nature medicine

Article

https://doi.org/10.1038/s41591-025-04173-w

A fasting-mimicking diet in patients with mild-to-moderate Crohn's disease: a randomized controlled trial

Received: 11 June 2025

Accepted: 10 December 2025

Published online: 13 January 2026

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In healthy individuals, short cycles of a fasting-mimicking diet (FMD) decrease systemic inflammatory markers and improve metabolic health. Potential benefits of FMD have not been investigated in Crohn's disease (CD). We conducted an open-label, randomized, controlled trial to assess the effects of FMD in adults with mild-to-moderate CD. Patients in the FMD group followed an FMD for five consecutive days per month for three consecutive months, returning to their regular baseline diet on non-FMD days. Control participants continued their baseline diet. The primary outcome of clinical response was a reduction in CD Activity Index (CDAI) of at least 70 points or CDAI of ≤150 after the third 5-day diet cycle. Forty-five patients in the FMD group (69.2%) and 14 patients in the control group (43.8%) met the primary outcome of clinical response ($P = 0.03$). Forty-two patients in the FMD group (64.6%) and 12 patients in the control group (37.5%) achieved the secondary outcome of clinical remission ($P = 0.02$). There was also a decline from baseline in fecal calprotectin (an inflammatory marker) in the FMD group compared with the control group (−22.0% versus 8.0%, $P = 0.03$). Exploratory analyses of plasma metabolites and peripheral blood mononuclear cell gene expression revealed post-FMD decreases in key inflammatory lipid mediators and immune-effector transcripts, concordant with reduced CD activity. Together, these findings demonstrate that FMD is superior to a baseline diet for inducing clinical response, clinical remission and biochemical improvement in mild-to-moderate CD, and support further investigation of FMD as an adjunctive therapy for chronic inflammatory diseases. ClinicalTrials.gov registration: NCT04147585.

Crohn's disease (CD), a type of inflammatory bowel disease (IBD), is a chronic disorder of the gastrointestinal tract characterized by intestinal inflammation that affects about 5 million patients worldwide[1]. Approximately 20–30% patients with CD have a milder disease course, generally characterized by minimal endoscopic inflammation as determined by standardized endoscopic scoring, and lack of stricturing or penetrating complications[2]. In the United States, except for corticosteroids, which are known to have many side effects and are therefore used sparingly, there are no FDA-approved medical therapies for mild CD. Hence, there is substantial uncertainty regarding the best management strategy for these patients[2]. Although there are multiple medications approved for moderate-to-severe CD, these medications are immunosuppressive, and it is uncertain whether the potential benefit of using these medications outweighs the risk in patients with mild CD. There is a clear clinical need for treatments to fill this therapeutic gap.

The most common question asked by patients with IBD to gastroenterologists is, 'what should I eat?' and there is considerable interest from physicians and patients alike in using diet as a therapeutic

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modality for IBD[3]. Despite substantial interest, the majority of evidence for diet as induction or maintenance therapy in adult CD comes from nonrandomized or small studies[4]. A notable exception is a randomized trial evaluating a specific carbohydrate diet versus Mediterranean diet (MD) in mild-to-moderate CD, which showed that specific carbohydrate diet was not superior to MD in achieving clinical remission[5]. However, the study was limited by lack of a control group.

A key barrier to the therapeutic use of diet is the challenge of sustaining long-term dietary changes, as evidenced by low adherence rates across dietary interventions[6,7]. Given these limitations, a fasting-mimicking diet (FMD) is an attractive solution as it does not require patients to make long-term changes to their baseline diet. FMD is a plant-based, calorie-restricted diet that is consumed for only 5 consecutive days per month. The diet is low in calories, sugars and protein, but high in unsaturated fats and is designed to mimic the benefits of fasting[8]. Participants eat their regular baseline diet for the remaining days of the month. The 5-day cycle is repeated twice for a total of three cycles over 3 months. It has been tested in multiple clinical trials related to cardiometabolic and oncologic disorders[8,9].

FMD has been previously shown to improve metabolic parameters in healthy volunteers[8]. Preclinical evidence has shown that the diet attenuates inflammation and promotes intestinal healing through increased abundance of Lactobacillaceae and increased expression of cytokines associated with tissue repair in a mouse model of colitis[10]. In healthy human participants with mildly elevated baseline C-reactive protein (CRP), three 5-day cycles of FMD resulted in reduction in CRP levels compared with patients who continued their usual diet[10]. A recently published pilot trial assessed two cycles of FMD as an adjunctive intervention in patients with ulcerative colitis undergoing induction therapy, the majority of whom (~90%) were treated with a Janus kinase inhibitor. The study did not achieve its primary endpoint of clinical response—limited by only 23 patients completing the study—but patients in the FMD group did show greater clinical improvement when compared with those receiving only standard induction[11].

Given FMD's benefits in human studies and mouse colitis models, we hypothesized that FMD would be effective at reducing clinical disease activity and improving intestinal inflammation in patients with mild-to-moderate CD.

