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Distinct microbial mediators link diet to inflammation in Crohn's disease and ulcerative colitis

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ABSTRACT

Background Inflammatory bowel disease (IBD) arises from complex interactions among diet, host and gut microbiome. Although diet influences intestinal inflammation, the microbial and metabolic pathways involved, and their differences between Crohn's disease (CD) and ulcerative colitis (UC), the two main subtypes of IBD remain unclear.

Objective To investigate how the gut microbiome mediates the effects of habitual diet on inflammatory activity in IBD.

Design This longitudinal study included 198 adults (100 healthy controls, 49 CD, 49 UC), participants completed a validated food frequency questionnaire. Dietary quality was evaluated using established indices (Alternative Mediterranean Diet, Healthy Eating Index-2015, Índice de Alimentación Saludable, Mean Adequacy Ratio, Plant-Based Dietary Indexes, Healthy Food Diversity). Participants also provided two stool samples (baseline and 6 months). Shotgun metagenomics (n=366) enabled taxonomic and functional profiling. Causal mediation analyses were used to identify microbial features mediating the effect of diet on inflammation.

Results IBD patients exhibited lower dietary diversity, fibre intake and nutritional adequacy compared with controls. Microbiome diversity was lowest in CD, intermediate in UC and correlated positively with higher intake of fibre, fruit, vegetables and nuts, and negative with processed foods and sugary beverages. Causal mediation analyses revealed that in CD, coffee, whole wheat bread and healthier diets lowered the Harvey-Bradshaw index through specific bacterial species and metabolites. In UC, Mediterranean-like diets, fruits and coffee reduced C reactive protein via greater microbial richness, reduced dysbiosis and short-chain fatty acid-related functions.

Conclusion Diet quality influences inflammation in IBD through distinct microbiome pathways: specific taxa and metabolites mediate effects in CD, whereas microbial richness and global composition drive protection in UC.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Diet is a key modulator of intestinal inflammation in inflammatory bowel disease (IBD), but the specific microbial and metabolic pathways involved, and their differences between Crohn's disease (CD) and ulcerative colitis (UC) remain unclear.

WHAT THIS STUDY ADDS

⇒ IBD patients showed lower diet quality and microbiome diversity. CD showed the lowest microbial diversity, with coffee and whole wheat bread reducing inflammation via short-chain fatty acid (SCFA)-producing taxa. In UC, Mediterranean-like, fibre-rich diets lowered C reactive protein and calprotectin through enhanced microbial richness and reduced dysbiosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support the development of personalised, microbiome-informed dietary interventions, targeting specific bacterial taxa and SCFA-producing pathways in CD and promoting overall microbial diversity and composition in UC, to complement medical therapy and reduce intestinal inflammation. Identified microbial and metabolic pathways may serve as biomarkers for monitoring diet responsiveness and guiding individualised nutritional management in IBD patients.

INTRODUCTION

Inflammatory bowel disease (IBD), which primarily includes Crohn's disease (CD) and ulcerative colitis (UC), is a multifactorial disorder influenced by host genetics, the gut microbiome and dietary factors. Affecting up to 10 per 1000 individuals in industrialised countries,[1] IBD is associated with a reduced life expectancy of five to 8 years.[2]

Family studies provide strong evidence that host genetics play a substantial role in the aetiology of IBD, with approximately 8%–12% of patients having a first-degree relative affected by the disease, underscoring the importance of familial clustering.[3] Twin studies further reinforce this genetic contribution, reporting concordance rates of up to 55% for CD in monozygotic twins, compared with considerably lower rates of up to 17% for UC.[4–6] These findings indicate a stronger heritable component for CD than for UC. The remaining variance in

disease risk is likely attributable to environmental factors, particularly diet and gut microbiome composition.

Microbiome alterations in IBD can be considered at multiple levels, including changes in alpha diversity, shifts in overall microbial community structure from a eubiotic to a dysbiotic state and variations in the relative abundance of specific taxa. In general, CD exhibits greater diversity loss and higher dysbiosis scores compared with UC.[7–9]

Diet is a key determinant of human health and one of the most powerful environmental modulators of the gut microbiome.[10 11] Both short-term and long-term dietary patterns influence microbial diversity, taxonomic composition and functional potential, thereby shaping host metabolism, immune responses and susceptibility to disease.[12 13] Diets rich in plant-based, fibre-dense and diverse foods are consistently associated with higher microbial diversity and increased production of beneficial metabolites such as short-chain fatty acids (SCFAs).[14–16] Conversely, Westernised diets rich in fat, sugar and animal protein are often linked to dysbiosis and proinflammatory profiles.[17]

Prospective and interventional studies consistently link dietary patterns to IBD risk and disease course. High fibre intake, especially from fruit, has been shown to protect against CD, whereas high consumption of ultraprocessed foods (UPFs) increases IBD risk.[18–20] Mediterranean-style, plant-forward diets are increasingly recommended for disease management, emphasising reduced UPFs and red/processed meat.[21 22] Exclusive enteral nutrition and the CD exclusion diet have also demonstrated efficacy in inducing remission.[23 24] Mechanistically, fibre-rich diets promote SCFA-linked mucosal homeostasis, whereas UPFs disrupt microbial and metabolic pathways driving inflammation.[25]

However, the extent to which these dietary effects on disease activity are mediated through the gut microbiome remains incompletely understood, and whether such modulation differs between CD and UC. To address this gap, we conducted a prospective longitudinal study aiming to elucidate the mediating role of the gut microbiota in linking dietary intake with clinical and phenotypic characteristics of patients with IBD.

METHODS

Recruitment of participants

Healthy controls (HC, non-IBD) were recruited between December 2020 and March 2025 through announcements on social media platforms (Facebook, LinkedIn and Instagram) and the Hospital Vall d'Hebron website. IBD patients were enrolled between January 2023 and April 2025 during routine follow-up visits at the hospital. Patients' clinical activity status was based on the Harvey-Bradshaw Index (HBI)[26] for CD and the Colitis Activity Index (CAI)[27] for UC.

Inclusion criteria for all participants were age over 18 years and, for HC participants, no antibiotic use within the previous 3 months. Additionally, HCs were required to have no diagnosis of chronic intestinal disorders including IBD, type 2 diabetes and autoimmune diseases, before entering the study. All participants signed a consent form, provided two stool samples and filled a simplified Food Frequency Questionnaire at baseline and 6 months later. Characteristics of the participants are found in table 1.

Metadata and sample collection

Participants filled out an in-house questionnaire, which enabled the collection of demographic, lifestyle, clinical and dietary data and shipped their stool samples to the microbiome laboratory at baseline and month 6. The questionnaire was administered online (https://manichanh.vhir.org/sFFQ/login.php). It included 58 food items (online supplemental table S1) organised into 24 food groups, and nine macronutrients (online supplemental table S2 and S3). Frequency of consumption was categorised into six possible options: 'never', "1 or 3 times per month', '1 or 2 times per week', "3 or more times per week', 'once per day' and '2 or more times per day'. Serving size consisted of a 'standard portion' estimated using the ENALIA2 Survey 12 as well as our own expertise, 'half of the standard' and 'double of the standard'.[28] Additional information such as age, sex, weight, height, birth type, smoking habit, blood type, specific diet, consumption of ready-to-eat food or sweeteners, liquids and supplements, or medication was also recorded. Participants preserved their stool samples immediately after collection using a simple, home-prepared setup, consisting of a sterile screw-cap tube prefilled with 97% ethanol. The tubes were then sealed and placed in the participants' domestic freezers until shipment. Ethanol preservation at this concentration has been shown to effectively stabilise microbial communities and prevent microbial overgrowth during transportation.[29] On arrival at the laboratory, all samples were immediately stored at −80°C until DNA extraction.

