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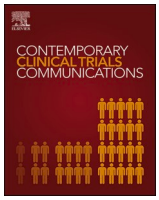

Dieta Anti-Inflamatoria or DAIN: A Crohn's disease management strategy tailored for Puerto Ricans

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A B S T R A C T

Diet has been increasingly shown to be of therapeutic benefit for patients with inflammatory bowel diseases (IBD), especially Crohn's disease (CD). Yet dietary guidelines are nonexistent. Moreover, diets tailored to Puerto Ricans with IBD living on the island, have not been developed and tested. The rising prevalence of IBD in Puerto Rico warrants exploring the use of diet as part of the treatment strategies for these patients [1]. Here, we describe the study design of "Dieta Anti-Inflamatoria" or DAIN, a parallel two-arm randomized pilot trial aiming at testing the efficacy of IBD-Anti-inflammatory diet (IBD-AID) adapted for adults with CD living in Puerto Rico (clinical trial registration number: NCT05627128). We tailored the IBD-AID to the local cuisine preferences and food availability by creating and adapting recipes consistent with the IBD-AID principles [2,3]. In focus groups with a Community Research Advisory Panel and one-on-one consultations with implementation experts, we identified several aspects of the intervention to adapt before the implementation. The objectives of the stakeholder/expert-informed adaptation were to improve feasibility and compliance while developing the culturally tailored dietary intervention. DAIN was designed for adults living in Puerto Rico with CD and geared to be affordable, appropriate, and acceptable for patients with mild-to-moderate CD. The significance of this work is the validation of culturally appropriate nutritional guidelines to help manage CD symptoms. DAIN provides a blueprint for a comprehensive nutritional program that can be adapted to regional preferences and local food availability allowing wider implementation of diet as an adjunct treatment in diverse clinical settings.

1. Introduction

There is emerging evidence that the prevalence of Crohn's disease (CD) in Hispanics is increasing, along with the general USA population [4,5]. Hispanics account for over 17% of the U.S. population [6], yet knowledge of CD in this population, including research on diet as therapy for CD, is scarce. In Puerto Rico, the prevalence of CD has risen steeply in the past decades with a prevalence of 72.71/100,000 in 2013 [1,5,7,8].

Therefore, identifying modifiable health behaviors, such as diet, for the adjunct management of CD is critically needed to improve the quality of life of CD patients in Puerto Rico. Specific dietary habits, such as high consumption of ultra-processed foods, low fiber consumption, and high fat intake, are linked to an increased IBD risk as well as the microbial dysbiosis exhibited by IBD patients, in several large cohorts [9–13]. To date, several clinical trials have shown that diet, in conjunction with medication, is effective in inducing IBD remission within a few weeks after the dietary intervention [2,14–25]. Moreover, those studies have also shown that changes in diet can be tolerated by IBD patients without adverse effects. However, nutritional clinical guidelines for patients with IBD are inexistent.

In Puerto Rico, more than 30% of adults report consuming a fair/poor diet [26]. In fact, a recent study reports that only a small fraction of adults living in the Metropolitan area of Puerto Rico met the recommended daily intake for fruit (2%), vegetable (20%), or whole grains (21%) while having high intakes of sweets and desserts, rice, starches, and sugar-sweetened beverages [27]. We created a nutritional program based on diets that have shown efficacy in inducing IBD remission (i.e., increased intake of fruits and vegetables, lower consumption of refined sugar and ultra-processed foods) but tailored for Puerto Ricans affected by CD: *Dieta Anti-Inflamatoria* or DAIN (Anti-inflammatory Diet, in English). This nutritional program incorporates many food groups and ingredients that are common in Hispanic cuisine including other Caribbean, Central, and South Americans and readily accessible on the

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island. Thus, we expect that DAIN will transcend geographical boundaries and can serve as a blueprint for the development of tailored diets to greater than 60 million Hispanics living in the USA.