Results

Patients and characteristics

Between 2019 and 2023, a total of 97 of 279 patients screened in a national recruiting campaign were randomized 2:1 to either FMD or control (continue baseline diet); 65 participants were assigned to the FMD group and 32 were assigned to control. A Consolidated Standards of Reporting Trials diagram documenting patient flow and overview of the study design is shown in Fig. 1. Patients in the FMD group followed the FMD for five consecutive days each month over 3 months, while the control group maintained their regular diet throughout the study (Fig. 1).

Baseline characteristics of the enrolled participants were generally well-balanced between the two groups, although the FMD group had a higher proportion of females (80.0% versus 56.3%, standardized mean difference (SMD) = 0.54) compared with control (Table 1). The median age was 45.0 years (interquartile range (IQR) = 35.0–55.0). The control and FMD groups had very similar proportions of patients with overweight body mass index (BMI; 40.6% versus 40.0%), but the control group had a greater proportion of patients with obesity (BMI of 30 kg m^{-2} or higher) compared with the FMD group (31.3% versus 15.4%). CD phenotype, as determined by Montreal classification, was similar between the groups, although notably stricturing disease (B2), a more aggressive form of CD, was more common in the FMD group (30.8% versus 9.4%, SMD = 0.51)[12]. CD Activity Index (CDAI) is a widely used clinical scoring system to assess the severity of CD. It incorporates factors such as weight, number of bowel movements, abdominal pain and hematocrit; CDAI is commonly used as an endpoint in clinical trials in CD[13]. The median CDAI was 196.0 (IQR = 155.0–231.0). Advanced IBD therapy, defined as use of a biologic, immunomodulator or Janus kinase inhibitor, was used by 60.0% of the FMD group and 71.8% of the control group (SMD = 0.24). The use of antitumor necrosis factor (anti-TNF) therapy was more common in control (37.5%) compared with FMD patients (20.0%), while 5-aminosalicylates (5-ASA) use was more common in FMD (26.2%) compared with control patients (9.4%). A greater proportion of patients in the FMD arm (21.5%) used corticosteroids compared with control patients (12.5%). As is reported in the literature on mild-to-moderate CD, at baseline only a minority of participants had elevated inflammatory markers such as CRP (>10 mg l^{-1}) and fecal calprotectin (>120 μg g^{-1})[14]. After observing a slight imbalance in a few baseline characteristics, multivariable logistic regression was used to assess the presence of residual confounding. None of the factors tested—including sex, ethnicity, race, smoking status, BMI or the use of biologics or corticosteroids at baseline—significantly altered the odds for clinical remission (Supplementary Table 1).

FMD is superior to baseline diet in inducing clinical response and clinical remission

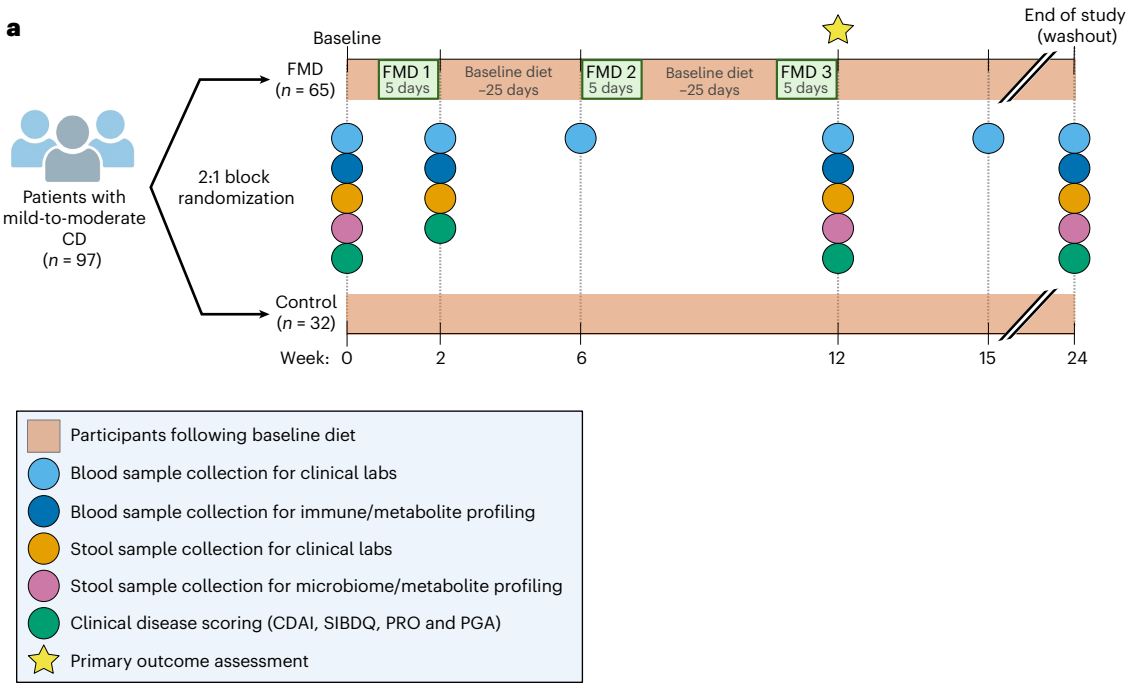
In intention-to-treat analysis, a significantly higher percentage of participants achieved the primary outcome of clinical response 70 (decline in CDAI of at least 70 points from baseline or achieving CDAI ≤ 150) in the FMD group compared with control (69.2% FMD versus 43.8% control, $P = 0.03$; Fig. 2a). Median decline in CDAI was −105 (IQR = −48 to −155) for the FMD group, compared with −76 (IQR = 0 to −119) for control ($P = 0.02$). A significantly higher percentage of participants also attained clinical remission (CDAI ≤ 150) with FMD after three cycles of treatment (64.6% FMD versus 37.5% control, $P = 0.02$; Fig. 2b). There was a significant difference in the percentage of patients in the FMD group who achieved clinical response 100 (decline in CDAI of at least 100 points from baseline or achieving CDAI ≤ 150) compared with control (66.2% versus 40.6%, $P = 0.02$; Fig. 2c). After completing the first cycle of FMD, more participants achieved clinical response 70 (66.2% versus 43.8%, $P < 0.05$; Fig. 2d) and clinical remission compared with participants who made no diet changes (60.0% versus 37.5%, $P = 0.04$; Extended Data Fig. 1a). There were no significant differences in either clinical response or remission after a 3-month washout period after the third cycle of FMD (Extended Data Fig. 2). Throughout the study period, there was no difference in therapy escalation (corticosteroid prescription, starting new advanced therapy or dose escalation of advanced therapy) between both groups (27.7% FMD versus 25.0% control, $P = 0.99$).