Dietary pattern indices

We utilised various eating quality indexes to assess the nutritional quality of diets. These indexes encompass the Healthy Eating Index-2015 (HEI-2015), the IASE (derived from its Spanish acronym 'Índice de Alimentación Saludable para la Población Española'),[30] the plant-based dietary indexes (PDI), uPDI (u=unhealthy), hPDI (h=healthy),[31] the Healthy Food Diversity Index (HFD-index),[32] the Alternative Mediterranean Diet (aMED) score[33 34] and the Mean Adequacy Ratio (MAR).[35] A detailed description of each dietary index is provided in online supplemental methods.

Microbiome analysis

Genomic DNA was extracted from the stool samples in accordance with the International Human Microbiome Standards (http://www.microbiome-standards.org), incorporating an initial mechanical disruption step to ensure effective cell wall lysis.[36] The DNA shotgun library was prepared and underwent sequencing using the Illumina Novaseq X Plus platform. The sequencing process generated an average of 5.7 Gbp per sample, corresponding to approximately 38 million reads with an average read length of 150 bp. The KneadData V.0.7.4 pipeline was used to preprocess and decontaminate the sequence reads (https://huttenhower.sph.harvard.edu/kneaddata). KneadData performed a quality filtering of the reads using trimmomatic and then mapped them against a human reference genome database using Bowtie V.2. Reads with lengths below 50% of the total input length and also those that mapped with the human genome were discarded from further analysis.

Taxonomic profiles were provided by the MetaPhlan4's intermediary output file in the HumanN3.6 pipeline (from phylum to SGB level) and functional profiles from the final output.[37] Alpha and beta diversity analyses were computed using Chao1 and Shannon indexes and the adonis2 function (PERMANOVA, Permutational Multivariate Analysis of Variance). Functional profiles, output of HumanN3, provided MetaCyc pathways, which were filtered to remove unmapped and unintegrated reads. All features that did not achieve 0.001 abundance and 0.1 prevalence (pathways that did not achieve 0.1% of the total sample abundance in at least 10% of the samples) were also

Table 1 Clinical characteristics of the cohorts

	CD		UC		HC	
Timepoints (TP0=baseline; TP1=month 6)	TP0	TP1	TP0	TP1	TP0	TP1
Number of subjects	49	49	49	48	100	100
Female/male	24/25	24/25	22/27	22/26	50/50	50/50
Mean (IQR) age (years) at sample collection	42.31 (19–71)	43.14 (19–71)	42.16 (19–68)	42.33 (19–69)	43.99 (22–69)	44.49 (22–70)
Disease location (Montreal classification)						
L1 ileal (%)	19 (38.77)	19 (38.77)	–	–	–	–
L2 colonic (%)	9 (18.36)	9 (18.36)	–	–	–	–
L3 ileocolonic (%)	20 (40.81)	20 (40.81)	–	–	–	–
L4 isolated upper disease (%)	2 (4.08)	2 (4.08)	–	–	–	–
Disease behaviour at sampling (Montreal classification)						
B1 non-stricturing, non-penetrating (%)	20 (40.81)	20 (40.81)	–	–	–	–
B2 stricturing (%)	14 (28.57)	14 (28.57)	–	–	–	–
B3 penetrating (%)	14 (28.57)	14 (28.57)	–	–	–	–
p perianal disease (%)	11 (22.44)	11 (22.44)	–	–	–	–
Disease extent at sampling (Montreal classification)						
E1 proctitis (%)	–	–	3 (6.12)	3 (6.12)	–	–
E2 left-sided colitis (%)	–	–	15 (30.61)	15 (30.61)	–	–
E3 extensive colitis (%)	–	–	30 (61.22)	30 (61.22)	–	–
Disease activity scores						
HBI, median (IQR)	1 (0–3.75)	2 (1–3)	–	–	–	–
CAI, median (IQR)	–	–	1.5 (0–3)	2 (1–2.75)	–	–
Active smoking at baseline						
Yes (%)	8 (16.32)	8 (16.32)	2 (4)	2 (4.16)	10 (10)	10 (10)
No (%)	19 (38.77)	19 (38.77)	29 (59.18)	29 (60.41)	70 (70)	70 (70)
Ex-smoker (%)	22 (44.89)	22 (44.89)	18 (36.73)	17 (35.41)	20 (20)	17 (17)
Medication at sampling						
Corticosteroids (%)	8 (16.32)	4 (2.55)	11 (22.44)	11 (22.91)	–	–
Oral immunosuppressants (%) (AZA, TOFA)	14 (28.57)	12 (24.48)	18 (36.73)	16 (33.33)	–	–
Anti-TNF (%)	28 (57.14)	27 (55.10)	20 (40.81)	18 (37.50)	–	–
5-aminosalicylic acid	6 (12.24)	7 (14.28)	33 (67.34)	33 (68.75)		
Antibiotics (%)	8 (16.32)	4 (8.16)	11 (22.44)	10 (20.83)	3 (3)	8 (8)

Because healthy controls were recruited through open calls, a few participants reported baseline antibiotic use despite the exclusion criteria. This variable was included as a confounder in all relevant analyses to prevent bias.
AZA, azathioprine; CAI, Colitis Activity Index; CD, Crohn's disease; HBI, Harvey-Bradshaw Index; HC, healthy controls; TNF, tumour necrosis factor-α; TOFA, tofacitinib; UC, ulcerative colitis.

discarded. Then, pathway abundances were then transformed using the centred log-ratio method before downstream analyses.

Mediation analysis

To evaluate the extent to which the gut microbiome or specific taxa mediated the association between dietary variables and health outcomes, we performed causal mediation analyses, accounting for age, gender, body mass index (BMI), smoking status, infliximab, mesalazine and recent antibiotic use as confounders.

To study the effect of continuous microbiome variables as mediators, such as diversity indices (Chao1 and Shannon) or dysbiosis score, we employed the 'mediation' R package (V.4.5.1). Outcomes and treatment variables were coerced into numeric or binary vectors as appropriate. Depending on data distribution, the function fit linear regression models for continuous outcomes, logistic regression for binary outcomes, Poisson regression for counts and quasibinomial regression for proportions. Indirect (mediated), direct and total effects were estimated using bootstrap resampling with 1000 simulations.

Linear model assumptions were evaluated for all regression models used in the mediation analyses. Normality of residuals was assessed using the Shapiro-Wilk test from the R 'stats' package (V.4.3.3), and homoscedasticity was tested using the Breusch-Pagan test from the 'lmtest' package (V.0.9.40). In cases where heteroskedasticity was detected, quasi-Bayesian simulations were performed with heteroskedasticity-consistent SEs.