2. STUDY approach and design

2.1. Study objectives

To create ***Dieta Antiinflamatoria*** or DAIN, a nutritional program tailored for an understudied population with a rising prevalence of Crohn's disease. DAIN is informed by our results with the IBD-AID and other diets used to treat CD [2,14–25]. Similar to the IBD-AID, DAIN is based on the inclusion of a variety of foods that contain probiotics (i.e., fermented foods) and prebiotics (i.e., foods rich in soluble fiber) known to favor anti-inflammatory bacteria. In addition, DAIN emphasizes the increased consumption of beneficial nutrients to meet dietary requirements for safe long-term use while excluding adverse foods (i.e., lactose, wheat, ultra-processed foods) known to trigger gastrointestinal symptoms [3]. Moreover, the DAIN program will be built to overcome the challenges of nutritional therapy for CD, such as dietary compliance, by including hands-on experiences and individually tailored dietary counseling.

To test the efficacy of DAIN in a randomized controlled trial, using a newly created DAIN nutritional program.

2.2. Creation of the DAIN program

Cultural adaptation: The Framework for Reporting Adaptations and Modifications-based Implementation Strategies was used for the cultural adaptation of DAIN as previously described [28]. We sought input from the Community Research Advisory Panel and implementation experts to identify aspects of the intervention to adapt. The Community Research Advisory Panel was composed of four individuals: two patients with CD, a gastroenterologist with vast experience in CD, and a dietitian (not involved in the creation of recipes), all Spanish-speaking individuals native of Puerto Rico. The criteria for the selection of the two patients in the Community Research Advisory Panel were: (i) having at least five years of CD diagnosis, thus are experienced with symptoms, (ii) willingness to participate in six in-person meetings over a six-month period, (iii) live in the San Juan metro area, and (iv) are responsible for grocery shopping and/or cooking at home. Patients participating in the panel were financially compensated for their effort. There were six focus group sessions occurring monthly in the first six months of 2022. In focus groups with the Community Research Advisory Panel and one-on-one "think-alouds" with implementation experts (n = 5), we identified several aspects of the intervention to adapt, such as cost and availability of ingredients, local cooking preferences, experienced adverse reactions to ingredients in the recipes created, the inclusion of nutritional messages to the intervention material key for patients with CD (i.e., suggestions when introducing fiber, hydration tips, short cooking videos, practical advice on how to shop in the supermarket, etc.), as well as better practices to carry out surveys, sample collection, and execution of cooking classes. The adaptation of the program occurred before the implementation and informed decision-making by program leaders, researchers, and nutritionists.

Recipe adaptation: Based on the aspects identified by the Community Research Advisory Panel and one-on-one "think-alouds" with implementation experts, a registered dietitian expert on the IBD-AID worked together with an experienced nutritionist from Puerto Rico to adapt recipes for the DAIN program from our IBD-AID archives and develop recipes tailored to the target population. As per the IBD-AID, recipes in DAIN are categorized into three phases according to the patient's symptomatology and manifestations of disease (i.e., fistulas, strictures), and texture-modified to improve digestion and absorption of nutrients. Each phase of DAIN builds on the earlier phase with the goal of managing symptoms. Phase 1 is geared towards individuals that are currently experiencing an active flare or symptoms such as increased frequency of bowel movements, bleeding, urgency, and/or pain. Phase 2 is intended for individuals with improved symptoms but still experiencing some intermittent symptoms. Phase 3 is designed for individuals that are no longer experiencing symptoms, have well-controlled and solid bowel movements, and are without strictures. In Phase 3, individuals feel more comfortable including a wider variety of foods. A trained nutritionist will assign each participant to a DAIN phase and individualize specific foods in each phase, according to tolerance. During weekly counseling calls, the trained nutritionist from Puerto Rico will reassess symptoms and reassign participants to an appropriate DAIN phase as needed and review foods that can be included in the assigned DAIN phase. Each phase focuses on the inclusion of prebiotic foods, probiotic foods, optimal nutrients, and substitution of avoided foods thought to trigger gastrointestinal symptoms, in a form tolerated (Table 1). All recipes were vetted by the Community Research Advisory Panel.

Printed and multimedia material for the DAIN curriculum: We created a full-color cooking manual featuring DAIN recipes. Each recipe in the manual has been classified by DAIN phase and has additional comments with suggested ingredients/cooking adjustments that may improve tolerance.