There was a decrease in mean change in CRP compared with baseline in the FMD group, whereas the control group showed an increase from baseline; however, this finding did not reach statistical significance (−1.0% versus 36.9%, $P = 0.06$; Fig. 2e). There was a significant decline in mean percentage change in fecal calprotectin at the end of the third diet cycle compared with baseline in the FMD group, whereas there was an increase in the control group (−22.0% versus 8.0%, $P = 0.03$; Fig. 2f). In post hoc analysis, a greater proportion of participants in the FMD group had a 50% or greater decline in fecal calprotectin (37.0% versus 6.3%, $P = 0.01$; Fig. 2g). There was no statistically significant difference in the mean percentage change in erythrocyte sedimentation rate (10.7% versus 15.2%, $P = 0.87$).

Subgroup analysis consistently shows a superior clinical response to FMD compared with baseline diet

More patients with mild CD achieved clinical response 70 on FMD compared with baseline diet (75.0% versus 47.8%, $P = 0.03$; Fig. 3a). Similarly, more patients with moderate CD achieved clinical response 70 on FMD compared with those on the baseline diet (57.1% versus 11.1%, $P = 0.04$; Fig. 3b). Participants with nonstricturing, nonpenetrating disease were more likely to have clinical improvement with FMD compared with

https://doi.org/10.1038/s41591-025-04173-w



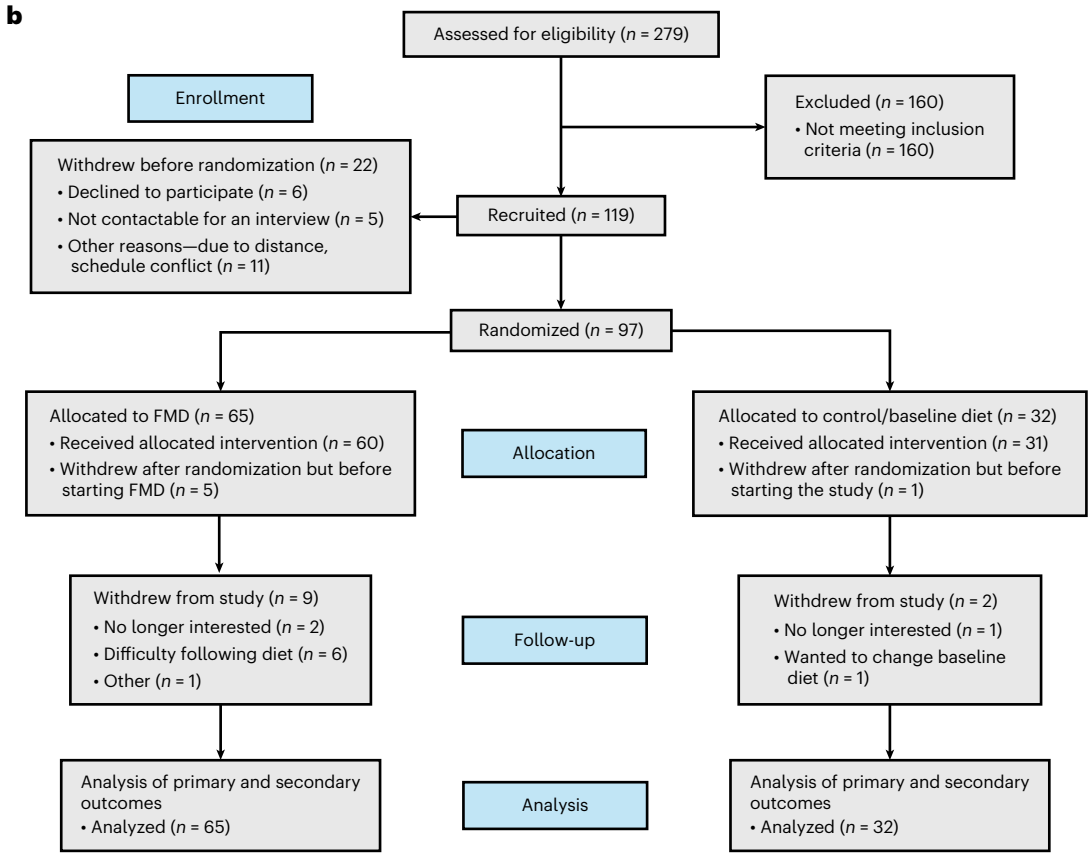


Fig. 1 | Study protocol overview of the FMD trial and CONSORT diagram. **a**, Study protocol overview of the FMD trial. For participants in the FMD group—baseline assessments were completed up to 14 days before the first FMD cycle (FMD 1); subsequent assessments occurred after completion of each FMD cycle. Between consecutive FMD cycles, participants resumed their usual diet for approximately 25 days. **b**, CONSORT diagram of participant flow. All randomized participants were included in the intention-to-treat analysis. CONSORT, Consolidated Standards of Reporting Trials. Panel **a** created with BioRender.com.

Table 1 | Demographic and clinical characteristics of participants at baseline

Characteristic	FMD (*n*=65)	Control (*n*=32)	SMD
	n (%), median (IQR)	*n* (%), median (IQR)	
Age at enrollment, years	43.0 (34.0–53.0)	45.5 (33.0–57.3)	−0.19
Sex, female	52 (80.0)	18 (56.3)	0.54
Race			
White	47 (72.3)	24 (75.0)	−0.06
Black	0 (0.0)	2 (6.3)	−0.45
Asian	7 (10.8)	4 (12.5)	−0.05
