Gastroenterology 2025;169:1462–1474

INFLAMMATORY BOWEL DISEASE

Whole Food Diet Induces Remission in Children and Young Adults With Mild to Moderate Crohn's Disease and Is More Tolerable Than Exclusive Enteral Nutrition: A Randomized Controlled Trial

Yonat Aharoni-Frutkoff,[1,*] **Luba Plotkin**,[1,*] Daniel Pollak,[2] Jessica Livovsky,[1] Gili Focht,[1] Raffi Lev-Tzion,[1] Oren Ledder,[1] Amit Assa,[1] Dotan Yogev,[1] Esther Orlanski-Meyer,[1] Efrat Broide,[3] Jarosław Kierkuś,[4] Ben Kang,[5] Batia Weiss,[6,7] Marina Aloi,[8,9] Tobias Schwerd,[10] Dror S. Shouval,[11,12] Matteo Bramuzzo,[13] Anne M. Griffiths,[14] Moran Yassour,[2,15] and Dan Turner[1]

[1]The Juliet Keidan Institute of Pediatric Gastroenterology, Hepatology, and Nutrition, The Eisenberg Research and Development Authority, Shaare Zedek Medical Center, The Hebrew University of Jerusalem, Jerusalem, Israel; [2]Department of Microbiology and Molecular Genetics, Institute for Medical Research, Israel-Canada, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel; [3]Pediatric Gastroenterology Institute of Gastroenterology, Assaf Harofeh Medical Center, Zerifin, Israel; [4]The Children Memorial Health Institute, Warsaw, Poland; [5]Kyungpook National University Children's Hospital, School of Medicine, Kyungpook National University, Daegu, Korea; [6]Edmond and Lily Safra Children's Hospital, Tel-Hashomer, Israel; [7]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [8]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy; [9]Pediatric Gastroenterology, Hepatology and Cystic Fibrosis Unit, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Cà Granda, Ospedale Maggiore Policlinico di Milano, Milan, Italy; [10]Department of Pediatrics, Dr von Hauner Children's Hospital, University Hospital, Ludwig Maximilian University of Munich, Munich, Germany; [11]Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Petah Tikva, Israel; [12]Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel; [13]Institute for Maternal and Child Health, Istituto di Ricovero e Cura a Carattere Scientifico Burlo Garofolo, Trieste, Italy; [14]Inflammatory Bowel Disease Centre, SickKids Hospital and Research Institute, University of Toronto, Toronto, Ontario, Canada; and [15]School of Computer Science and Engineering, The Hebrew University of Jerusalem, Jerusalem, Israel

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e1. Learning Objective: Upon completion of this CME activity, successful learners will be able to evaluate the effectiveness, tolerability, and clinical applicability of an exclusive whole food diet compared with exclusive enteral nutrition for induction therapy in children and young adults with Crohn's disease.

See editorial on page 1344.

BACKGROUND & AIMS: Tasty&Healthy (T&H) is a whole food diet for Crohn's disease (CD) that excludes processed food, gluten, red meat, and dairy, without requiring formula or mandatory ingredients. TASTI-MM was a clinician-blinded, randomized controlled trial comparing tolerability and effectiveness of T&H vs exclusive enteral nutrition (EEN). **METHODS:** Patients with biologic-naïve mild to moderate CD and aged 6–25 years were randomized to either T&H or EEN for 8 weeks, receiving weekly dietary support. Tolerability was evaluated by weekly interviews, questionnaires, and intake diaries. Other outcomes included symptomatic remission, Mucosal-Inflammation Noninvasive index, calprotectin, C-reactive protein, and erythrocyte sedimentation rate. Fecal microbiome was analyzed by metagenomics at baseline, week 4, and week 8. Data were analyzed by the intention-to-treat approach unless specified otherwise. **RESULTS:** Among 83 included patients (n = 41 T&H, n = 42 EEN; mean ± SD age, 14.5 ± 3.7 years), 88% tolerated T&H vs 52% for EEN (adjusted odds ratio [aOR], 7.7; 95% CI, 2.4–25; $P < .001$). Calprotectin, C-reactive protein, and erythrocyte sedimentation rate decreased significantly in both groups, with no between-group differences. Symptomatic remission was achieved in 56% of the T&H group vs 38% of the EEN group (aOR, 2.5; 95% CI, 0.98–6.3; $P = .1$; per-protocol: 67% vs 76%; $P = .47$). Calprotectin <250 μg/g was achieved in 34% vs 33% (aOR, 0.97; 95% CI, 0.37–2.6; $P = .84$) and Mucosal-Inflammation Noninvasive index score <8 in 44% vs 31% (aOR, 1.8; 95% CI, 0.7–4.5; $P = .33$). Microbiome α-diversity improved in the T&H arm and declined in the EEN arm, showing superior species richness at both week 4 and week 8. Species associated with bowel inflammation, such as *Ruminococcus gnavus,* decreased in T&H and increased in EEN ($q < .001$). **CONCLUSIONS:** T&H demonstrated better tolerability than EEN for inducing remission in mild to moderate CD, while positively affecting the microbiome. ClinicalTrials.gov, Number: NCT04239248.

Keywords: Crohn's Disease; Nutritional Therapy; Tasty&Healthy Diet; Exclusive Enteral Nutrition; Induction of Remission; Microbiome.

Nutritional therapy is the first-line recommended treatment for inducing remission in pediatric Crohn's disease (CD),[1] but is also rapidly evolving in the management of adults.[2] Exclusive enteral nutrition (EEN) with elemental or polymeric formula is highly effective in CD,[3] possibly modulated through changes in the microbiome and intestinal permeability.[4,5] However, EEN is difficult to tolerate, posing emotional and social challenges for patients. To increase the feasibility of nutritional interventions, several whole food diets have been proposed, the most notable of which is the Crohn's Disease Exclusion Diet (CDED). Multiple studies have demonstrated its effectiveness in inducing and possibly also maintaining remission in patients with mild to moderate, uncomplicated disease.[6–9] However, CDED is not an exclusive whole food diet; it requires partial enteral nutrition with supplementary liquid formula, despite a clinical trial suggesting that this may not be needed for inducing remission,[10] and some mandatory food ingredients, which may further limit feasibility. Of the exclusive whole food diets, only the Specific Carbohydrate Diet[2,11,12] and the Mediterranean diet[13–15] were evaluated in a well-designed randomized controlled trial (RCT), both showing effectiveness in inducing clinical remission but not biological remission, as measured by C-reactive protein (CRP) and calprotectin.[16] It should be acknowledged, however, that the trial did not include a control group, many patients did not have biologically active disease at baseline, and dietary adherence was partially captured. The CD Treatment With Eating diet shows promise,[17] but its effectiveness in inducing remission remains to be evaluated in the controlled trial setting.

Tasty&Healthy (T&H) is an exclusive whole food diet, first published in a charity cookbook in 2014.[18] A prospective case-series demonstrated initial encouraging results with a high rate of clinical remission and calprotectin response in mild to moderate CD.[19] The T&H diet was developed to reduce proinflammatory dietary exposures by excluding gluten, animal fat (ie, red meat and dairy, except for plain yogurt), as well as all processed food (anything that comes in a package except for those with 1 unprocessed ingredient; see details and supportive references in Supplementary Appendix 1).

Taken together, there is no exclusive whole food diet proven in the RCT setting to effectively induce clinical as well as biological remission in patients with CD. In this clinician-blinded RCT, we aimed to explore the tolerability and effectiveness of the T&H diet compared with EEN in children and young adults with mild to moderate uncomplicated CD. We also aimed to explore the microbial changes associated with T&H intervention vs EEN.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Exclusive enteral nutrition induces remission in Crohn's disease but is poorly tolerated; no exclusive whole food diet has yet proven efficacy and tolerability in a randomized controlled trial.

NEW FINDINGS

The Tasty&Healthy whole food diet was significantly more tolerable than exclusive enteral nutrition, while achieving comparable rates of clinical and biological remission in children and young adults with mild to moderate Crohn's disease, as well as healthier microbiome.

LIMITATIONS

This study did not include patients with severe or complicated Crohn's disease and lacked endoscopic end points.

CLINICAL RESEARCH RELEVANCE

This multicenter randomized controlled trial demonstrates that the Tasty&Healthy exclusive whole food diet is a feasible alternative to exclusive enteral nutrition for inducing remission in children and young adults with mild to moderate Crohn's disease. Its superior tolerability and comparable effectiveness may expand nutritional therapy options in clinical practice and the research setup.