On the other hand, 'miMediation' PhyloMed (V.0.3)[38] function was used to perform the analysis using microbiome composition as a mediator, performing the test at each phylogenetic node. Microbial abundances derived from phyloseq objects were filtered based on relative abundance (≥0.1%) and prevalence (≥10%), and mapped onto a phylogenetic tree. Mediation significance was assessed with 1000 permutations, controlling the false discovery rate (FDR=0.1).

Statistical analyses

All statistical analyses were conducted in R (V.4.3.3). Dietary intake data were analysed at three levels of resolution: individual food items, aggregated food groups and macronutrients. For each dataset, participants were stratified by health status (HC, CD, UC). Missing values were removed prior to analysis.

To explore major dietary patterns, principal component analysis (PCA) was applied using the prcomp function in R. PCA

results were visualised with the ggfortify package (V.0.4.17), displaying ordination plots of individuals coloured by health status, together with variable loadings representing the strongest dietary contributors to separation between groups. To statistically evaluate group differences in dietary profiles, PERMANOVA tests were applied using the adonis2 function from the vegan package (V.2.6–4). Analyses were performed with Euclidean distance as the dissimilarity metric and 999 permutations. Where overall group differences were significant, pairwise PERMANOVA tests were applied using the pairwise.perm.manova function to assess pairwise contrasts between HC, CD and UC groups.

Correlation analyses were performed using the Spearman rank correlation test to evaluate monotonic associations between variables. For comparisons between groups, normally distributed continuous variables, assessed by the Shapiro-Wilk test, were analysed using Student's t-test, while non-normally distributed continuous variables were tested with the Mann-Whitney U test. Categorical variables were compared using Pearson's χ^2 test and Fisher's exact test with the R package gtsummary (V.2.3.0). To account for multiple comparisons, p values were adjusted using the FDR method (Benjamini-Hochberg procedure).

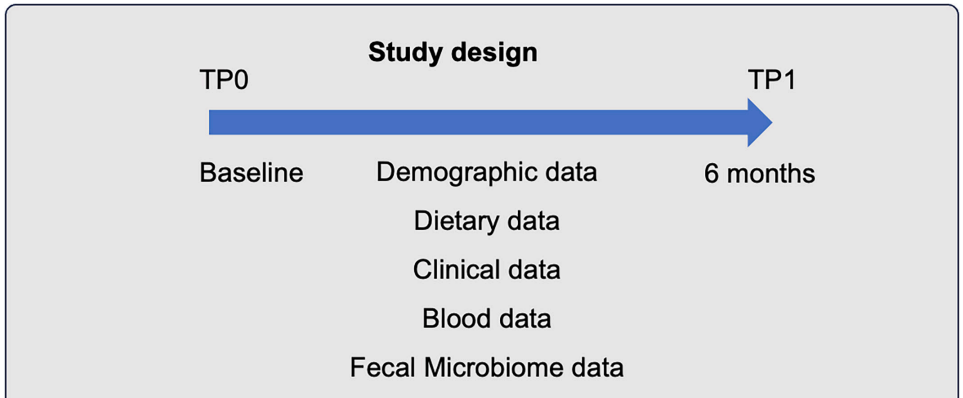
Although measurements were obtained from the same individuals at two time points, the observations were treated as independent in the analyses. This decision was justified because the primary aim was to assess cross-sectional associations between dietary data levels and gut microbiota composition, rather than longitudinal changes. As dietary patterns were not expected to vary substantially over the study period and data were available for the majority of participants at both time points, treating these measures as independent is unlikely to bias the results. The residual within-individual correlation between time points is therefore considered minimal and does not affect the relationships of interest.

For comparisons of dietary intake between HCs and IBD patients, Mann-Whitney U tests were applied. Given the limited expected dietary variation within individuals and the focus on group-level differences rather than within-subject changes, treating repeated measures as independent observations was considered appropriate for these non-parametric comparisons.

RESULTS

Study design and population characteristics

Participants were recruited via social media platforms for HCs (n=100) and through clinician consultations at the Hospital Vall d'Hebron for patients with IBD (CD, n=49; UC, n=49). At baseline and again 6 months later, all participants completed a custom-designed online questionnaire capturing demographic, lifestyle, clinical, treatment and dietary information. Dietary data were collected using a short food frequency questionnaire (sFFQ) comprising 58 food items, which were grouped into 24 food groups and nine macronutrients[28] (online supplemental tables S1–S3). Blood and stool samples from IBD patients were obtained during physician consultations to measure clinically relevant biomarkers, including calprotectin and C reactive protein (CRP), respectively. Stool samples were self-collected by all participants and mailed to the laboratory at both time points for microbiome analysis. Despite some missing data, approximately 90% of the planned measurements were successfully obtained, as summarised in figure 1. Notably, clinical and blood marker data were unavailable for HC (table 1). We also included a descriptive comparison of population characteristics and medication intake across the three participant cohorts. The results showed that although age and gender did not differ significantly between groups, other variables, such as medication intake, did show significant differences (online supplemental table S4). We then performed an effect size analysis to evaluate the impact of these characteristics and medications on dietary patterns and microbiome composition. While some variables (gender, azathioprine, tofacitinib) showed effect on the consumption of food items, these effects were not significant at the food group and



	HC		CD		UC		Total
	TP0	TP1	TP0	TP1	TP0	TP1	
Demographic data	100	100	48	32	42	31	353
Dietary data	100	100	48	32	42	31	353
Clinical data	NA	NA	49	49	49	48	195
Blood data	NA	NA	49	30	46	35	160
Fecal sample	100	100	48	36	46	36	366

Figure 1 Study design. Data types and number of participants providing, TP0=baseline; TP1=6 months after baseline. Dietary and demographic data, along with stool samples, were self-collected by all participants via an online questionnaire, while blood parameters and clinical data for IBD patients were obtained during a physician consultation. CD, Crohn's disease; HC, healthy controls; IBD, inflammatory bowel disease; UC, ulcerative colitis.