Native Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)	0.00
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0.00
Other	2 (3.1)	0 (0.0)	0.22
Unknown	9 (13.8)	2 (6.3)	0.24
Ethnicity			
Hispanic or Latino	4 (6.2)	2 (6.3)	0.00
Not Hispanic or Latino	52 (80.0)	28 (87.5)	−0.20
Unknown	9 (13.9)	2 (6.3)	0.24
BMI at inclusion, $kg\,m^{-2}$	24.4 (21.7–28.1)	27.8 (23.7–31.5)	−0.39
Normal (18.0–23.9)	29 (44.6)	9 (28.1)	0.34
Overweight (24.0–29.9)	26 (40.0)	13 (40.6)	−0.01
Obesity (≥30.0)	10 (15.4)	10 (31.3)	−0.40
Smoking status			
Never	40 (61.5)	20 (62.5)	−0.02
Past	12 (18.5)	5 (15.6)	0.07
Current	2 (3.1)	3 (9.4)	−0.28
Alcohol use at baseline			
Never	32 (49.2)	14 (43.8)	0.11
Light	29 (44.6)	16 (50.0)	−0.11
Moderate	4 (6.2)	2 (6.3)	0.00
Heavy	0 (0.0)	0 (0.0)	0.00
CD phenotype[a]			
Age at CD onset, years	38.0 (27.0–46.0)	34.0 (25.5–50.0)	−0.09
A1 (≤16 years)	7 (10.8)	2 (6.3)	0.16
A2 (17–39 years)	26 (40.0)	15 (46.9)	−0.11
A3 (≥40 years)	31 (47.7)	14 (43.0)	0.08
CD distribution[b]			
Ileum alone (L1)	18 (27.7)	10 (31.3)	−0.08
Colon alone (L2)	17 (26.2)	9 (28.2)	−0.04
Ileocolon (L3)	28 (43.1)	10 (31.3)	0.24
Upper GI alone (L4)	1 (1.5)	0 (0.0)	0.15
CD behavior[c]			
Nonstricturing, nonpenetrating (B1)	39 (60.0)	23 (71.8)	−0.39
Stricturing (B2)	20 (30.8)	3 (9.4)	0.51
Penetrating (B3)	6 (9.2)	3 (9.4)	−0.01
History of perianal disease (p)	19 (29.2)	7 (21.9)	0.17
CDAI score at baseline	196.0 (154.0–229.0)	194.5 (170.3–231.3)	−0.02
Mild (151–220)	44 (66.7)	23 (71.9)	−0.06
Moderate (221–450)	21 (32.3)	9 (28.1)	0.06
CD medications at baseline			
Any biologic, small molecule or immunomodulator	39 (60.0)	23 (71.8)	−0.24
Anti-TNF	13 (20.0)	12 (37.5)	−0.40
Anti-IL-12, IL-23	12 (18.5)	5 (15.6)	0.07
Anti-integrin	7 (10.8)	4 (12.5)	−0.05
Immunomodulator (6-mercaptopurine, azathioprine, methotrexate)	9 (13.9)	4 (12.5)	0.04
Small molecule (JAK inhibitor)	2 (3.1)	0 (0.0)	0.22
5-Aminosalicylate	17 (26.2)	3 (9.4)	0.42
Corticosteroids	14 (21.5)	4 (12.5)	0.21
Antibiotics	3 (4.6)	0 (0.0)	0.34
Duration of advanced therapy, months	8.0 (4.0–27.0)	12.0 (4.0–36.0)	−0.12
CRP, $mg\,l^{-1}$	3.0 (1.0–8.0)	3.0 (1.0–6.5)	0.12
CRP>10 $mg\,l^{-1}$	14 (21.5)	6 (18.8)	0.04
ESR, $mm\,h^{-1}$	10.0 (4.0–24.0)	12.5 (4.3–18.3)	0.22
ESR elevated	11 (16.9)	4 (12.5)	0.11
Fecal calprotectin, $\mu g\,g^{-1}$	115.0 (30.0–276.0)	88.5 (52.0–224.5)	0.26
Fecal calprotectin, >120 $\mu g\,g^{-1}$	31 (48.4)	15 (46.9)	0.02