BASIC RESEARCH RELEVANCE

The Tasty&Healthy diet led to greater microbial diversity and enrichment of species linked to intestinal health, suggesting a potentially more favorable gut microbiome profile than exclusive enteral nutrition. These findings support further investigation of personalized dietary modulation of the microbiome as a therapeutic pathway in Crohn's disease.

Materials and Methods

Trial Design

The Tasty and Healthy Induction in Mild-Moderate Disease (TASTI-MM) trial was an investigator-initiated, prospective, randomized, open, blinded end-point, multicenter clinical trial in which the T&H diet was compared with EEN in children and young adults with CD using a 1:1 allocation ratio (ClinicalTrials.gov, Number: 04239248).

Participants

We enrolled biologic-naïve children and young adults from 17 international centers (Supplementary Appendix 2), aged 6–25 years with mild to moderately active CD, defined as a weighted Pediatric CD Activity Index (wPCDAI) score of

*** Authors share co-first authorship.**

Abbreviations used in this paper: **aOR, adjusted odds ratio; CD, Crohn's disease; CDED, Crohn's Disease Exclusion Diet; CRP, C-reactive protein; EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate; FFQ, food frequency questionnaire; IBD, inflammatory bowel disease; IQR, interquartile range; ITT, intention to treat; MINI, Mucosal-Inflammation Noninvasive; RCT, randomized controlled trial; SFRL, Satisfaction with Food-Related Life; T&H, Tasty&Healthy; wPCDAI, weighted Pediatric CD Activity Index.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2025.06.011

12.5–57.5 points in children and CDAI score of 150–450 points in adults, during the first year after diagnosis. The major exclusion criteria were stenotic or internal penetrating disease, previous bowel resection, draining perianal fistula, ulcerative colitis–like isolated Crohn's colitis, prior failure of dietary treatment, the use of steroids or enteral nutrition during the previous month, celiac disease, and pregnancy. Treatment with immunomodulators was allowed if the dose was stable for at least 16 weeks before enrollment and with mesalamine for at least 8 weeks.

Interventions and Assessments

Participants were randomized to receive either the T&H dietary intervention (the diet's rationale is outlined in the Introduction, Discussion, and in the Supplementary Appendix) for 8 weeks, or EEN with Modulen IBD (Nestlé Health Science) via the oral route. Alternative polymeric formulas were offered to those intolerant to Modulen. The Daily Recommended Intake of EEN was determined according to the Food and Nutrition Information Center, under the US Department of Agriculture (https://fnic.nal.usda.gov/fnic/dri-calculator/). Participants randomized to EEN received the formula at no cost and those randomized to T&H received vouchers for purchasing the ingredients. The latter group also received a recipe book and were given access to a website with further optional recipes compatible with the T&H approach.

Participants in both arms were seen at baseline, week 4, and week 8 for assessment of anthropometric features, disease activity, physical examination, adverse events, dietary intake, change in medications, quality of life, and adherence. In addition, virtual visits were held at weeks 2 and 6. The same degree of nutritional support was provided to both arms and included consultation with the study dietitian every 2 weeks, as well as weekly phone calls and e-mail communications throughout the study as needed. A food frequency questionnaire (FFQ) was completed at baseline to assess habitual dietary patterns in countries with a locally or regionally validated FFQ version. Ultraprocessed food intake was calculated from FFQ data as the proportion of energy derived from foods classified as ultra-processed according to the NOVA classification.[20] In addition, 24-hour dietary recall interviews were conducted at baseline, week 4, and week 8 by trained dietitians using a structured script, and were used to assess intake of macronutrients and micronutrients. Three-day food diaries were completed by the participants at weeks 4 and 8 to assess adherence, following verbal and written instructions.

Those entering symptomatic and biological remission after the 8-week intervention were eligible to be enrolled in the MyTasty open-label maintenance trial, not reported in this article. Data were recorded on a REDCap platform with remote monitoring to sites on a weekly basis.

Outcomes

The primary end point was tolerance to the diet by week 8, defined as completion of the 8-week intervention period with good adherence, based on 3-day food diary[21] or the modified Medication Adherence Report Scale questionnaire (Supplementary Appendix 3)[22] aided by an exploratory weekly adherence questionnaire (Supplementary Appendix 4). The definition of nonadherence required at least 2 independent assessments 1-week apart. Similar to the original CDED trial,[7] the choice of the primary end point was based on the rationale that EEN is highly effective, but adherence is low. Thus, EEN would be replaced only if the alternative nutritional intervention proved to be better tolerated with higher rates of adherence. Nonetheless, effectiveness was captured as a major secondary outcome with a variety of measures, including symptomatic remission (ie, CDAI score <150 in adults and wPCDAI score <12.5 in children), Physician Global Assessment of remission based on all clinical and laboratory data available at the clinic visit (using both a Likert scale and 100-mm visual analogue scale), fecal calprotectin, CRP, and other laboratory measures, as well as the Mucosal Inflammation Noninvasive (MINI) index. The latter is a weighted sum of categorized calprotectin levels, CRP, erythrocyte sedimentation rate (ESR), and stooling pattern, with MINI index score <8 validated to reflect endoscopic healing with 88% sensitivity and 85% specificity.[23] The MINI index has demonstrated responsiveness to change after dietary intervention in pediatric CD.[24] Quality of life was assessed using the IMPACT-III questionnaire in children and the short IBD questionnaire in adults. Additional end points were weight z score and microbial changes. Treatment satisfaction was assessed with the Satisfaction with Food-Related Life questionnaire[25] and response to 1 open-label question (ie, "how do you feel about your diet?") with a 5-point scale. The Satisfaction with Food-Related Life questionnaire is a validated 5-item food-related satisfaction questionnaire, each scored on a 5-point scale. Adverse events were reported by the sites using standard criteria.

Sample Size

Based on prior publications,[7,26,27] we hypothesized that failure to tolerate the intervention will be approximately 30% with EEN vs approximately 7% with T&H. To be able to reject the null hypothesis that the failure rates between the groups are equal with a power of 80% and a type I error probability of .05, we needed to study 44 patients in each group. Assuming a 10% dropout rate, we randomized 97 subjects.

Randomization, Concealment of Allocation, and Blinding

After obtaining informed consent, eligible patients were allocated using the randomization function in REDCap in a 1:1 ratio to either T&H or EEN. In this prospective, randomized, open, blinded end-point trial, the treating physician was blinded to the allocation throughout the 8-week trial, and the study dietitians were provided all study-related instructions. The patients were instructed not to discuss the intervention with their physician. If unblinding occurred, another physician assessed the effectiveness end points.

Stool for Microbiome, Calprotectin, and Gluten

At each visit, stool was collected for measuring calprotectin, the microbiome, and fecal gluten as another proxy for assessing adherence (as both intervention groups excluded gluten). In addition, participants determined their calprotectin level at weeks 2 and 6 using home kits. Therefore, calprotectin results were available every 2 weeks throughout the intervention period.

Details of handling of the stool samples and microbiome analysis are found in the Supplementary Methods. Briefly,

samples were stored at −80°C after fixation in ethanol for performing microbiome analysis and measuring fecal calprotectin (CalproLab enzyme-linked immunosorbent assay test) and stool gluten (iVYLISA GIP stool test) on completion of the study. In addition, calprotectin was measured by the patients every 2 weeks using home kits (CalproSmart; Calpro AS, at all sites except for Canada, which used QuantOn Cal; Preventis GmbH). To increase the precision of the calprotectin values at the most important visits—baseline and week 8—two home kit tests were performed on consecutive days in addition to the enzyme-linked immunosorbent assay testing. If there was a significant difference between the 2 home kits results, a third test was performed. The final calprotectin value was obtained by averaging all available results for each visit (home kits and enzyme-linked immunosorbent assay). The microbiome was determined using metagenomic analysis of samples collected at weeks 0, 4, and 8 by shotgun sequencing aiming for a depth of 30 Gbp/sample, 2 × 150 paired end reads (mean, 96.8 million reads per sample). Bioinformatic analysis was performed to identify and examine the differences between the dietary groups in terms of abundance of bacterial species, richness, diversity, and stability (ie, between-group comparisons). The change in microbial diversity was also explored during the intervention (baseline vs week 4 and week 4 vs week 8; within-group comparisons).