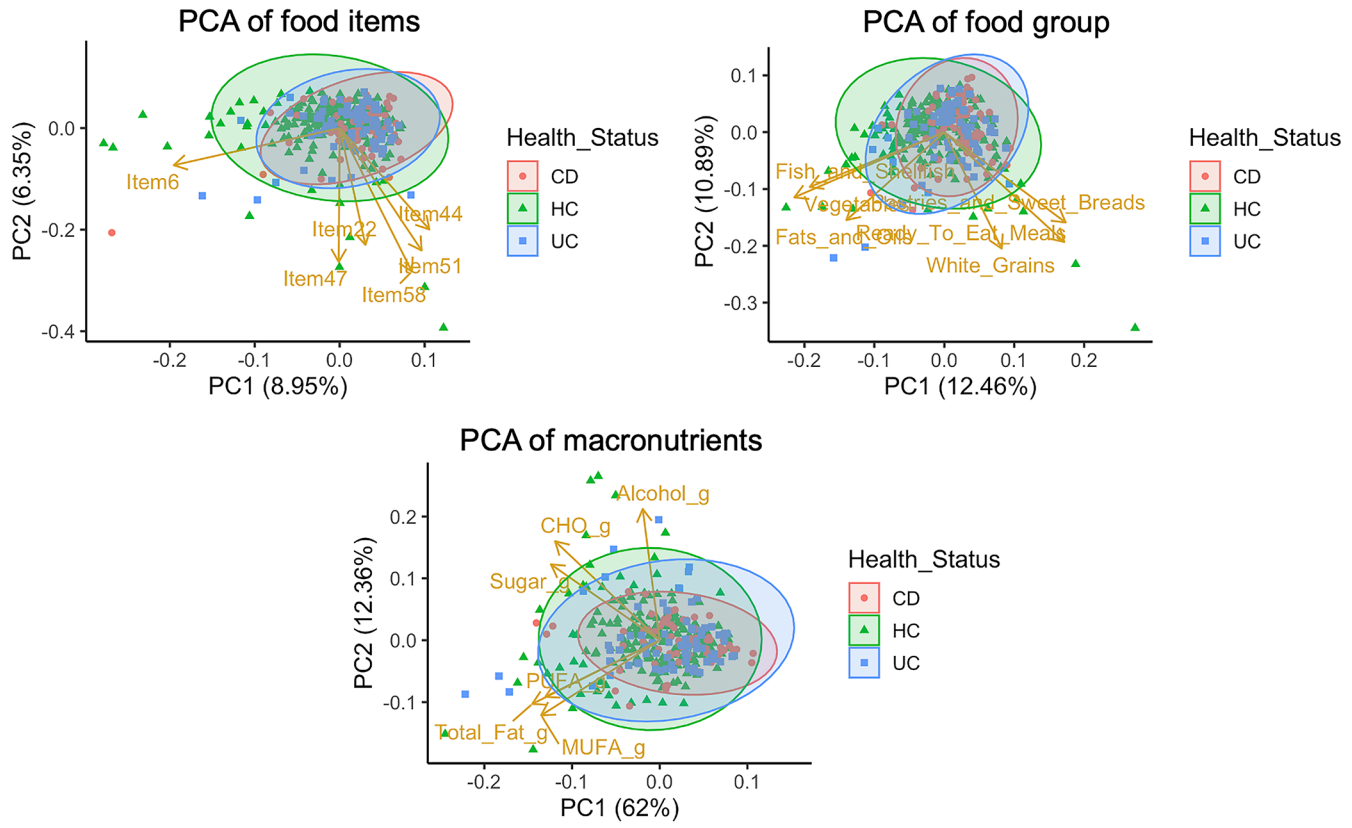


Figure 2 Clustering by health status using principal component analysis (PCA). Dimensionality of the dietary information (food items, food groups and macronutrients) was reduced using PCA. Item6: Carrot, pumpkin and beet; Item 22: Cooked cereal and pasta such as noodles, macaroni, spaghetti, white rice, couscous, bulgur and other grains; Item 44: Pastries such as doughnuts, muffins, croissants, 'palmera', churros, cakes and puff pastry; Item 47: Packaged tomato sauce and canned tomato; Item 51: Soft drinks such as cola, diet soda and isotonic or flavoured drinks; Item 58: Processed food such as pizza, lasagna, cannelloni, chicken nuggets and potato omelette. The complete list of food item's, food group's, macronutrient's description is provided in online supplemental tables S1–S3. CD, Crohn's disease; HC, healthy controls; UC, ulcerative colitis.

macronutrient levels (online supplemental figure S1). Interestingly, medications such as infliximab, antibiotics and mesalazine did influence microbiome composition. These variables were, therefore, included as confounders in the subsequent mediation analyses (see below).

Homogeneous dietary profiles in IBD compared with controls

Dimensionality reduction of dietary data using PCA, followed by PERMANOVA testing, revealed significant group differences between both IBD subtypes and HC, at the level of food items (q=0.0015), food groups (q=0.0015) and macronutrients (q=0.0015). Notably, pairwise comparisons showed no significant differences between CD and UC patients, whose profiles clustered more tightly than those of HC participants (figure 2, online supplemental table S5). This more homogeneous dietary pattern among CD and UC patients may reflect disease-related dietary restrictions, reduced intake diversity or shared nutritional adaptations associated with disease management.

Impaired diet quality and disease-specific eating behaviours in IBD

Next, we assessed diet quality by evaluating how closely participants' dietary intake aligned with established nutritional guidelines and health-promoting dietary patterns. To this end, we applied several dietary indices to data collected through the sFFQs, including the aMED, developed in the USA based on adherence to Mediterranean dietary principles; the HEI-2015, reflecting compliance with the US Dietary Guidelines; the IASE, a Spanish adaptation of the HEI-2015; the plant-based dietary indices, hPDI (healthy) and uPDI (unhealthy), which differentiate between healthy and less healthy plant-based foods; the HFD-index, developed in Germany to capture dietary variety and balance; and the MAR, a nutrient-based indicator summarising overall adequacy across key macronutrients and micronutrients. A detailed description of each dietary index is provided in online supplemental methods.

The analyses revealed that patients with CD and UC exhibit dietary quality patterns distinct from those of HCs (figure 3). Both CD and UC patients had lower scores on the aMED, HEI-2015, IASE, MAR and hPDI indices compared with HC. In addition, CD patients showed reduced HFD scores, while UC patients had higher hPDI scores relative to CD.

These findings indicate that the overall quality of the IBD patient diets is diminished compared with HCs. This is particularly evident in the reduced intake of recommended and moderated food groups (aMED, HEI-2015, IASE), essential micronutrients (MAR) and dietary diversity and nutrient density (HFD, in CD). Notably, UC patients appear to follow a relatively healthier dietary pattern than CD patients, as reflected by their higher hPDI scores compared with HCs.

We now compared dietary profiles at multiple levels of dietary classification, including individual food items, food groups and