[a]As determined per Montreal classification guidelines. [b]L4 (upper GI) is assigned as a mutually exclusive category if disease is only present proximal to the terminal ileum. If disease involves both proximal and distal regions relative to the terminal ileum, L4 is used as a modifier in combination with categories L1–L3. [c]Participants without evidence of stricturing or penetrating disease were assigned to B1 (inflammatory) phenotype. Participants who reported perianal fistulae and/or abscesses of CD diagnosis were considered to have a history of perianal disease. IL, interleukin; JAK, Janus kinase; ESR, erythrocyte sedimentation rate.

control (71.8% versus 40.0%, $P = 0.02$; Fig. 3c). Participants with colonic disease had a greater rate of clinical response 70 after three cycles of FMD compared with the baseline diet (82.4% versus 33.3%, $P = 0.01$; Fig. 3d). A similar pattern was seen in participants with ileocolonic disease (71.4% versus 30.0%, $P = 0.03$; Fig. 3e) but not in participants with isolated ileal disease (55.5% versus 60.0%, $P = 0.99$; Fig. 3f). Notably, FMD was effective in inducing clinical remission and response in patients who were not on any medical therapy compared with baseline diet without medical therapy (76.9% versus 33.3%, $P = 0.04$; Fig. 3g).

FMD is superior to baseline diet in improving patient-reported outcomes and quality of life

Patient-reported outcome (PRO) and quality-of-life measures were prespecified secondary outcomes that were measured after the completion of three FMD cycles (Extended Data Fig. 3).

In the FMD group, 47.7% participants achieved remission by PRO (defined as fewer than four loose or watery (Bristol type 6 or 7) stools per day and minimal abdominal pain (severity rated less than or equal to 1 on a 0–3 Likert scale)) compared with 25.0% in the control group ($P < 0.05$; Extended Data Fig. 3a). Quality of life was assessed using the short IBD