Analytic Approach

Odd ratios were adjusted by recruiting region by the Cochran-Mantel-Haenszel test, after verifying the test's assumptions (eg, test of homogeneity). Student *t* test or Wilcoxon rank sum test was used for the continuous variables of the secondary analyses, as appropriate. We used a modified intention-to-treat (ITT) approach in which all randomized eligible participants were included in the final analyses if they completed at least 24 hours of the intervention when central reassessment of eligibility of patients enrolled in the various sites was conducted. This was meant to improve the position of the EEN group, as it was hypothesized that more participants will not tolerate EEN compared with a whole food diet. Along the same lines and in order to provide a fair chance for EEN, missing data for the ITT analysis used the last observation carried forward method because it was anticipated that more patients in the EEN arm would discontinue treatment due to intolerance than in the T&H arm and not necessarily due to ineffectiveness; using the nonresponse imputation approach would have shifted the effectiveness results towards T&H. Moreover, after the main ITT analyses, we also report the per-protocol results to compare the success rates only for those who completed the 8-week intervention. Paired analysis of repeated measures (such as laboratory results at baseline, 4 weeks and 8 weeks) used Friedman's 2-way analysis of variance by ranks.

For subgroup exploratory analyses, the study outcomes were examined in those with negative fecal gluten as a proxy for full adherence per-protocol exploratory analyses; no formal statistical comparisons were made, given the exploratory nature of this analysis and the small sample size in each subgroup. Finally, a logistic regression model was constructed to explore factors associated with clinical remission in addition to the randomization group, including age (continuous), new-onset disease vs established disease, baseline disease activity (mild vs moderate/severe), presence of extraintestinal manifestations (dichotomous), and the presence of colonic vs isolated ileal disease. The ethics committees of the participating centers approved the study and all participants signed informed consent before randomization. All authors had access to the study data and reviewed and approved the final manuscript.

Results

A total of 97 participants were included from March 2020 to December 2023 from 17 international sites (Supplementary Appendix 1). Seven in each group dropped out within the first 24 hours after randomization for reasons outlined in Figure 1, yielding 42 patients (51%) in the EEN arm and 41 patients (49%) in the T&H arm retained for the ITT analyses. The 2 groups had similar baseline characteristics across all measured variables, including demographic characteristics, disease phenotype, and severity (Table 1). The mean ± SD age of participants was 14.5 ± 3.7 years; the majority were children younger than 18 years (86%). Of the included patients, 25 (59%) in the EEN arm did not complete the 8-week follow-up period for reasons outlined in Figure 1, vs 6 (15%) in the T&H arm (adjusted odds ratio [aOR], 10; 95% CI, 2.4–32; $P < .001$).

Tolerability

The primary outcome was met, with significantly more patients in the EEN arm experiencing intolerance: 20

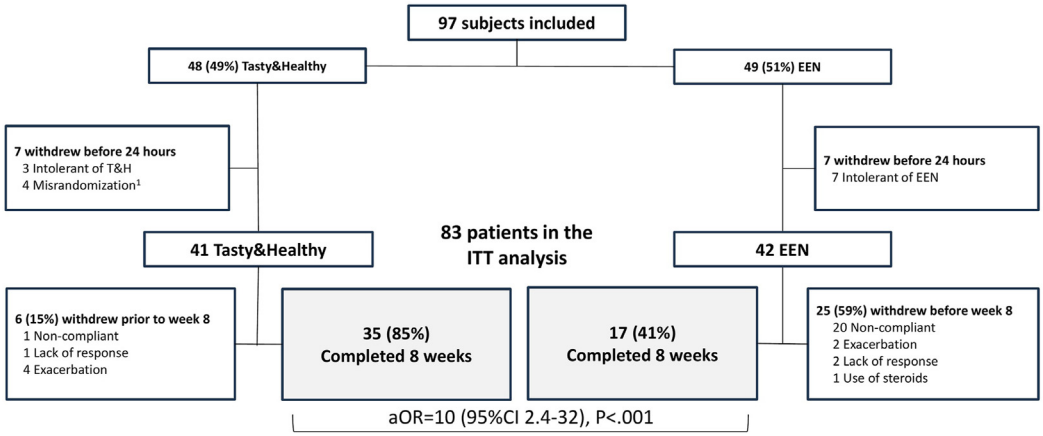


Figure 1. Consolidated Standards of Reporting Trials[28] diagram of participants. [1]Determined centrally after site inclusion, including 1 misdiagnosis (did not have CD), 2 with severe disease by wPCDAI, and 1 previously failed nutritional therapy.

patients (48%) in the EEN group (all withdrew prematurely from the trial due to inability or unwillingness to continue the intervention), compared with 5 (12%) in the T&H arm (1 withdrew and 4 completed 8 weeks with low adherence; aOR, 7.7; 95% CI, 2.4–25; $P = .001$). Of those withdrawing prematurely, 18 of 20 (90%) in the EEN group did so during the first 4 weeks compared with 1 of 6 (17%) in the T&H group ($P < .001$).

Of the 35 patients completing T&H, 24 (69%) reported high or very high satisfaction with the diet, compared with only 4 of 17 (24%) with EEN (OR, 6.5; 95% CI, 1.7–24; $P = .005$). As expected, the Satisfaction with Food-Related Life total score decreased in both groups from baseline, but the decrease was sharper in the EEN group; the between-group difference was significant at week 4 ($P = .043$), but not at week 8 despite a larger effect size, likely given the smaller sample size at this time point (Supplementary Figure 1).

Effectiveness and Quality of Life

Both the T&H and EEN arms were effective for inducing symptomatic and biologic remission, as ascertained by the various outcomes and laboratory tests, with comparable rates between the 2 intervention groups, whether measured by ITT or per-protocol analyses (Figures 2 and 3). Specifically, week-8 remission defined by the wPCDAI/CDAI was achieved by 23 of 41 (56%) in the T&H arm vs 16 of 42 (38%) in the EEN arm in the ITT analysis (aOR, 2.5; 95% CI, 0.98–6.3; $P = .09$) and 23 of 35 (66%) vs 13 of 17 (76%) in the per-protocol analysis (aOR, 0.83; 95% CI, 0.2–3.4; $P = .92$) (Figure 2). Approximately one-third of those completing the interventions achieved symptomatic remission with calprotectin <250 μg/g at week 8 (30% with T&H and 35% with EEN; aOR, 0.92; 95% CI, 0.93–3.7; $P = .82$). The week-8 MINI index score <8 and the more stringent MINI index score <6 rates were similar across arms in both analyses (Figure 2). Other outcomes, including calprotectin <150 μg/g, calprotectin response, normal CRP/ESR, showed similar results without significant differences between the groups (Figure 2).

The blinded physician judged 23 of 33 (70%; 2 missing data) of the T&H and 13 of 17 (77%) of the EEN arms as being in clinical remission at week 8 (aOR, 0.71; 95% CI, 0.19 to 2.7; $P = .61$). Similarly, the median Physician Global Assessment scored on 100-mm visual analogue scale decreased significantly from baseline in both arms (from 40 mm [interquartile range {IQR}, 30 to 50 mm] to 12 mm [IQR, 5 to 30 mm] in the T&H arm and from 36 mm [IQR, 25 to 50 mm] to 10 mm [IQR, 0 to 23 mm] in the EEN arm; both $P < .001$), and there was no difference in the medians at week 8 in the ITT analysis (20 mm [IQR, 6 to 45 mm] vs 25 mm [IQR, 11 to 35 mm], respectively; $P = .8$) or per-protocol analysis (12 mm [IQR, 5 to 30 mm] vs 10 mm [IQR, 0 to 23 mm]; $P = .8$). Quality of life improved in both groups from baseline, with no difference at week 8 ($P = .85$; Supplementary Figure 2). There were also no differences between the groups in the week-8 median weight z scores on analysis by ITT (–0.55 [IQR, –1.5 to 0.2] in the T&H arm vs –0.51 [IQR, –1.4 to 2.8] in the EEN arm; $P = .61$) or per-protocol (–0.58 [IQR, –1.5 to 0.1] vs –0.55 [IQR, –1.5 to 0.23]; $P = .93$).

When considering the outcomes as continuous variables in an exploratory analysis, clinical disease activity and fecal calprotectin improved significantly in both groups over the follow-up period, with no between-group differences, regardless of whether analysis was by the ITT or per-protocol approach (Figure 3*A*). The mean ± SD MINI index improved from baseline to week 8 in both the T&H arm (14.4 ± 4.8 to 8.5 ± 6.6; $P < .001$) and the EEN arm (15.2 ± 5.4 to 7.3 ± 5.9; $P < .001$) (Figure 3*A*), with no differences in the week 8 scores in the ITT analysis (9.5 ± 6.9 vs 10.8 ± 6.4; $P = .44$) or per-protocol analysis (8.5 ± 6.6 vs 7.3 ± 5.9, respectively; $P = .54$) (Figure 3*A*). All laboratory values (ie, albumin, ESR, CRP, and calprotectin) improved significantly from baseline to week 8 in those completing the study in both groups (Figure 3*B*). Although not statistically significant, there seemed to be a numerical trend for quicker improvement in the blood tests among the EEN-treated patients by week 4; however, by week 8, the T&H patients continued to improve and eventually there were no differences between the groups, except for albumin in the per-protocol analysis (Figure 3*B*), but not the ITT analysis (mean ± SD, 4.3 ± 0.5 in the T&H arm vs 4.4 ± 0.42 in the EEN arm; $P = .33$).