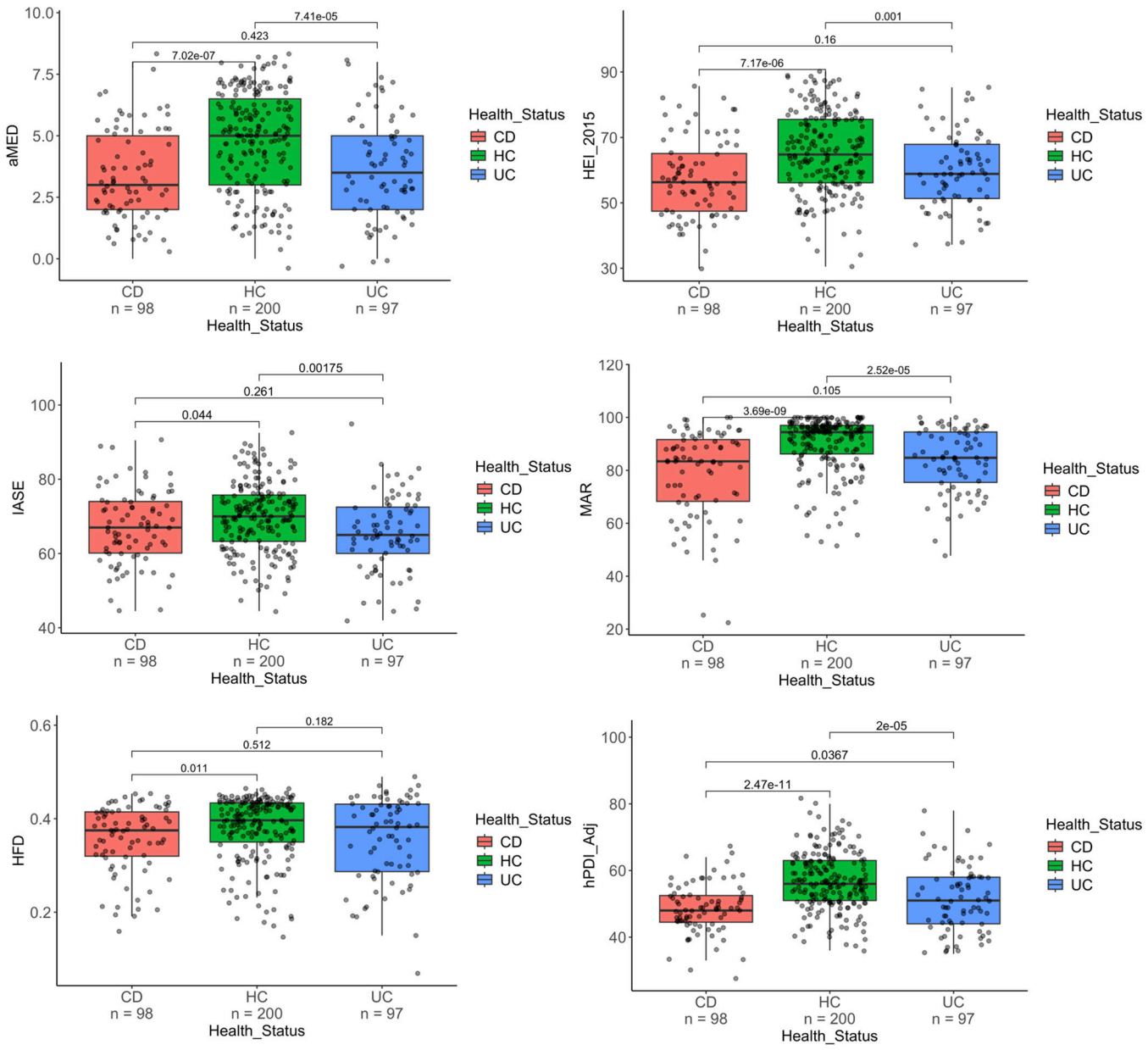


Figure 3 Comparison of dietary profiles according to health status using Eating Quality Indices (EQIs). Only indices showing significant differences are displayed (Wilcoxon rank-sum test followed by Benjamini–Hochberg (BH) correction; q<0.05). aMED, Alternative Mediterranean Diet score; CD, Crohn's disease; HC, healthy controls; HEI-2015, Healthy Eating Index–2015 (U.S.); HFD, Healthy Food Diversity index; hPDI, Healthful Plant-Based Diet Index; IASE, Healthy Eating Index for the Spanish population; MAR, Mean Adequacy Ratio (essential nutrients); UC, ulcerative colitis.

macronutrients across health status groups (HC, CD and UC). Analysis of variance (ANOVA) was applied to normally distributed variables, while the Kruskal-Wallis test was used for non-parametric data, followed by appropriate post hoc analyses. Overall, both CD and UC patients reported a reduced intake of a wide range of food items and food groups, which translated into lower consumption of several macronutrients, including fibre, fat, alcohol and sugar. In addition, CD patients showed further deficits in carbohydrate and protein intake (online supplemental tables S6–S8). Among these dietary reductions, both IBD groups reported particularly low intake of vegetables, fruits and nuts/seeds, corresponding to a markedly reduced overall fibre intake (online supplemental figure S2). Despite these deficits, both patient groups reported a higher consumption of packaged fruit juices compared with HC. CD patients, in particular, showed greater intake of soft drinks, including cola and diet soda (item 51) and packaged fruit juices (item 52). Few significant dietary differences were observed between CD and UC patients; however, CD patients reported significantly higher consumption of processed foods (item 58), canned fish in oil and packaged tomato compared with UC.

We then explored whether habitual fibre intake was related to inflammatory burden or clinical activity. Overall, fibre intake showed no significant correlation with biochemical markers of inflammation (CRP or faecal calprotectin) or disease activity scores (online supplemental figure S3A), except for a modest inverse association between fibre intake and HBI in CD ($\rho=-0.23$, $p=0.049$). This suggests that higher fibre intake