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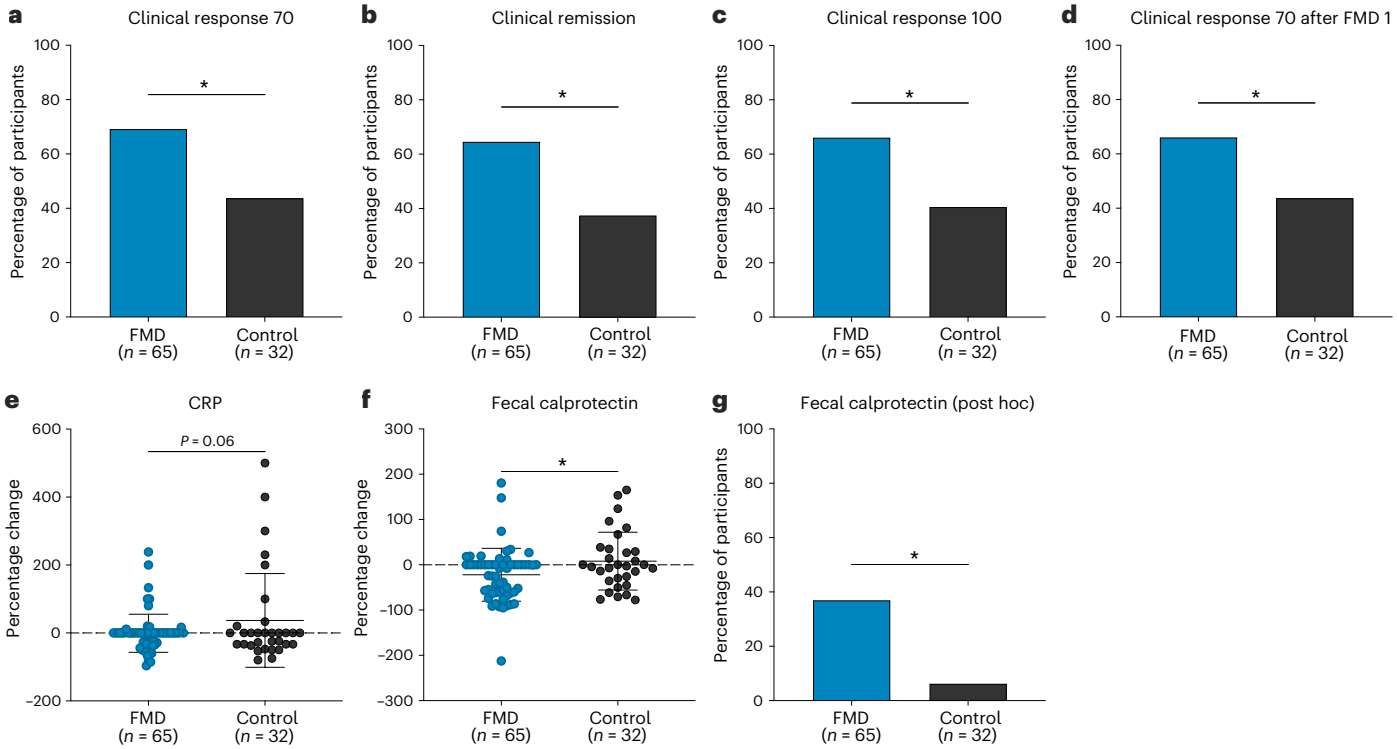

Fig. 2 | Clinical and laboratory outcomes after FMD. a, A significantly higher proportion of participants met the primary outcome (clinical response 70, CDAI decrease of ≥70 points or CDAI ≤ 150) after 3 cycles of FMD compared with 12 weeks of baseline diet (69.2% versus 43.8%, $P = 0.03$). **b**, A greater proportion of participants in the FMD group achieved clinical remission (CDAI ≤ 150) after 3 FMD cycles versus baseline diet (64.6% versus 37.5%, $P = 0.02$). **c**, There was a significant difference in the proportion of participants who achieved clinical response 100 (reduction in CDAI by ≥100 or CDAI ≤ 150) after completing the third FMD cycle versus control (66.2% versus 40.6%, $P = 0.02$). **d**, More participants achieved clinical response 70 after only 1 cycle of FMD compared with 2 weeks of baseline diet (66.2% versus 43.8%, $P < 0.05$). **e**, After the third FMD cycle, the mean percentage change in CRP from baseline was not statistically different between the two groups (−1.0% versus 36.9%, $P = 0.06$). **f**, There was a significant decline in mean percentage change in fecal calprotectin (−22.0% versus 8.0%, $P = 0.03$) after the third FMD cycle. **g**, Analysis showed a significantly higher proportion of participants in the FMD group (37.0%) had a ≥50% decline in fecal calprotectin from baseline compared with controls (6.3%) after the third FMD cycle ($P = 0.01$). In **a**–**d**, percentages of participants meet the criteria for response. In **e**,**f**, Percentage change was measured from baseline compared with after the third FMD cycle, where error bars represent s.e.m. In **g**, percentages of participants meet the criteria for response. *P* values were calculated by two-sided Fisher's exact test or chi-square test; *P* values are shown or $^*P < 0.05$.

questionnaire (SIBDQ)[15,16]. In the FMD group, 46.2% participants reported an SIBDQ score of greater than 50 after three cycles of FMD, compared with only 25.0% in the control group[15] ($P < 0.05$; Extended Data Fig. 3b). In addition, each participant's perception of their remission status was assessed through the patient global assessment (PGA). A significantly higher percentage of participants in the FMD group reported feeling that they were in remission by PGA compared with the control group (24.6% versus 6.3%, $P = 0.03$; Extended Data Fig. 3c).

Endoscopic outcomes

Due to the COVID-19 pandemic and patient hesitation to undergo elective colonoscopy, only six participants elected to have colonoscopy to assess for endoscopic evaluation of response to dietary therapy, of which five were in the FMD group and one was in the control group. Disease activity was determined by a blinded endoscopist using the Simple Endoscopic Score for CD (SES-CD). In the FMD group, four of five participants showed endoscopic remission after the third cycle; this included one participant who showed improvement from severe activity (SES-CD 19) to complete remission (SES-CD 0) and one participant who showed improvement from moderate activity (SES-CD 12) to remission (SES-CD 2)[17]. In the control group, the only participant who underwent colonoscopy maintained mild activity.