We also created a website with a member's password-protected area that contains DAIN recipes, information with guidance on how to adjust to the diet, short cooking videos, information on "how to shop at the supermarket", and examples of weekly menus per DAIN phase.

Finally, we created private social media groups (Facebook and Instagram) to engage participants during the intervention by delivering messages to encourage healthy eating habits. Content on private social media includes DAIN recipes, facts about DAIN ingredients, cooking videos, and digested peer-review scientific articles with up-to-date research on diet, microbiome, and CD (see Supplementary Fig. 1).

2.3. Target population and setting for the clinical trial

The efficacy of DAIN is currently being tested in a parallel two-arm randomized pilot trial at the University of Puerto Rico Medical Sciences Campus in San Juan, Puerto Rico (clinical trial registration number: NCT05627128). At this site, the Center for IBD at the University of Puerto Rico (CIBD-UPR) serves more than 900 unique IBD patients annually. After screening, participants are randomized in a 1:1 ratio into two arms: participants on the DAIN intervention (*Arm 1*), or participants following their habitual diet with no intervention (*Arm 2*). The trial encompasses three periods: Baseline (1 week), Intervention (10 weeks), and Follow-up period (4 weeks). The study has been approved by the Medical Sciences Campus Institutional Review Board (Protocol #1250122) along with a compliance agreement with the University of Massachusetts Chan Medical School (Docket #STUDY00000084).

Table 1
DAIN phases: symptoms and examples of dietary recommendations.

Phases	Symptoms/Indicators	Examples of Dietary Recommendations
DAIN Phase 1	Active flare, increase in bowel movement frequency, bleeding, urgency, and/or pain.	Soft-cooked and pureed foods. No stems, seeds, or peels.
DAIN Phase 2	Symptoms have improved significantly but are not entirely alleviated.	Gradual introduction of more foods with fiber and fat, in a form tolerated. Soft-cooked vegetables, ground or finely minced proteins, and well-cooked mashed/pureed beans. No stems, seeds, or hard peels.
DAIN Phase 3	No longer experiencing symptoms. Bowel movements are formed and well controlled. No strictures.	A wider variety of foods such as cruciferous vegetables, fermented vegetables, whole beans, whole nuts, etc.

2.4. Recruitment strategies

The primary focus for recruitment has been the Puerto Rico IBD Registry (+800 CD patients) and the CIBD-UPR clinic. We perform weekly pre-screening of potential participants by evaluating the information available on the IBD Registry and/or the electronic medical record of patients with an upcoming visit to the CIBD-UPR clinic. Detailed criteria for the inclusion and exclusion of participants are shown in Table 2. Participants will continue their current CD medication throughout the study.

Pre-screened potential participants are also being invited to quarterly recruitment outreach events via phone calls and/or e-mails. Recruitment outreach events consist of cooking demonstration classes featuring an acclaimed local chef. These events have been also advertised through social media and interested participants are pre-screened then. Thus far, two recruitment outreach events with cooking demonstration classes have been held.

In addition, we use other channels to publicize the trial and recruit participants. Specifically.

- Social media: DAIN Facebook (https://www.facebook.com/estudiodain/) and Instagram (https://www.instagram.com/thedainstudy/). We created short advertising videos and social media content that are posted regularly on the platforms.
- We are partnering with a local IBD foundation: "*Fundación Esther A Torres Pro-Enfermedades Inflamatorias del Intestino*" (FEAT, www.featpr.com). The Foundation is a non-profit organization focused on increasing awareness about IBD and being a channel for sharing critical information about IBD in Spanish. We have featured our advertising videos on the FEAT social media pages and created a patient-friendly "trial information and sign up" link.
- We are advertising our study on ResearchMatch.org and the study is listed on ClinicalTrials.gov (NCT05627128).
- We advertised in local radio, TV stations, and newspapers.