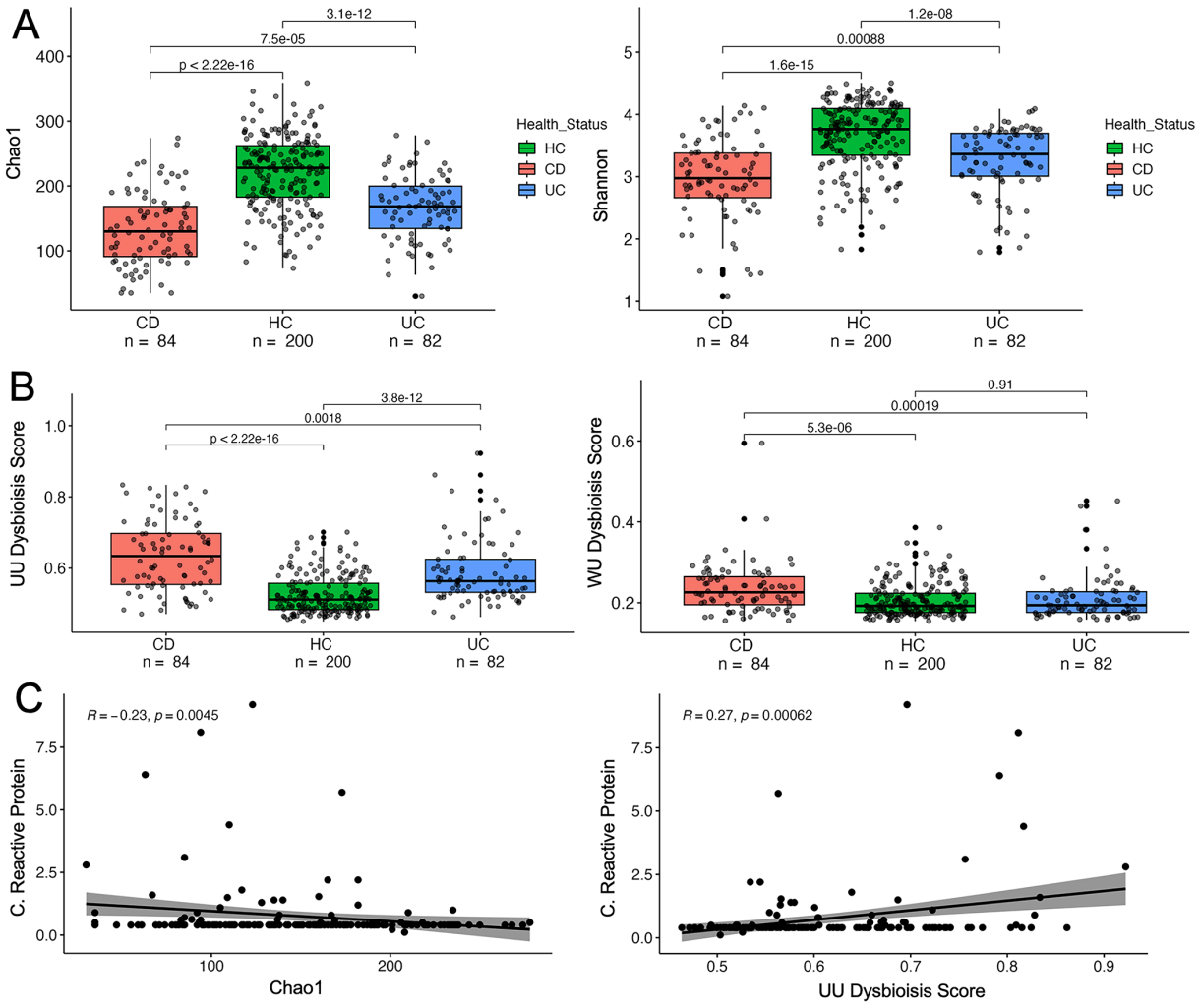


Figure 4 Microbiome alpha diversity, dysbiosis and correlations with clinical parameters. (A) Alpha diversity was evaluated using the Chao1 richness and Shannon diversity indices. (B) Microbial dysbiosis was quantified as the median unweighted (UU) and weighted (WU) UniFrac distance of each sample to a reference centroid constructed from 100 healthy control (HC) samples. Pairwise group comparisons were performed using the Wilcoxon rank-sum test. (C) Spearman correlation analysis between clinical variables (C reactive protein, calprotectin, HBI, CAI) and both alpha diversity indices and dysbiosis scores. Only statistically significant correlations are shown (p<0.05). CAI, Colitis Activity Index; CD, Crohn's disease; HBI, Harvey-Bradshaw Index; HC, healthy controls; UC, ulcerative colitis.

may be weakly associated with milder clinical activity in CD, although the effect size was small and should be interpreted with caution. Moreover, using the PERMANOVA test, we did not find significant differences in dietary intake (food items, food groups and macronutrients) between IBD patients in relapse and in remission (online supplemental figure S3B).

Greater dysbiosis and reduced diversity in CD compared with UC: associations with diet and inflammation

Alpha diversity analysis, based on Chao1 and Shannon indices, confirmed previous observations that CD is associated with reduced microbial diversity and evenness compared with both UC and HC, and that UC also exhibits lower values than HC (figure 4A). To further assess the extent of dysbiosis in IBD patients relative to healthy individuals, we calculated a dysbiosis score, defined as the median weighted UniFrac distance of each sample to a reference plane constructed from 100 HC samples. This analysis revealed that CD also harbours a more dysbiotic microbiome composition than UC when compared with HCs (figure 4B).

We next examined correlations between clinical variables, dietary quality indices and dietary intake data with both alpha diversity and dysbiosis scores in IBD patients using Spearman correlation tests. Alpha diversity showed significant negative correlations with the number of bowel movements and CRP levels (online supplemental table S9). In contrast, dysbiosis scores displayed the opposite pattern of associations (online supplemental table S10). Moreover, higher dietary quality, as measured by the aMED, HEI-2015, hPDI and MAR indices, was positively associated with alpha diversity and negatively correlated with dysbiosis scores (online supplemental tables S11 and S12).

Correlation analyses were conducted using food items, food groups and macronutrients. Consistent with our previous findings on a healthy population,[16] the intake of fruits, vegetables, legumes, nuts and seeds was associated with greater microbiome diversity, whereas vegetables, fruits, legumes, dark chocolate, nuts, seeds and wine were linked to lower IBD-related dysbiosis (online supplemental tables S13–S15). In contrast, higher consumption of soft drinks, packaged fruit juices and white bread was associated with reduced alpha diversity (online

supplemental table S13) and increased dysbiosis (online supplemental table S15 and S16). At the macronutrient level, higher fibre intake was similarly associated with greater diversity and lower dysbiosis scores (online supplemental tables S17 and S18).

As this was a longitudinal study, we also compared variables between the two time points. Specifically, we examined correlations between the changes (Δ) in Eating Quality Indices (EQIs) and inflammatory markers and performed mediation analyses using the changes in all relevant variables. None of these analyses yielded statistically significant results. This suggests that, over the 6-month follow-up, variations in diet quality and related parameters were not associated with measurable changes in inflammation, possibly reflecting the clinical stability of the cohort during this period.

Different microbiome pathways mediate diet-inflammation links in CD and UC

We conducted causal mediation analyses to evaluate whether gut microbiome features mediated the associations between dietary variables (EQIs, food items, food groups and macronutrients) and clinical outcomes, namely faecal calprotectin, CRP and disease activity indices (HBI and CAI), in patients with CD and UC. Two complementary strategies were applied to the microbiome data: (1) a global approach, incorporating microbial diversity indices and dysbiosis scores and (2) a taxon-specific approach, focusing on individual microbial taxa while accounting for phylogenetic relationships (PhyloMed; see the Methods section). Gender, age, BMI, smoking status, infliximab, mesalazine and recent antibiotic use were included as confounders in all models.

In CD, several EQIs, as well as the consumption of various food groups, were associated with reduced levels of CRP (hPDI, nuts and seeds, whole wheat bread), HBI (HEI-2015, aMED, nuts and seeds, tomato, broccoli, fruits, coffee) and increased levels of CRP, calprotectin and HBI (uPDI) (figure 5, online supplemental tables S19 and S20). However, these associations were not mediated by microbial α-diversity or dysbiosis scores. At the taxon-specific level, both the HEI-2015 and MAR indices, along with the intake of coffee and whole wheat bread, were linked to lower HBI values through mediation by several bacterial taxa (figure 5). Specifically, higher HEI-2015 and MAR scores and greater coffee consumption were associated with lower HBI levels via increased relative abundances of *Bacteroides caccae*, *B. faecis* and *B. thetaiotaomicron*, relative to that of *Bacteroides fragilis*. Similarly, whole wheat bread consumption was associated with lower HBI values through increased abundances of *Butyricimonas paravirosa*, *B. faecihominis* and *Odoribacter splanchnicus*, together with decreased *Coprobacter fastidiosus*. Both coffee and whole wheat bread were further linked to lower HBI indices via increased abundances of *Sutterella wadsworthensis*, *Parasutterella excrementihominis* and *Parasutterella* SGB9260, accompanied by reduced *Escherichia coli* abundance. Additionally, coffee intake was associated with lower calprotectin levels, an effect mediated by a higher abundance of *Lawsonibacter asaccharolyticus* and a lower abundance of *Clostridiales bacterium*. Notably, the association between coffee consumption and *Lawsonibacter asaccharolyticus* (also known as *Clostridium phoceensis*) has been recently reported by Manghi *et al*.[39]

In UC, higher uPDI scores were associated with higher calprotectin and CRP levels, with these effects mediated by decreased microbial richness (Chao1 index) and increased dysbiosis (figure 5, online supplemental table S21). aMED indices were also associated with lower CRP and calprotectin, although these effects were mediated exclusively through reduced dysbiosis. Together, these results indicate that both microbial diversity and overall community structure play important roles in modulating inflammation in UC. At the food level, consumption of fruits and coffee was associated with reduced calprotectin and CRP levels through enhanced microbial richness and decreased dysbiosis, whereas whole wheat bread intake was linked to higher calprotectin and CRP levels mediated by microbial richness (figure 5, online supplemental table S22). Notably, olive oil consumption was associated with lower calprotectin and CRP levels via reduced dysbiosis. Overall, these findings highlight the influence of specific dietary components on gut microbial ecology and their potential role in modulating intestinal inflammation. At the taxon-specific level, only chocolate consumption was associated with higher CRP levels, mediated by increased abundances of *Prevotella copri* and *Prevotella marseillensis*, and a reduced abundance of *Prevotella clara*.