Dietary adherence

Participants in the FMD group achieved 76.9% adherence to the diet for all three cycles. Adherence rates were similar across each of the three cycles. In the control group, 87.5% participants were adherent to their baseline diet during the study period (Supplementary Table 2).

Among those participants who reported adherence to their assigned diet at all times, the per-protocol analysis showed that 82.0% FMD patients and 50.0% control patients achieved the primary outcome of clinical response 70 ($P < 0.01$; Extended Data Fig. 4a). Furthermore, among these participants, a greater proportion of the FMD group achieved clinical remission (76.0% versus 39.3%, $P < 0.01$; Extended Data Fig. 4c). We observed concordant changes in both CRP (−15.7% versus 36.9%, $P < 0.01$; Extended Data Fig. 4f) and calprotectin (−36.5% versus 8.9%, $P < 0.01$; Extended Data Fig. 4g), favoring the FMD group among participants who were adherent to their assigned diet.

FMD attenuates lipid mediators and immune-effector gene expression associated with intestinal inflammation

Given the enhanced clinical response to FMD compared with baseline diet, we then examined whether these improvements were accompanied by biological changes that provide insight into the underlying mechanisms. We conducted untargeted plasma metabolomics on all samples collected at baseline and after FMD. Fourteen of the top 20 downregulated pathways mapped to arachidonic and linoleic acid metabolism, consistent with suppression of lipid mediator signaling and inflammation; by contrast, no pathway enrichment was observed among upregulated metabolites (Extended Data Fig. 5). Guided by

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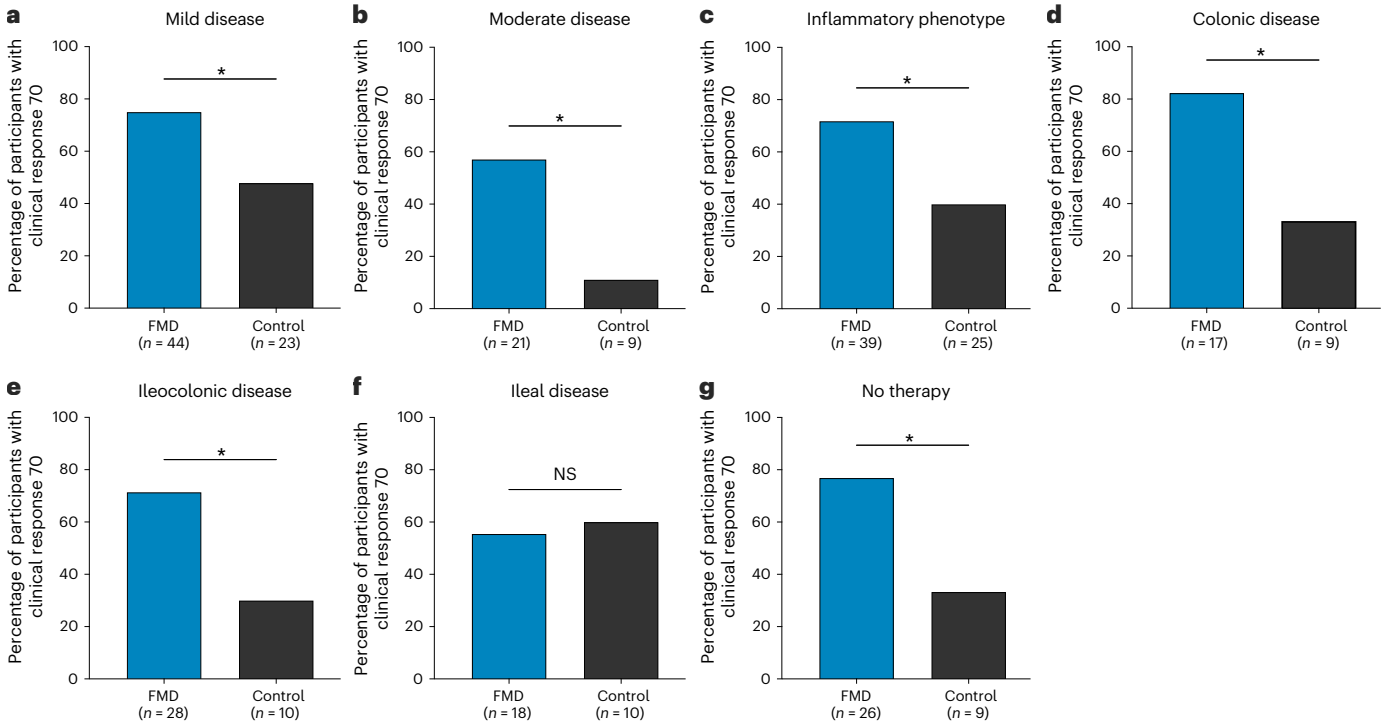

