northeast-area/beltsville-md-bhnrc/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/.

120. Division of Cancer Control and Population Sciences (DCCPS) of the National Institutes of Health(NIH). https://epi.grants.cancer.gov/hei/.

121. Mozaffari, H., Hosseini, Z., Lafrenière, J. & Conklin, A. I. The role of dietary diversity in preventing metabolic-related outcomes: Findings from a systematic review. *Obesity Reviews* **22**, (2021).

122. Jari Oksanen *et al. Community Ecology Package*. https://github.com/vegandevs/vegan (2024).

123. Benjamini, Y., Drai, D., Elmer, G., Kafkafi, N. & Golani, I. *Controlling the False Discovery Rate in Behavior Genetics Research*. *Behavioural Brain Research* vol. 125 www.elsevier.com/locate/bbr (2001).

124. Macia, L. *et al.* Microbial influences on epithelial integrity and immune function as a basis for inflammatory diseases. *Immunological Reviews* vol. 245 164–176 Preprint at https://doi.org/10.1111/j.1600-065X.2011.01080.x (2012).