Microbiome

The microbiome profile of patients treated with T&H was distinct from those treated with EEN (Figure 4*A*), independent of the medical site (Supplementary Figure 3). Those randomized to T&H had a more stable microbiome than the EEN-treated patients when comparing baseline with week 4 ($P = .009$), week 4 with week 8 ($P = .039$), or baseline with week 8 ($P = .005$; Figure 4*B*). There was a significantly more diverse microbial community in the T&H arm than the EEN arm at both week 4 and week 8 after treatment, as measured by Shannon index ($P = .0013$ at week 4 and $P = .0041$ at week 8) (Figure 4*C*) or Chao1 index ($P = .01$ and $P = .003$, respectively) (Figure 4*D*). Interestingly, the differences in diversity as measured by the Shannon index did not stem from a decrease in the diversity of the EEN microbiome, but rather an increase in the diversity of the T&H microbiome from baseline ($P = .015$ from baseline to week 4 and $P = .049$ from baseline to week 8; Figure 4*C*).

Finally, we searched for distinct microbes that were differentially abundant between the groups. No differences were apparent in any of the species at baseline before treatment (Figures 4*E*–*H*, Supplementary Table 1). After treatment, we found 2 *Ruminococcus* species, *R gnavus* and *R torques*, which were previously associated with gut inflammation, significantly enriched in the microbiome of EEN-treated subjects, with the former exhibiting more striking differences at both weeks 4 and 8 ($P < .0001$ and $q < .0001$ calculated by MaAsLin2) (Supplementary Methods; Figures 4*E* and *F*). However, 2 species associated with intestinal healing had a higher abundance in the T&H treatment group: *Faecalibacterium prausnitzii* ($P = .0002$ and

Table 1. Baseline Characteristics of the Exclusive Enteral Nutrition and the Tasty&Healthy Groups

Characteristic	All patients (n = 83)	EEN group (n = 42)	T&H group (n = 41)	*P* value	OR (95% CI)
Sex (male), n (%)	46 (55)	19 (45)	27 (66)	.09	2.3 (0.9 to 5.7)
Age, *y* (range, 7–25 y), mean ± SD	14.5 ± 3.7	15 ± 3.5	14 ± 3.9	.17	—
Children (<18 y), n (%)	71 (86)	33 (79)	37 (90)	.25	2.5 (0.7 to 8.9)
Disease duration, *mo*	1 (0–1.5)	1 (0–2)	0 (0–1)	.22	—
≤1 mo, n (%)	49 (59)	23 (55)	26 (63)	.15	2.1 (0.9 to 5.1)
Anthropometrics (children), *z* score, median (IQR)					
Height	–0.3 (–0.8 to 0.9)	–0.2 (–1.5 to 1)	–0.3 (–1.9 to 0.6)	.39	—
Weight	–0.3 (–1.2 to 0.4)	–0.3 (–1.1 to 0.4)	–0.4 (–1.3 to 0.3)	.57	—
Body mass index	–0.5 (–1 to 0.1)	–0.5 (–1. to 0.2)	–0.5 (–0.9 to –0.1)	.99	—
Anthropometrics (adults)					
Height, *cm*, mean ± SD	168.4 ± 8.2	168.4 ± 9.5	168.2 ± 5.9	.97	—
Weight, *kg*, mean ± SD	65.2 ± 11.3	67.3 ± 11	60.9 ± 12.2	.38	—
Body mass index, mean ± SD	23 ± 3.9	23.8 ± 4.27	21.4 ± 3	.33	—
Extraintestinal manifestations,[a] n (%)	21 (25)	14 (33)	7 (17)	.1	0.37 (0.1 to 1.1)
wPCDAI/CDAI,[b] n (%)				.83	
Mild	41 (51)	19 (47)	22 (54)	—	—
Moderate	36 (41)	20 (44)	16 (38)	—	—
Severe[c]	6 (8)	3 (9)	3 (8)	—	—
MINI index[d]	15 (5)	15 (5.6)	15 (4.6)	.74	1.3 (0.3 to 7.5)
≥6	76 (92)	38 (91)	38 (93)	1	—
Location,[e] n (%)					—
L1	46 (56)	22 (53)	24 (60)	.75	
L2	6 (7)	3 (7)	3 (8)	—	—
L3	30 (37)	17 (41)	13 (33)	—	—
L4a	26 (79)	15 (88)	11 (69)	.35	—
L4a + L4b	7 (21)	2 (12)	5 (31)	—	—
Blood tests				—	—
WBC count, 10^9/L, median (IQR)	7.6 (6.5 to 10.4)	8 (6.5 to 10.6)	7.3 (6.6 to 10)	.73	—
>10 10^9/L, n (%)	23 (28)	12 (29)	11 (27)	.99	0.9 (0.3 to 2.4)
Hemoglobin, *g/dL,* mean ± SD	12.1 ± 1.7	11.9 ± 1.8	12.3 ± 1.7	.35	—
Anemia, <10 g/dL, n (%)	7 (8.4)	4 (9.5)	3 (7)	.99	0.76 (0.1 to 3.9)
Platelets, median (IQR)	365 (291 to 466)	365 (326 to 469)	365 (287 to 458)	.79	—
>450,000/L, n (%)	59 (71)	13 (31)	11 (27)	.86	0.8 (0.3 to 2.1)
CRP,[f] *mg/L*, median (IQR)	0.9 (0.4 to 3.5)	1.15 (0.3 to 3.8)	0.84 (0.4 to 3.2)	.46	—
>0.5 mg/L, n (%)	60 (72)	30 (71)	30 (73)	.99	1.1 (0.4 to 2.9)
ESR,[g] *mm/h*, median (IQR)	27 (10 to 46)	27 (12 to 44)	29 (9 to 48)	.77	—
>25 mm/h, n (%)	52 (63)	27 (64)	25 (61)	.93	1.1 (0.4 to 2.9)
Albumin,[h] *g/dL*, median (IQR)	4.2 (3.7 to 4.5)	4.2 (3.7 to 4.5)	4.1 (3.8 to 4.5)	.83	—
High CRP/ESR,[i] n (%)	63 (76)	32 (76)	31 (76)	.99	0.96 (0.3 to 2.7)
High CRP/ESR/FC >250 μg/g, n (%)	75 (90)	37 (88)	38 (93)	.71	—
Calprotectin, *μg/g*, median (IQR)	991 (440 to 1263)	1021 (405 to 1343)	963 (633 to 1251)	.64	—

FC, fecal calprotectin; WBC, white blood cell count.
[a]Joints (n = 14), skin (n = 5), prolonged fever (n = 2), and aphthous stomatitis (n = 4).
[b]wPCDAI: remission: <12.5, mild: 12.5–40, moderate: 40–57.5, severe: >57.5; CDAI: remission: < 150, mild: 150–219, moderate: 220–450, severe: >450.
[c]Randomized with protocol deviation as the site investigator felt overall activity is nonsevere.
[d]MINI index: <8 mucosal healing, 8–11 mild inflammation, >11 moderate to severe disease.
[e]As per Paris classification.
[f]CRP was available in 95%.
[g]ESR was available in 85%.
[h]Albumin was available in 94%.
[i]CRP >0.5 mg/L or ESR >25 mm/h.