2.5. Additional screening and consent

If a patient is eligible for the study, two-step screening processes are required before consent. In the initial screening, the potential participant will be invited for an interview via phone call, via personal contact in the clinic or by letter; a telephone number to call and an e-mail address are provided to allow an individual to indicate if they do not want to be contacted about the study. Potential participants are called a week after the mailing/contact to confirm eligibility and to provide informational material with details of the study activities and timelines (no information on the diet will be provided). Medical record review by one of the investigators (EAT) is performed to confirm the absence of IBD-related exclusion criteria. Interested patients go on to the second screening. Here, the potential participant is provided with an overview of the study and its purpose (treatment of CD with diet), and the individual is encouraged to discuss with the study coordinator the study activities and timelines. If still eligible (i.e., no change on medication, disease activity) and willing to complete the study, the participant is invited to participate in the study and his/her consent will be obtained.

Table 2
Eligibility criteria to select participants for the study.

Inclusion Criteria
• 21–65 years old
• Confirmed CD diagnosis; with mild to moderate CD symptoms (sCDAI >220 < 450)
• Stable dose of medications at screening: thiopurines, natalizumab, vedolizumab, methotrexate (12 weeks), anti-TNF, ustekinumab (8 weeks), 5-ASA (2 weeks), steroids (1 week)
• Willing and able to comply with specimen collection and other study procedures, and to complete all study activities
Exclusion Criteria
• Ostomy
• Use of Specific Carbohydrate Diet or the IBD-AID within 4 weeks of screening
• Use of probiotics within 4 weeks of screening
• Use of >20 mg of prednisone or equivalent steroid treatment
• Recent *C. difficile* colitis
• Current pregnancy

2.6. Randomization

We will randomize 150 recruited participants in 15 blocks of 10 participants each. The allocation sequence will be generated by a computerized random number generator.

2.7. Study periods

Baseline: A one-week baseline or run-in period is included in the study. During this week, participants are expected to complete baseline assessments, three (3) 24 Hour Dietary Recalls, and collect samples (Fig. 1).

Intervention: A ten-week intervention immediately follows the baseline period. During the intervention, participants in Arm 1: DAIN intervention, have access to the newly created DAIN curriculum including a printed copy of the cooking manual, access to the password-protected portal, and a private social media group. Moreover, participants in Arm 1 have weekly counseling sessions (45–60 min phone/video calls) with a DAIN-trained nutritionist from the CIBD-UPR team and are invited to participate in the monthly cooking classes on DAIN recipes featuring a local chef. The criteria for a recipe selection for the classes are (1) inclusion of fruits and/or vegetables; (2) substitution of adverse foods; (3) representative of DAIN phases, (4) food availability/seasonal ingredients (5) and Puerto Rican holiday foods.

Participants in the Arm 2 or the habitual diet arm receive printed material in Spanish of the recently published "2020–2025 Dietary Guidelines for Americans" at the baseline visit but participants on this arm do not have access to the DAIN curriculum, diet counseling, or cooking classes.

Follow-up: Four additional weeks are completed by participants in both arms to assess long-term DAIN compliance.

Following recommendations from the Community Research Advisory Panel and the implementation experts consulted, participants in Arm 2 are granted access to the DAIN curriculum at the end of the follow-up period. Moreover, participants in Arm 2 can obtain one dietary counseling session, and up to three cooking classes. The rationale for granting access to the DAIN material, training, and counseling to participants in Arm 2 is that, if proven efficacious, participants are cognoscente of the treatment option. Access to this educational material is one of the potential benefits of participating in the study and depriving the control group of this benefit was considered discriminatory as well as a disincentive for participating in a study requiring multiple surveys, sample collections, etc.

2.8. Data collection

Data collection is carried out throughout all the periods of the study. There is a total of four-time points to assess study outcomes: one at baseline (week 0), two during the intervention (weeks 6 and 10), and one at the end of the follow-up (week 14, Fig. 1). At each time point, we assess disease activity and quality of life using two validated instruments for patients with Crohn's disease: the short CD Activity Index or sCDAI [29,30] and the IBD-Questionnaire or IBDQ-32 [31], respectively. We will also assess physical activity, fatigue, pain interference, social isolation, and sleep patterns using validated patient-reported outcome tools available through the NIH Common Fund's Patient-Reported Outcomes Measurement Information System® (PROMIS®; more at: https://commonfund.nih.gov/promis/index). Lastly, we will also include screening for anxiety (GAD) and depression (PHQ-9). All these patient-reported outcome tools have been validated for