As the bacterial taxa mentioned above (*Bacteroides caccae*, *Bacteroides faecis*, *Bacteroides thetaiotaomicron*, *Butyricimonas paravirosa*, *Butyricimonas faecihominis*, *Odoribacter splanchnicus* and *Clostridium phoceensis*) are known producers of SCFAs, particularly acetate, butyrate and propionate, causal mediation analyses were conducted to evaluate whether the effects of specific dietary features on inflammatory markers were mediated through microbial metabolic pathways involved in SCFA production (online supplemental table S23). In CD, significant indirect effects were observed for several diet-acetate pathway-inflammation relationships. For instance, coffee consumption was associated with a decrease in HBI, with a significant indirect effect mediated through the hexitol fermentation to lactate, formate, ethanol and acetate pathway. This result indicates that nearly one-third of the total anti-inflammatory effect of coffee on the HBI is explained by microbial acetate-related metabolism. Moreover, soft drink (Item 51) intake was associated with an increase in HBI, with an indirect effect mediated through a mixed-acid fermentation pathway, which accounted for more than 80% of the proinflammatory effect. In UC, significant indirect effects were also observed for several diet-acetate and propionate pathway-inflammation relationships. For instance, higher adherence to the Mediterranean diet index (aMED) showed a strong mediation effect on CRP levels through the acetylene degradation pathway, which accounted for about 60% of its anti-inflammatory effect.

DISCUSSION

Our findings reveal distinct and disease-specific dietary patterns in patients with CD and UC, with potential implications for nutritional adequacy, gut microbial composition and intestinal health. IBD groups reported more restrictive diets compared with HCs, characterised by lower intake across multiple food groups. This pattern likely contributes to deficiencies in both macronutrients and micronutrients, as reflected by lower MAR indices, potentially exacerbating malnutrition and impairing gut function. Interestingly, despite their restrictive patterns, patients reported higher consumption of packaged fruit juices, which are typically high in sugars and additives, perhaps reflecting a preference for 'safe' liquid calories or easily digestible foods during symptomatic periods.

The absence of a strong association between habitual fibre intake and inflammatory or clinical activity markers in our cohort is consistent with previous studies reporting variable or modest relationships between fibre consumption and disease activity in IBD.[40] While higher fibre intake has been associated