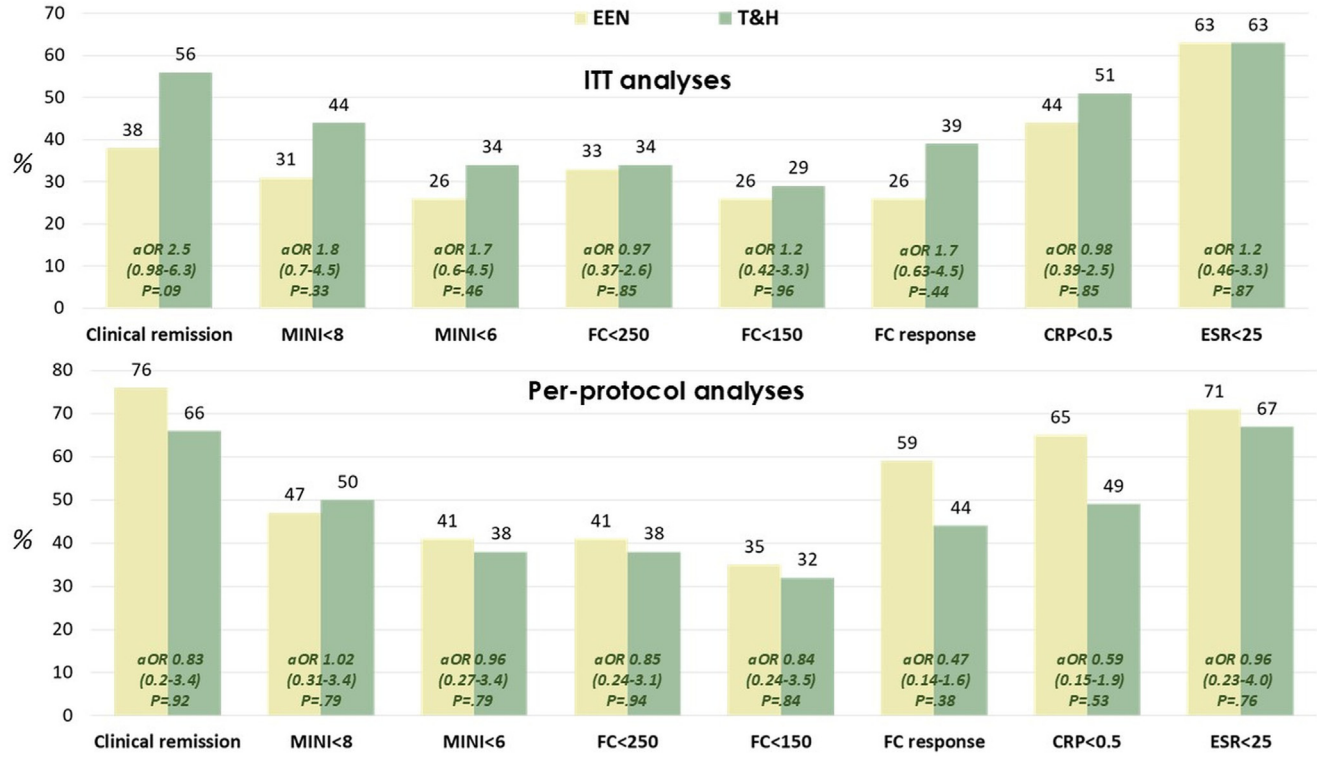


Figure 2. Effectiveness outcomes at week 8, in the ITT and per-protocol analyses of both intervention groups. The aOR with corresponding 95% CIs (presented in *brackets*) were calculated using the Mantel-Haenszel test. Fecal calprotectin (FC) response was defined as reduction of ≥50%.

$q = .002$; Figure 4*G*) and *Bacteroides uniformis* ($P = .006$ and $q = .027$) (Figure 4*H*). A comparison of the relative abundance of all species with a prevalence ≥10% and abundance ≥5%, between T&H and EEN, corrected for multiple comparisons and adjusted for age, is shown in Supplementary Table 1.

Nutritional Intake

The baseline FFQ revealed no significant differences in the proportion of total energy derived from ultraprocessed food between the EEN group (mean ± SD, 48.1% ± 13.6%) vs the T&H group (mean ± SD, 48.6% ± 11.4%; $P = .885$), as well as in food group intake, except for processed meat, for which the P value did not hold in multiple comparison adjustment (Supplementary Table 2). Similarly, the 24-hour recall data showed no significant differences in energy, macronutrient, fiber, or micronutrient intake (Supplementary Table 3). Using 24-hour recall questionnaires at baseline and at week 8, those treated with the T&H diet showed significant increases in fiber and potassium intake (Supplementary Table 3). No other nutrients showed statistically significant changes after Bonferroni correction, although a trend toward increased folate intake was observed.

Subgroup Analyses and Predictors of Response

In the multivariable logistic regression ITT model adjusted for various covariates outlined above, T&H had an aOR of 2.3 for achieving remission by wPCDAI/CDAI at week 8 vs EEN (95% CI, 0.91–5.7; $P = .079$). Response to the dietary intervention was independent of age (whether entered as continuous variable; aOR, 1.1; 95% CI, 0.95–1.3) or dichotomized with age 18 years as the cutoff (aOR, 0.32; 95% CI, 0.1–1.3), disease activity at baseline (mild vs moderate/severe; aOR, 0.46; 95% CI, 0.16–1.4), presence of extraintestinal manifestations (aOR, 1.4; 95% CI, 0.4–4.6), or colonic involvement (aOR, 1.1; 95% CI, 0.4–2.9). Disease duration was not significant when entered as a continuous variable (aOR, 0.88; 95% CI, 0.7–1.1), but as a dichotomized variable, treatment at disease onset was associated with higher response rate in both the EEN and the T&H arms (aOR, 3.4; 95% CI, 1.1–10.5).

Fecal gluten, which was positive in 93% of participants at baseline (lending support for its validity), was negative in 35 of the 46 participants (76%) for whom the week-8 measure was available, with no difference between the groups. All aforementioned outcomes at week 8 were generally similar across the groups in those without evidence of gluten in the stool, including symptomatic remission (67% in the T&H arm vs 69% in the EEN arm), MINI index score <8 (41% vs 39%), and calprotectin <250 μg/mL (32% vs 31%).

Adverse Events

There were 3 adverse events reported in this trial judged as at least possibly associated with the intervention, all of which were mild: 2 in the EEN arm (nausea and dizziness) and 1 in the T&H arm (constipation).