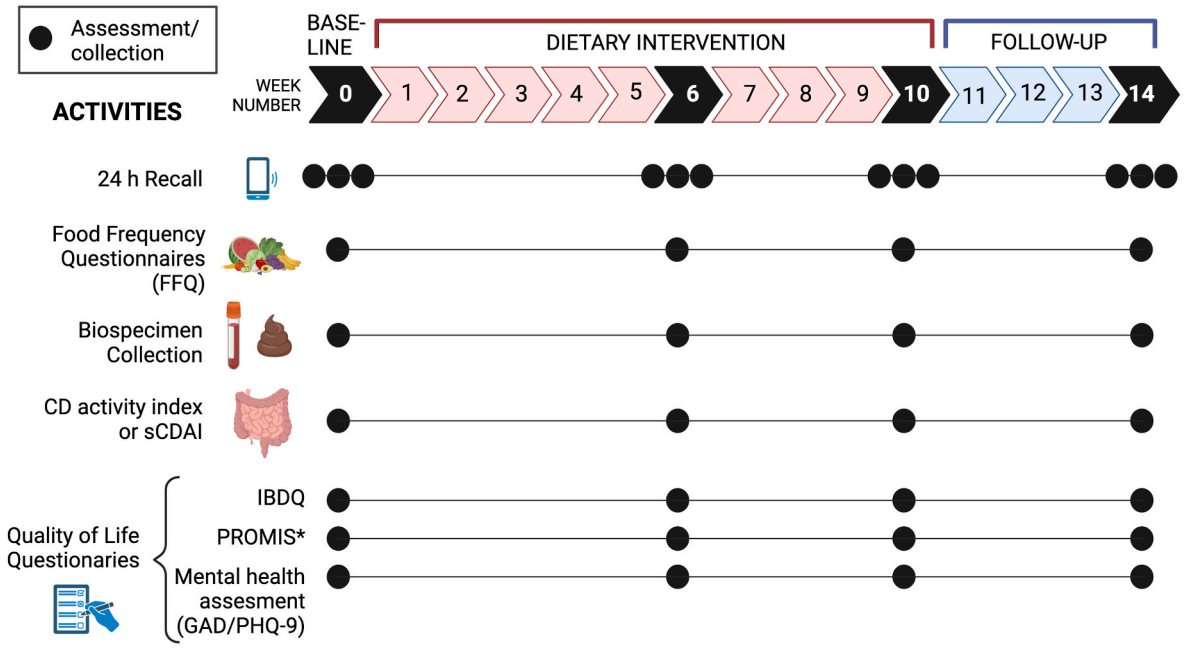

Fig. 1. Schedule of all the DAIN clinical trial study activities and sampling per time points.

Spanish-speakers (including Puerto Ricans) in the US and/or Puerto Rico [32–39]. At baseline we collect information on the patient's demographic and medical history.

2.9. Biospecimen collection

At-home biospecimen collection kits are mailed to the participants at each time point (Fig. 1). Each kit contains one EasySampler® Stool Collection Kit, one Styrofoam box, two cold gel packs, and instructions for sample collection (Supplementary Fig. 2). The EasySampler® Stool Collection Kit provides materials to complete stool collection by placing a sterile paper cutout and collecting samples with sterile spoons in a leak-proof container. After the production of stool samples, participants can either arrange sample pick up in less than 24 h after collection or deliver the sample in person to the research team. Samples are kept frozen at −80 °C until analyses. We will measure fecal calprotectin in stool using CalproLab™ (Calprotectin ELISA, CALPRO AS, Norway). Stool samples will be also used for microbiome analyses.

Collection of blood is performed at each time point by a member of the research team. Blood collection is completed with the FDA-approved Tasso™ Blood Collection Kit, which allows the collection of microliter capillary whole blood samples in a compatible blood collection reservoir. Following manufacturer recommendations, the participant is asked to rub the upper arm until it is warm to increase blood flow. Following this, a member of the research team cleans with alcohol the area of the upper arm where the device with a painless needle will be placed. The member of the research team opens the bag containing the Tasso™ Blood Collection Kit, places it in the cleaned area of the upper arm, and gently pushes the small painless needle into the skin. After 4–5 min blood collection reservoir with EDTA is filled.