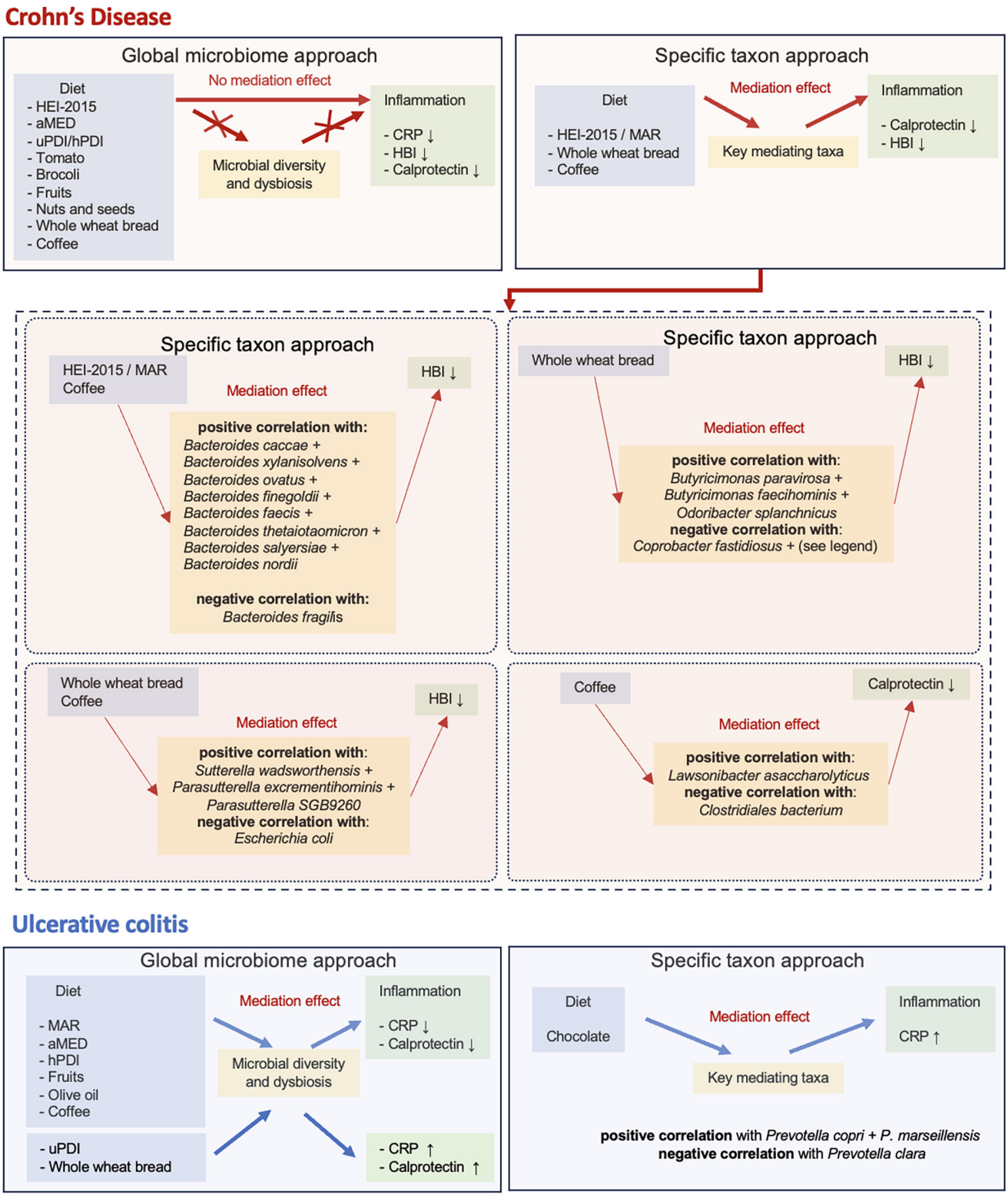


Figure 5 Microbiome pathways mediate diet-inflammation links in CD and UC. Mediation analysis to test whether gut microbiome features (alpha diversity, dysbiosis scores, or specific taxa) mediate the links between diet (EQIs, food items, food groups, macronutrients) and clinical outcomes (calprotectin, CRP, HBI, CAI) in patients with CD and UC. '*Coprobacter fastidiosus* +' is a shortcut for the involvement of the following bacterial species: *Coprobacter fastidiosus*, *Barnesiella intestinihominis, Prevotella copri clade A, Prevotella marseillensis, Paraprevotella clara, Bacteroides caccae, Bacteroides xylanisolvens, Bacteroides ovatus, Bacteroides finegoldii, Bacteroides faecis, Bacteroides thetaiotaomicron, Bacteroides salyersiae, Bacteroides nordii, Bacteroides fragilis, Bacteroides cellulosilyticus, Bacteroides uniformis, Bacteroides clarus, Bacteroides stercoris, Bacteroides eggerthii, Phocaeicola plebeius, Phocaeicola dorei, Phocaeicola vulgatus, Phocaeicola massiliensis, Parabacteroides merdae, Parabacteroides johnsonii, Parabacteroides distasonis*. aMED, Alternative Mediterranean Diet score; CAI, Colitis Activity Index; CD, Crohn's disease; CRP, C reactive protein; EQI, Eating Quality Indices; HBI, Harvey-Bradshaw Index; HEI-2015, Healthy Eating Index–2015 (U.S.); hPDI, healthy plant-based dietary indexes; MAR, Mean Adequacy Ratio; UC, ulcerative colitis.

with a reduced risk of developing CD, these findings do not extend to the disease course of established IBD, and thus do not directly support an association with clinical activity. Accordingly, emerging evidence suggests that the physiological impact of dietary fibre in IBD may depend more on an individual's microbial fermentative capacity than on total intake alone, with interindividual variability in SCFA production likely mediating heterogeneous responses.[41] Interventional studies assessing specific fibre types and their effects on mucosal inflammation and microbiome composition are required to clarify these relationships.

The observed gradient in microbial diversity and dysbiosis across disease groups, being most pronounced in CD and intermediate in UC, adds further support to the concept that host-microbiome interactions are central to IBD pathogenesis. Family and twin studies have long established that host genetics contribute substantially to disease susceptibility, particularly in CD, which shows higher familial aggregation and twin concordance rates than UC.[3] The stronger heritable component of CD may in part explain its greater degree of microbiome disruption, as genetic variants linked to innate and adaptive immune responses, such as *NOD2*, *ATG16L1* and *IRGM*, directly influence microbial recognition, autophagy and mucosal barrier function.[42 43] Consequently, individuals genetically predisposed to CD may be more prone to loss of microbial diversity and community stability under environmental challenges. Conversely, the comparatively milder dysbiosis observed in UC may reflect a disease process more tightly linked to mucosal immune responses and environmental triggers rather than deep alterations of the gut ecosystem.

The observed negative correlations between microbial diversity and both CRP and bowel frequency, alongside positive associations with dietary quality indices (aMED, HEI-2015, hPDI, MAR), reinforce the close link between diet, microbiome and inflammation. Diets richer in plant-based foods, fibre and micronutrients, typical of Mediterranean-like or high-quality dietary patterns, were associated with higher microbial diversity and reduced dysbiosis, consistent with prior reports.[20 44] These results suggest that adherence to nutrient-dense dietary patterns may promote a more balanced and resilient gut ecosystem, potentially mitigating dysbiosis and inflammation in IBD.

Our mediation analyses further delineate disease-specific microbial routes through which diet may modulate intestinal inflammation. In CD, the associations between higher dietary quality and lower inflammatory burden were not mediated by broad microbial metrics such as α-diversity or dysbiosis but instead by shifts in specific bacterial taxa. Taxa such as *Bacteroides thetaiotaomicron*, *B. caccae* and *B. faecis*, which increased with higher dietary quality, have known roles in maintaining epithelial integrity and modulating T-cell responses.[45 46] Similarly, enrichment of *Butyricimonas spp*. and *Odoribacter splanchnicus*, both butyrate producers, supports a mechanistic route through enhanced SCFA synthesis, which promotes epithelial integrity and regulatory T-cell differentiation.[47] The reduction of *B. fragilis* and *Escherichia coli*, coupled with increased *Sutterella* and *Parasutterella*, indicates a shift away from pathobiont-dominated profiles towards communities with lower pro-inflammatory potential.[48] Conversely, the positive association of *Prevotella copri* with CRP after chocolate intake might highlight the strain-dependent duality of this genus.[49]

In UC, dietary effects on inflammation were mediated by global community features, including greater microbial richness and reduced dysbiosis, as well as by specific foods that enhanced diversity. This suggests that UC inflammation may be more sensitive to broad ecological balance, whereas CD may depend more on targeted shifts in functionally relevant taxa. The functional mediation analyses further support these patterns: in CD, coffee's anti-inflammatory effect on HBI was mediated through acetate-related pathways, while in UC, both adherence to a Mediterranean diet and consumption of polyphenol-rich foods (eg, dark chocolate) were associated with lower CRP levels via the same microbial pathways. Together, these findings highlight a coherent mechanistic route whereby diet influences inflammation through modulation of microbial SCFA production and related metabolic functions.

From a translational perspective, our results provide mechanistic support for dietary interventions as adjuncts to medical therapy in IBD. Diets rich in whole grains, nuts, fruits, coffee and Mediterranean-type foods were associated with reduced inflammation and enrichment of beneficial SCFA-producing taxa. In CD, targeted strategies that promote specific immunomodulatory microbes (eg, *Odoribacter*, *Butyricimonas*) may be most effective, while in UC, interventions enhancing overall microbial diversity and community stability may yield greater benefit. These taxonomic and functional mediators also represent promising biomarkers for monitoring dietary therapy responses.

Our study has some limitations. Future studies should confirm these mediations in controlled dietary intervention trials and independent IBD cohorts to ensure generalisability. Although dietary assessment based on self-reported questionnaires is inherently prone to misclassification, our instrument has been previously validated in a population-based study demonstrating its ability to capture diet–microbiome relationships.[16]

In summary, our results reveal disease-specific mechanisms by which diet may modulate intestinal inflammation. In UC, diet appears to modulate inflammation primarily through restoration of microbial diversity and functional balance, whereas in CD, selective modulation of specific taxa and metabolic pathways may play a dominant role. These findings underscore the potential of personalised, microbiome-informed dietary strategies as complementary tools for precision management of IBD.

Contributors LM and CM designed the study. CH-dG, VR-A and NB recruited the IBD patients and collected clinical data; ZS, MP-T, LC and CM recruited the healthy controls and processed the samples; ANS, SV-A, GS-G and CM performed the bioinformatics analysis; LM and CM interpreted the results; CM supervised the project, obtained the funding and wrote the manuscript; CM is the guarantor. I have used AI for language revision.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the Vall d'Hebron University Hospital; (PR(AG)84/2020). Participants gave informed consent to participate in the study before taking part.

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