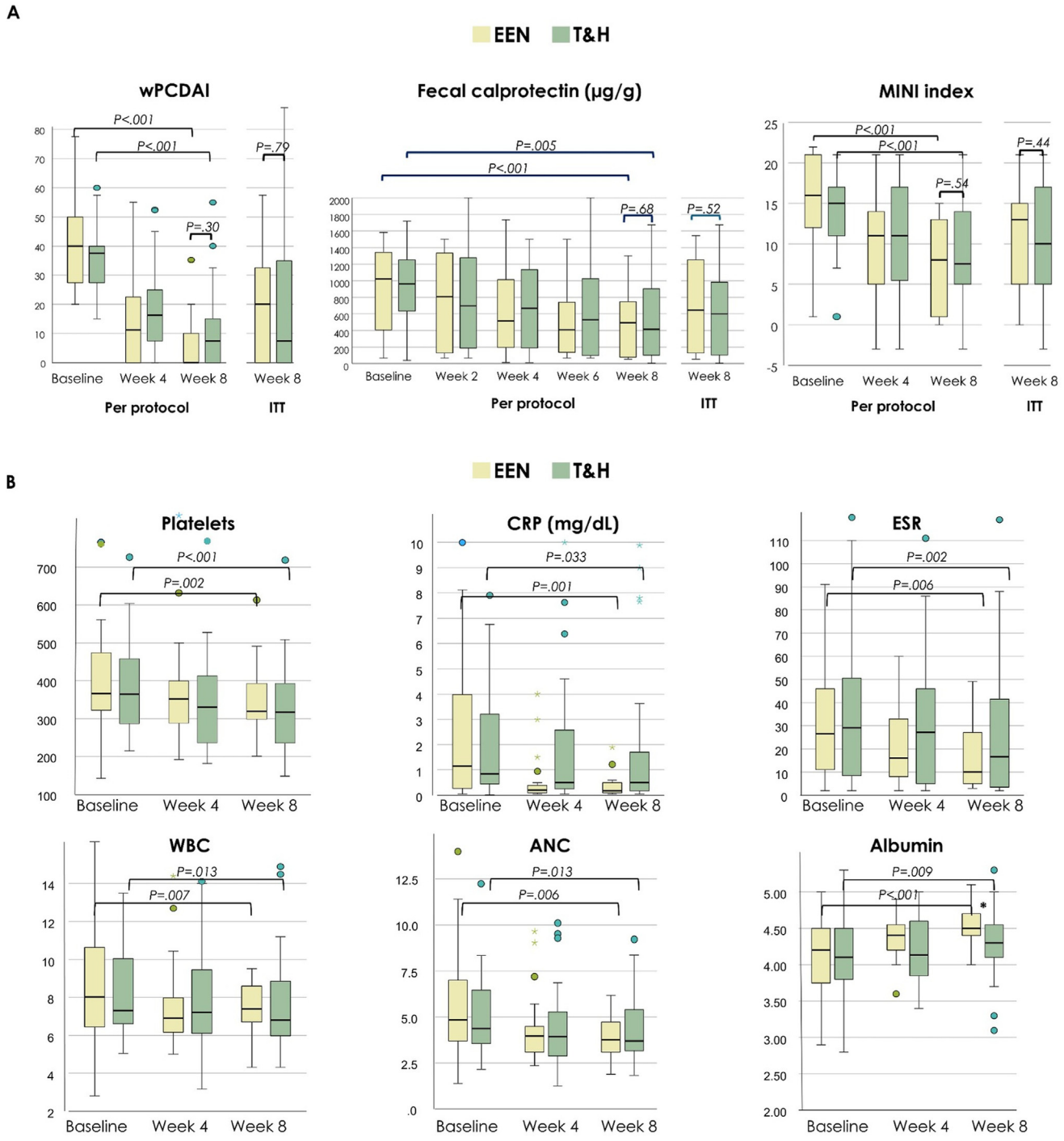
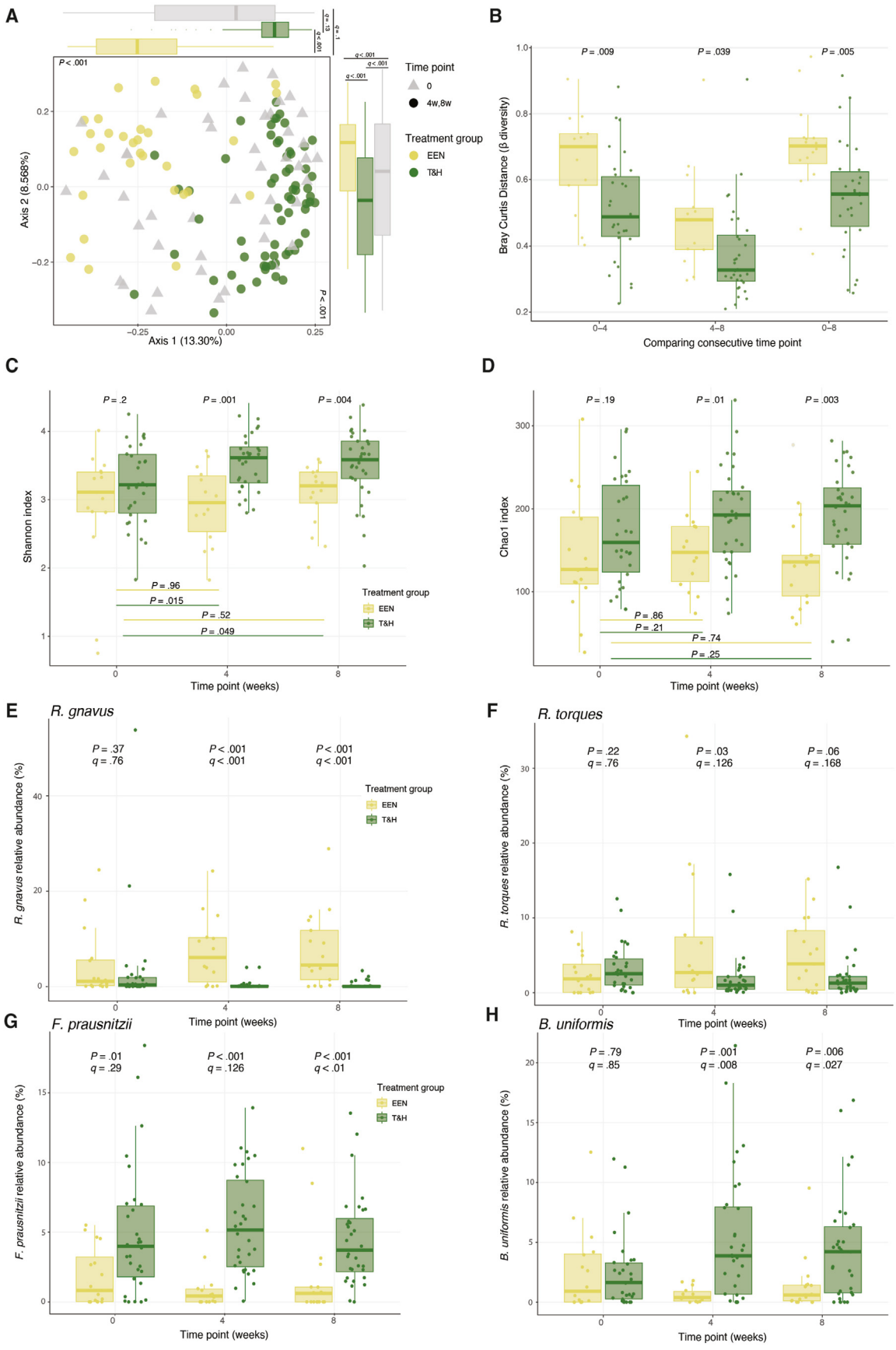


Figure 3. Effectiveness outcomes throughout the follow-up period for both intervention groups. (*A*) Improvement in fecal calprotectin, MINI index, and wPCDAI, in both per-protocol and ITT analyses. (*B*) Improvement in blood tests in per-protocol analysis. None of the between-group comparisons are statistically significant (all, $P > .05$) except albumin with $P = .043$.

Discussion

In this multicenter RCT, we evaluated the tolerability, effectiveness, and the microbiome of the T&H diet compared with EEN in children and young adults with mild to moderate CD. Both interventions were highly effective, with 67%–76% of patients achieving symptomatic remission when adherent to the intervention, and 40%–50% achieving biologic remission as judged by calprotectin and the MINI index. T&H had superior tolerability with effectiveness comparable with EEN across the multiple clinical and laboratory outcomes. Quality of life improved in both groups without significant differences at week 8. Finally, patients following the T&H diet exhibited greater microbial diversity, with an increased presence of beneficial species leading to a microbiome with healthier characteristics than EEN.

EEN is the first-line therapy for inducing remission in children with CD[1] with symptomatic remission rates


A
P < .001
Axis 2 (8.568%)
Axis 1 (13.30%)
Time point
0
4w,8w
Treatment group
EEN
T&H
B
P = .009
P = .039
P = .005
Bray Curtis Distance (β diversity)
Comparing consecutive time point
C
P = .2
P = .001
P = .004
Shannon index
P = .96
P = .015
P = .52
P = .049
Time point (weeks)
D
P = .19
P = .01
P = .003
Chao1 index
P = .86
P = .21
P = .74
P = .25
Time point (weeks)
E
R. gnavus
P = .37
q = .76
P < .001
q < .001
P < .001
q < .001
R. gnavus relative abundance (%)
Time point (weeks)
F
R. torques
P = .22
q = .76
P = .03
q = .126
P = .06
q = .168
R. torques relative abundance (%)
Time point (weeks)
G
F. prausnitzii
P = .01
q = .29
P < .001
q = .126
P < .001
q < .01
F. prausnitzii relative abundance (%)
Time point (weeks)
H
B. uniformis
P = .79
q = .85
P = .001
q = .008
P = .006
q = .027
B. uniformis relative abundance (%)
Time point (weeks)

approximating 75%.[3] However, its implementation is limited by poor palatability and lifestyle constraints. Our study confirmed these limitations, as 59% of the patients in the EEN arm did not complete the 8-week follow-up period, compared with only 15% in the T&H arm, with a tolerability rate of 52% vs 88%, respectively. Moreover, patients' satisfaction was significantly higher in the T&H arm, with 67% reporting high or very high satisfaction compared with 24% in the EEN arm. Notably, the possibility of transitioning to T&H during the study may have influenced some participants to discontinue EEN prematurely, despite efforts from the dietitian to support adherence. Nevertheless, this further reinforces the attractiveness of T&H as a more feasible intervention for inducing remission. Reassuringly, in the per-protocol analyses, including only those completing the trial, the outcomes were still similar across the groups.