Blood samples are stable at room temperature for 2 days. Serum separation is performed (<2 days after sample collection) by centrifugation of samples at room temperature at 1,500 g for 10 min. The serum is stored at −70° until analysis. Levels of CRP are measured in blood using quantitative enzyme immunoassays (Enzo Life Sciences CRP ELISA kit, NY, USA).

2.10. Dietary assessment

We use 24hr dietary recalls (24HDRs) [40] and a food frequency questionnaire (FFQ) [27,41] to assess diet. Both instruments have been validated for Puerto Ricans and have been previously used by our team in Latino populations [40]. Briefly, 24HDRs are collected using the USDA Automated Multiple Pass Method [42] in conjunction with the University of Minnesota Nutrition Data for Research (NDSR) software (Current version: NDS-R 2022) [43–46]. The FFQ adapted for Puerto Ricans [27,41] is self-administered.

We administer three 24HDRs per time point and one online FFQ also in each time point. A total of twelve 24HDRs and four FFQ per participants are administered in the 15 weeks of active participation in the study. Change over time, relative to baseline, is used to establish the degree of modification and compliance to DAIN throughout the study.

3. STUDY outcomes

3.1. Primary outcome

Clinical response (reduction of the short Crohn's Disease Activity Index or sCDAI by 70 points) and remission (sCDAI<150) at weeks 6, 10, and 14.

3.2. Secondary outcomes

(1) Reduction of inflammation measured by fecal calprotectin in stool and C-Reactive Protein in blood (<250 μg/g and <5 mg/L; respectively, or reduction of >50% from screening); (2) gut microbiome changes related to diet, clinical response, and inflammation; (3) improvement on quality of life and mental health; and (4) dietary compliance calculated by AHEI-2010. These outcomes will be evaluated by comparing baseline measurements with measurements at weeks 6, 10, and 14. We will also perform comparison between arms at each time point.

4. Data analyses

4.1. Power calculation

To obtain a significant correlation ($p < 0.05$) with a strong effect size ($r = 0.8$), and high power (0.9), we need 40 independent individuals per group. To account for an ~40% dropout rate, loss to follow up, or incomplete assessments/drop-out/inability to complete study activities due to natural disasters often experienced in the island, our goal is to recruit 75 participants per arm: 75 CD patients will be randomized to DAIN intervention, and 75 CD patients randomized to the habitual diet; for a total of 150 participants.

4.2. DAIN efficacy

Welch's *t*-test will be used to calculate the differences in primary (sCDAI) and secondary endpoints (CRP and fecal calprotectin levels) between arms at weeks 6, 10, and 14. A sCDAI reduction of 70 points on patients on Arm 1- but not Arm 2- will be considered clinical response to DAIN; plus, sCDAI reduction to <150 points will be considered remission caused by DAIN. Similarly, DAIN efficacy will be assessed by reduction of inflammation measured by calprotectin and CRP (<250 μg/g and <5 mg/L; respectively, or reduction of >50% from screening). First, we will disaggregate the analyses by sex, if no differences are found we will aggregate the data. We will also apply multivariate analyses to estimate the odds of achieving remission from 0 to 6 or 10 weeks as previously described [19]. We will use the Prism software for these analyses.

We expect high rates of compliance to the diet. However, based on our IBD-AID studies where participants with an improvement of symptoms achieved >50% of compliance, we will perform disaggregate analyses based on high (>50%) and low (<50%) compliance. Disaggregate analyses will be also carried out on respondents vs. no responders.

We will also use machine learning regression and random forest regression analyses to predict foods or food groups that positively associate with clinical outcomes: clinical response and remission. Here, we will combine data from multiple sources (i.e., individual food intakes, HEI-2015, diseases activity scores, fecal calprotectin levels, QoL) and modality (i.e., continuous and/or categorical) to identify the main predictors of the primary outcomes: clinical response and remission, and secondary outcomes: inflammation, changes in the microbiome, quality of life and mental health. Machine learning regression and the random forest regression analyses perform intrinsic feature selection from the combined data resulting in the selection of only strongly predictive variables within the data set (i.e., prebiotics intakes, disease activity scores, levels of fecal calprotectin). As done previously by our team [47,48], we will include confounding factors, such as disease location, medication doses/type, sex, age, BMI, to test the efficacy of DAIN in the regression modeling.