In multiple studies CDED has been found to induce symptomatic remission in 62%–77% of patients with mild to moderate uncomplicated CD, including biologic remission in a subset of patients[7,10,29–31] Although conceptually similar to CDED in the exclusion of proinflammatory food groups, the T&H diet differs in structure—requiring no formula and no mandatory components, thus offering greater dietary flexibility. The T&H diet was tested across multiple international centers, while still achieving similar outcomes compared with EEN. The use of any exclusion diet requires guidance of a dietitian to ensure balanced nutrition, and this becomes even more important in diets when formula is not needed. Other exclusive whole food diets studied in the RCT setting are the Specific Carbohydrate Diet and Mediterranean diet, which were effective in inducing symptomatic remission, but demonstrated insufficient biologic remission rates.[2,11–15,32–34] In the largest RCT to date exploring nutritional therapy in CD, both diets achieved symptomatic remission in 44%–47% of patients, but normalization of calprotectin and CRP was uncommon[16] and the Mediterranean diet is currently recommended as a general lifestyle modification in addition to other treatments for CD.[2] The CD Treatment With Eating diet attempts to replicate the components of EEN using exclusive whole foods offering a high-starch and low-fiber diet. It showed promising initial uncontrolled prospective results in terms of symptomatic response and a decrease in calprotectin with centrally prepared meals,[17,35] but there are no published data on remission or calprotectin normalization rates. The Anti-Inflammatory Diet for Inflammatory Bowel Disease is the fourth major exclusive whole food diet, but effectiveness data are lacking in the setting of inducing remission in active CD.[36,37]

At baseline, participants in both groups consumed a Western pattern diet, with nearly one-half of total caloric intake derived from ultraprocessed foods, a clear risk factor for developing inflammatory bowel disease (IBD).[38] The T&H diet was specifically designed to exclude components potentially linked to intestinal inflammation. The exclusion of processed foods was based on overwhelming data supporting their role as drivers of inflammation in IBD, gluten on several mechanistic observations linking its consumption with bowel inflammation, such as zonulin-induced increased intestinal permeability and other immunologic effects; a low-fat diet, protective of IBD in numerous epidemiologic studies and animal models, was achieved by limiting animal fat from red meat and dairy products, while plain yogurt was allowed as a source of calcium (references in Supplementary Appendix 1). After the intervention, the observed increase in potassium and fiber intake may reflect a broader dietary shift toward minimally processed, plant-based foods, which are protective for IBD. Dietary intake was assessed using validated FFQs, 24-hour recalls, and the NOVA classification, allowing for structured analysis of diet composition and processing level.

We found that response to T&H was independent of disease severity at baseline or disease location, as was previously found for EEN.[1] It should be emphasized, however, that the cohort included uncomplicated, biologic-naïve patients with moderate disease activity at most. Severe or complicated disease should still be treated with EEN if nutritional treatment is considered, because almost all evidence supporting the use of whole food diets, including CDED, has relied on mild to moderate uncomplicated patients. The only baseline variable predictive of treatment response was disease duration, a well-known phenomenon across all intervention types in CD.

In the past, dietary interventions have not been as widely adopted in adults as in children, possibly because of the paucity of studies supporting their use and low adherence. However, increasing evidence suggests that EEN and whole food diets may have a positive effect in adults as well, and nutritional interventions are increasingly being incorporated into clinical guidelines beyond pediatrics.[2,39] Although EEN use has been hampered by the thought that adults will not tolerate nutritional interventions, the advent of whole food diets has changed that notion and good adherence has been shown for the Anti-Inflammatory Diet for Inflammatory Bowel Disease, Mediterranean diet, and even CDED, despite the required supplementary formula.[2,10,16,34,36,37,40] In this study, we found that not only were the included adults

Figure 4. Microbiome of EEN vs T&H dietary treatments. (*A*) Principal coordinates analysis using Bray-Curtis dissimilarity, comparing all microbiome samples (n = 141), marked by treatment group and timing. The post-treatment microbiome profiles are statistically distinct on both axis 1 and axis 2 ($P < .00001$ for both). (*B*) Microbiome similarity in consecutive time points in the same patients, using Bray-Curtis dissimilarity. The microbiome of EEN-treated subjects was less stable than the T&H-treated subjects for both comparisons of 0–4 weeks and 4–8 weeks ($P = .0085$ and $P = .039$, respectively). (*C, D*) Microbial diversity (Shannon index and Chao1 indexes) of samples prior and during treatment. (*C*) Diversity by Shannon index was higher in the T&H arm vs EEN at week 4 ($P = .0013$) and week 8 ($P = .0041$). T&H diet resulted in a statistically significant difference before and after treatment ($P = .015$ for baseline to week 4 and $P = .049$ for baseline to week 8). (*D*) Diversity was also higher in the T&H arm vs the EEN arm by Chao1 index ($P = .01$ and $P = .003$, respectively). (*E–H*) Relative abundance of bacteria, which were significantly enriched in the EEN diet (*E, F*) and the T&H diet (*G, H*); *q* and *P* values were calculated using linear regression by MaAsLin2.

adherent to the T&H diet, it was as effective as in children and treatment response was not associated with age.

Compared with EEN, patients following the T&H diet exhibited greater microbial diversity, which has previously been consistently associated with mucosal healing.[41] Moreover, we observed a higher abundance of beneficial species in the T&H group, such as *F prausnitzii* and *B uniformis*, reported to confer health benefits in IBD,[42–44] with *F prausnitzii* depleted in active disease.[45,46] Conversely, patients on EEN exhibited a higher abundance of species known to be associated with active IBD, including *R gnavus* and *R torque.*[42,47,48] Similar to our findings, EEN has been previously associated with decreased microbial diversity and a lower abundance of *F prausnitzii.*[49,50] These findings suggest that although the T&H diet provided similar clinical benefits to EEN, it also fostered a healthier gut microbiome. Notably, the microbial beneficial composition observed in the T&H group aligns with that of the Mediterranean diet[51] and, to some extent, also with CD Treatment With Eating diet,[17,35] both exclusive whole food diets. Although patients on the CDED diet had a healthier microbiome than EEN, they did not exhibit an increase in microbial diversity during treatment, possibly a result of the 50% formula provided as partial enteral nutrition as part of CDED.[7] Nonetheless, a recent study published as an abstract did report increased microbial diversity in children compared with adults.[52] It is likely that 2 contradicting factors influenced the gut composition in the EEN patients, explaining their less healthy microbiome despite achieving similar clinical outcomes as T&H. Besides the reduced inflammation observed in both arms, which is associated with a more diverse and healthier microbiome, EEN is a monotonous diet and thus likely enhances a narrower line of preferential bacteria, as opposed to a whole food diet, which is richer in nutrients and, therefore, promotes a richer microbiome. Larger studies and possibly those comparing the microbiome of different whole food diets may reveal microbial and nutritional features that impact the magnitude of the response.

This trial has several strengths, including the multicenter RCT design, the blinding of the treating physicians, the comprehensive dietary and adherence assessments, as well as the biosampling and microbiome analysis. We overcame the limited reliability of calprotectin by averaging at least 2 separate results at each visit. The lack of endoscopic assessment is a limitation, but we used several objective biomarkers of inflammation, including the MINI index, which was validated as an approximation for endoscopic healing in CD. A noninferiority design may have been the optimal way to study effectiveness because placebo or nontreatment cannot be used in children with active disease.[53] However, such a trial would have required enrolling more than 400 patients, making it unfeasible by pediatric standards, especially because this is an investigator-initiated study in a research area where industry funding and interest are lacking. The significant pre–post changes in the T&H arm for the various effectiveness outcomes and the comparable rates with the EEN group, lend support to the effectiveness of T&H, but, in accordance with other trials of available whole food diets, we did not aim to prove noninferiority to EEN, but rather powered the study to prove tolerability. We assumed that the latter would lead to better outcomes in the ITT analysis, as more patients in the T&H arm completed the intervention, but comparable outcomes were also seen in the per-protocol analysis. Another limitation is that it was impossible to blind the dietitians who judged the tolerability of the participants. Nonetheless, in practice, except for 3 participants, all intolerant participants were classified as such after they discontinued the intervention early, a criterion unrelated to the dietitian judgment, and the 3 who completed the trial were judged based on a 3-day diary, a fairly objective criterion. Moreover, we added an objective measure of adherence (ie, fecal gluten) and the results based on this outcome were similar. Finally, it should be noted that we excluded patients with severe or complicated CD, for whom EEN, biologics and/or steroids remain the mainstay of treatment.

In conclusion, this is the first controlled trial to provide comprehensive evidence for the effectiveness of an exclusive whole food diet in inducing remission in active CD. T&H appears to be a more feasible dietary intervention than EEN, with comparable effectiveness in children and young adults with mild to moderate uncomplicated CD. Overall, our findings underscore the potential of the T&H diet to not only induce remission, but also promote a healthier gut microbiome compared with EEN. The very high feasibility of T&H with 88% adherence may pave the way for exploring it as an intervention for maintenance therapy (alone or as an add-on therapy) and for the prevention of CD in at-risk individuals as currently assessed in the ongoing PIONIR trial (ClinicalTrials.gov, Number: NCT05211518).

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2025.06.011.