4.3. Microbial metagenomic and metabolomic analyses

DNA from stool will be extracted according to established protocols [49]. To assess microbial composition, metagenomic shotgun sequencing will be performed as previously done by us [3]. Briefly, library generation of fragmented DNA will be performed using Illumina Nextera XT kits followed by 150bp paired-end sequencing to a depth of ~8 M reads per sample on the Illumina NextSeq 500 platform. Both Kraken [50] and MetaPhlan2 [51] will be used to determine the species composition of bacterial, fungal, parasitic, and viral genomes. This will result in a table reporting the abundance of microbial species, genes, and functional pathways in every profiled participant sample.

We will build on our experience with 1) penalized generalized linear models [52–55] and 2) random forest classification and regression [56,57] to identify microbial features predicted to be significantly affected by food categories of DAIN or is associated with inflammation or with clinical outcomes: clinical response and remission (adjusted p-value <0.05). For the penalized generalized linear models, we will use the R package glmnet and an L1 (or LASSO) penalization to infer each modeled species contribution to individual food category (i.e., prebiotics, probiotics, etc.) as done previously [55,58]. For random forest classification and regression, we will use the R package randomForest to build (>2000) decision trees. Food categories significantly affecting each microbial taxa will be ranked based on the Permutation Variable Importance Index obtained over multiple (>1000) cross-validated trials [57]. We propose to use this non-parametric regression analysis to complement the penalized linear regression models and capture effects that may be caused by the existence of non-linear diet-microbiome relationships. We have experience developing and using maximum likelihood and Bayesian statistics-based regression methods [59–61] that will also be used to corroborate inference results.

To determine microbial metabolites, a subset of 200 fecal samples (50 participants, four samples per participant) will be assayed for untargeted profiling of lipids and water-soluble metabolites via ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) and compared with a reference database of more than 2500 compounds performed by Metabolon, as previously described [29]. Metabolon will provide already-scaled normalized abundances for the profiled metabolites. Two-tailed unpaired student's t-test will be used to calculate differences in metabolites per group.

4.4. Diet compliance analysis

The recommended serving sizes per food category for DAIN align with the validated Alternate Healthy Eating index-2010 or AHEI-2010. The AHEI-2010 predicts the risk of chronic disease [62,63] and has been frequently used as measurement of dietary quality in this population [27,64,65]. The AHEI-2010 will be calculated using dietary intakes recorded on each of the instruments for dietary assessments. Namely, we will average the reported serving size per time point for each of the 11 food categories included in the AHEI-2010: vegetables (≥5 servings/-day), fruit (≥4 servings/day), whole grains (Women: 75 g/day or Men: 90 g/day), sugar-sweetened beverages and fruit juice (0 servings/day), nuts and legumes (≥1 servings/day), red/processed meat (0 servings/-day), *trans*-fat (≤0.5% fat), omega-3 long-chain polyunsaturated fatty acids (EPA + DHA; 250 mg/day), polyunsaturated fatty acids (PUFAs; ≥10% of energy), sodium, and alcohol (Women: 0.5–1.5 drinks/day or Men: 0.5–2.0 drinks/day); and score them from non-adherence = 0, to perfect adherence = 10 as previously done [62,63]. The total sum of the averaged food intakes represents the degree (expressed in percentage) of overall dietary compliance per time point [62,63]. To compare AHEI-2010 between arms, before and after the DAIN, and by sex, we will use a non-parametric Mann-Whitney *U* test.