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Received February 26, 2025. Accepted June 11, 2025.

Correspondence
Address correspondence to: Dan Turner, MD, PhD, The Juliet Keidan Institute of Pediatric Gastroenterology and Nutrition, Shaare Zedek Medical Center, 12 Shmuel Beyth Street, Jerusalem, Israel 91031. e-mail: turnerd@szmc.org.il.

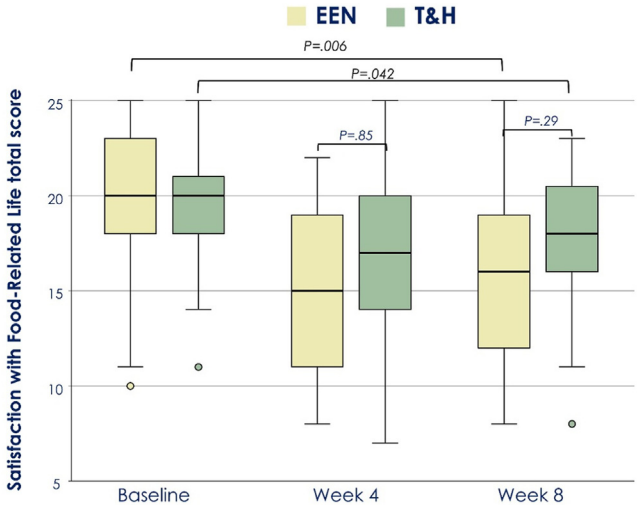
Acknowledgments
The authors would like to thank Zivia Shavit for coordinating the trial; Konstantinos Gerasimidis, Lihi Godny, and Rotem Sigall-Boneh for providing comments during the study; Inez Martincevic for providing dietary support in Canada; Rami Elyakim for chairing the data safety monitoring board; and the team of physicians and dietitians in the 17 centers enrolling in the T&H clinical trials (Supplementary Appendix 1).

CrediT Authorship Contributions
Yonat Aharoni Frutkoff, RD (Data curation: Equal; Formal analysis: Equal; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Luba Plotkin, RD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Daniel Pollak, BMedSc (Formal analysis: Equal; Methodology: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Jessica Livovsky, RD (Data curation: Equal; Writing – review & editing: Equal)
Gili Focht, MSc (Conceptualization: Supporting; Data curation: Supporting; Formal analysis: Supporting; Funding acquisition: Equal; Methodology: Equal; Writing – original draft: Supporting; Writing – review & editing: Equal)
Raffi Lev-Tzion, MD (Conceptualization: Supporting; Data curation: Equal; Methodology: Equal; Writing – review & editing: Equal)
Oren Ledder, MD (Data curation: Equal; Writing – review & editing: Equal)
Amit Assa, MD (Data curation: Equal; Writing – review & editing: Equal)
Dotan Yogev, MD (Data curation: Equal; Writing – review & editing: Equal)
Esther Orlanski-Meyer, MD (Data curation: Equal; Writing – review & editing: Equal)
Efrat Broide, MD (Data curation: Equal; Writing – review & editing: Equal)
Jarosław Kierkuś, MD (Data curation: Equal; Writing – review & editing: Equal)
Ben Kang, MD, PhD (Data curation: Equal; Writing – review & editing: Equal)
Batia Weiss, MD (Data curation: Equal; Writing – review & editing: Equal)
Marina Aloi, MD, PhD (Data curation: Equal; Writing – review & editing: Equal)
Tobias Schwerd, MD, PhD (Data curation: Equal; Writing – review & editing: Equal)
Dror S. Shouval, MD (Data curation: Equal; Writing – review & editing: Equal)
Matteo Bramuzzo, MD (Data curation: Equal; Writing – review & editing: Equal)
Anne M. Griffiths, MD (Conceptualization: Supporting; Data curation: Equal; Writing – review & editing: Equal)
Moran Yassour, PhD (Formal analysis: Equal; Methodology: Equal; Resources: Equal; Supervision: Equal; Writing – original draft: Supporting; Writing – review & editing: Equal)
Dan Turner, MD, PhD (Conceptualization: Lead; Formal analysis: Equal; Funding acquisition: Lead; Investigation: Lead; Methodology: Equal; Project administration: Supporting; Supervision: Equal; Writing – original draft: Lead; Writing – review & editing: Equal)

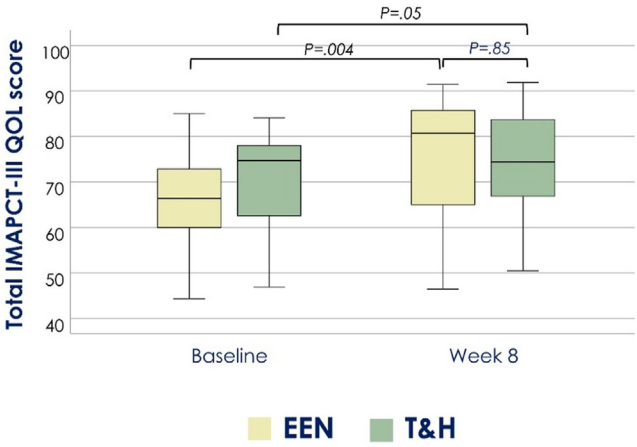
Conflicts of interest
The authors disclose no conflicts.

Funding
This Tasty & Healthy clinical trial was funded by an academic grant from the Leona M. and Harry B. Helmsley Charitable Trust.

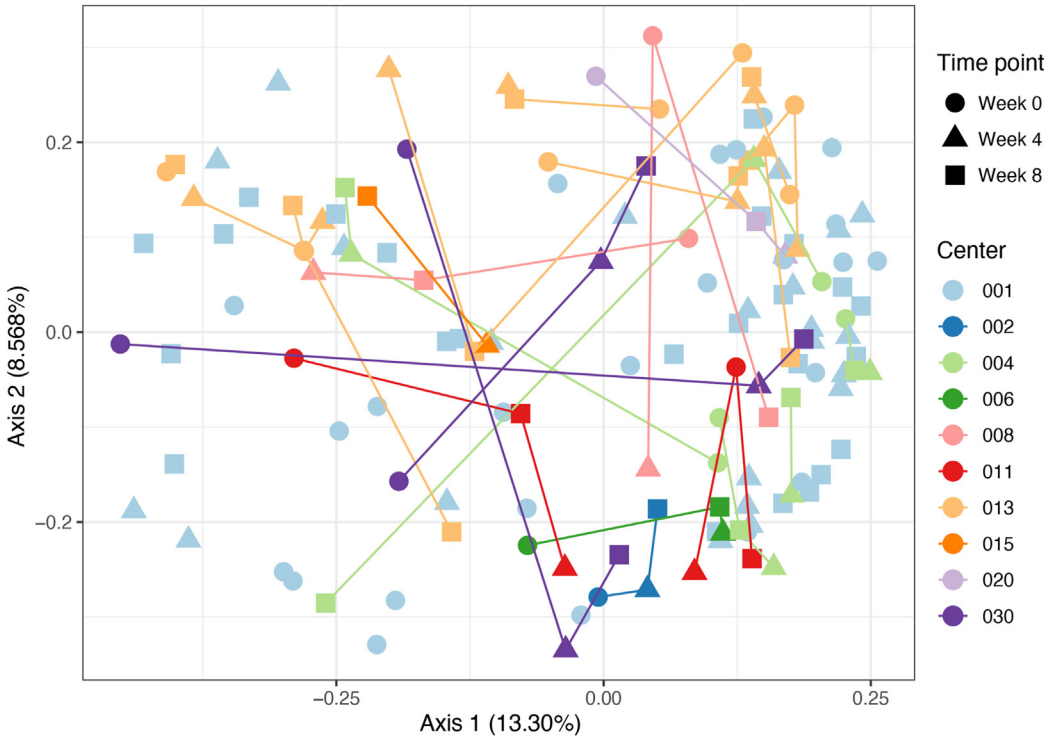
Data Availability
Deidentified individual participant data be shared upon a reasonable request to the corresponding author for a period of 5 years after the publication date.



Supplementary Figure 1. Change in the Satisfaction with Food-Related Life (SFRL) score during the dietary treatment. Higher scores reflect higher satisfaction with food-related life.



Supplementary Figure 2. IMPACT-III quality of life (QOL) change, stratified by treatment arm (per-protocol analysis of those completing the interventions).



Supplementary Figure 3. Microbiome species analysis by study center. Principal coordinate analysis using Bray-Curtis dissimilarity, comparing all microbiome samples, marked by timing and study medical center. *Arrows* are drawn between samples of the same patient.