5. Protocol management

5.1. Study safety and data management

Study design, implementation, and progress is evaluated quarterly. Adverse events are also monitored and promptly reported to both the investigator team and the institution's IRB. Adverse event documentation includes description of the event, ratings of severity and relationship to study medication/study procedures, and follow-up (if any) and outcome. All adverse events, both serious and non-serious, are summarized in the required report to the IRB Committee(s) for annual study review and renewal. All adverse events and serious adverse events that occur in the proposed study are reported to the institution's IRB, regardless of whether they are study related or not. Serious adverse events are immediately referred to the participant's health practitioner or clinical staff from hospitals nearby participants' address.

All data is collected using the HIPAA-compliant Research Electronic Data Capture or REDCap, hosted at UMASS Chan Medical School.

REDCap is a secure application supported by Partners Research Computing, Enterprise Research Infrastructure & Services (ERIS). ERIS has all the necessary physical and operational securities in place to meet or exceed Federal and State security and privacy regulations for data transmission and storage using REDCap. At each time point, participants receive e-mails with a link that directs the participant to the questionaries on our REDCap database. All data are anonymized before analysis.

Principles underlying our approach to quality control include: (i) standardization of measurements and interventions; (ii) use of clear and specific protocols for all activities, including training for nutritionists delivering the intervention to provide consistent counseling to participants, and data collection/processing; (iii) validation and verification of all data collection and management procedures through data editing, double entry of data, bias detection (e.g., digit preference or unexpected runs) and use of software capable of checking for out-of-range values and other sources of outliers; and (iv) regular meetings and progress reports to provide specific, well-documented feedback to the project personnel concerning potential difficulties as well as sufficient follow-up to ensure that problems are resolved in a timely fashion. Any changes to data sets resulting from these queries will be recorded through an electronic audit trail. We will also develop extensive reports on data quality, including inter-interventionist (nutritionist) and study staff variability, drift over time, comparisons of data trends over time, and reasonableness checks of data collected to date against expectations and that of other studies, as available and appropriate.

5.2. Intervention fidelity and blinding

Intervention fidelity is monitored to ensure that the intervention is carried out as designed and that participants receive the intervention with individualized recommendations. We monitor the training of the nutritionists involved in the intervention, delivery of the intervention and receipt of the treatment by participants in the intervention arm. Nutritionists are provided a script that includes weekly topics which are customized for each participant's needs. The nutritionist involved in the intervention documents assigned DAIN phase, nutrition goals, and assesses participants' motivation to follow the diet during each weekly session. We also assess diet for the participants in the control group as they may acquire some of the material/content from their own providers, encounters with the health care system, or seeking knowledge from the public domain. Our study portal has a built-in tracking system that allows us to monitor and measure when/if participants interact with the material, the number of times, which specific material was viewed (menus, recipes, videos, etc.) and for what length of time. We also assess the value to participants of the individual components of the intervention such as printed material, social media content, and nutritional counseling sessions via a survey at the end of the trial. The monitoring plan (Table 3) allows us to identify and correct any drift in the intervention as soon as possible and to monitor treatment receipt so we can interpret results appropriately.

Blinding participants is not feasible given the nature of the intervention. The nutritionist involved in dietary counseling during the intervention needs to know the participant's arm assignment but is not involved in data collection and analysis. However, all staff collecting data (e.g., dietary assessment) or assaying samples (e.g., fecal calprotectin, cytokines, sequencing), are blinded to the participant's arm assignment. Participants are instructed to not divulge their arm assignment when communicating with the staff collecting data.

Table 3
Intervention fidelity and monitoring plan.

Process to be Monitored	Data to be Reviewed	Timing of review/ monitoring
Protocol/ Procedures	Procedure Manual	Every 3 months
Intervention Training	Nutritionist knowledge of the content	Every 3 months
Intervention Delivery	Nutritionist completion of fidelity intervention checklist	After each counseling session
	Dietician debriefing moderated by an IBD-AID expert	Weekly
Intervention Receipt	Intervention group participants will complete a checklist of content provided and skills taught	At 3 and 6 months
	We will monitor intervention group participants interaction with material on our website via built-in tracking system	Every month
	Intervention group participants will be asked to complete a survey capturing their utilization of and perceived value of different components of the intervention	At 3 months
	Participants in the control group will complete a survey asking about acquisition of knowledge similar to that provided to the intervention group and about any change to their dietary intake	At 3 months

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2023.101162.

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