Fig. 3 | Clinical response at the primary endpoint by CD severity and phenotype. a,**b**, More participants with mild (**a**; 75.0% versus 47.8%, $P = 0.03$) and moderate (**b**; 57.1% versus 11.1%, $P = 0.04$) disease severity achieved the primary outcome (clinical response 70, CDAI decrease of ≥70 points or CDAI ≤ 150) in the FMD group compared with control. **c**, Participants with inflammatory CD were significantly more likely to respond to the FMD versus control (71.8% versus 40.0%, $P = 0.02$). **d**–**f**, Clinical response was higher in the FMD group than in controls among patients with colonic (**d**; 82.4% versus 33.3%, $P = 0.01$) and ileocolonic (**e**; 71.4% versus 30.0%, $P = 0.03$) diseases, but no significant difference was observed in participants with ileal CD (**f**; 55.5% versus 60.0%, $P = 0.99$). **g**, Of participants not on medical therapy at baseline, participants in the FMD group had a higher rate of clinical response versus participants in the control group (76.9% versus 33.3%, $P = 0.03$). Results are shown as percentages of participants meeting the criteria for response. *P* values were calculated by two-sided Fisher's exact test or chi-square test; NS, $P \geq 0.05$, $^*P < 0.05$.

this pathway analysis, we then examined the detected lipid mediators within these specific downregulated pathways. In line with the enrichment analysis, we observed a broad reduction in intestinal inflammation-associated lipid mediators after FMD compared with baseline[18–21]. In the arachidonic acid-derived leukotriene (LT) pathway, FMD significantly reduced downstream oxidation products of both LTB_4 and LTE_4, key pro-inflammatory mediators elevated in IBD[22–26]. After FMD, we also observed significant decreases in recognized markers of oxidative stress and inflammation, including the oxidized linoleic acid derivatives 13-hydroxyoctadecadienoic and 9-hydroxyoctadecadienoic acids (13-HODE and 9-HODE), as well as their downstream trihydroxyoctadecenoic acids (TriHOMEs)—all elevated in active IBD[19,20,27,28] (Fig. 4a). Notably, FMD increased 15-oxo-LXA_4/LXB_4, anti-inflammatory lipoxin (LX) metabolites known to suppress nuclear factor-κ B-dependent transcription[29,30].

Next, we asked whether the anti-inflammatory effects of FMD extended to key pathogenic inflammatory mediators of CD. To test this, we measured expression of a prespecified panel of genes with established relevance to CD pathogenesis in peripheral blood mononuclear cells (PBMCs) from participants, comparing post-FMD levels to baseline using reverse transcription quantitative polymerase chain reaction (RT–qPCR; Fig. 4b and Supplementary Table 3). FMD significantly reduced expression of several canonical pro-inflammatory cytokines, specifically *TNF*, *NLRP3*, *IL-1β* and *IL-18*. FMD also significantly decreased expression of chemokines *CCL20* (C-C motif chemokine ligand 20) and *CXCL10* (C-X-C motif chemokine ligand 10), which mediate immune cell recruitment, compared with baseline (Fig. 4b). Together, these data indicate that FMD lowers pro-inflammatory lipid mediators and downregulates immune-effector transcripts, providing a molecular basis for the observed reduction in CD activity.

Safety

FMD was well-tolerated throughout the study. There were no significant changes in weight in either the FMD group (median = 0.0%, IQR = −3.1 to 0.5%) or the control group (median = 0.0%, IQR = 1.0–1.0%).

No participants in the FMD group reported severe (grade 3) adverse events, while seven (21.8%) participants in the control group reported severe adverse events at the time of primary outcome assessment. In the FMD group, fatigue ($n = 34$, 52.3%) and headache ($n = 33$, 50.8%) were the most common adverse events and are commonly reported in fasting[31]. Among those who reported either headache or fatigue, the vast majority reported only mild symptoms (headache ($n = 27$, 81.8%) and fatigue ($n = 26$, 76.5%)). In the control group, diarrhea (50.0%) and abdominal pain (37.5%) were the most common adverse events (Table 2). Fourteen (21.5%) participants withdrew from the FMD group compared with three (9.4%) from the control group, but none of these withdrawals were due to adverse effects. The reasons for withdrawal are noted in Supplementary Table 4.

Discussion

This randomized, controlled, clinical trial compared the effectiveness of FMD versus baseline diet to reduce clinical disease activity and intestinal inflammation in adult patients with mild-to-moderate CD. FMD significantly improved the primary outcome compared with the baseline diet, with nearly 70% participants achieving clinical response and over 60% participants achieving remission. FMD was also effective in eliciting biochemical response, with a significantly greater average decline in fecal calprotectin in the FMD group compared with the control group. Although the percentage changes in CRP between the FMD and control groups did not quite meet statistical significance ($P = 0.06$), the study was powered only for the primary

https://doi.org/10.1038/s41591-025-04173-w

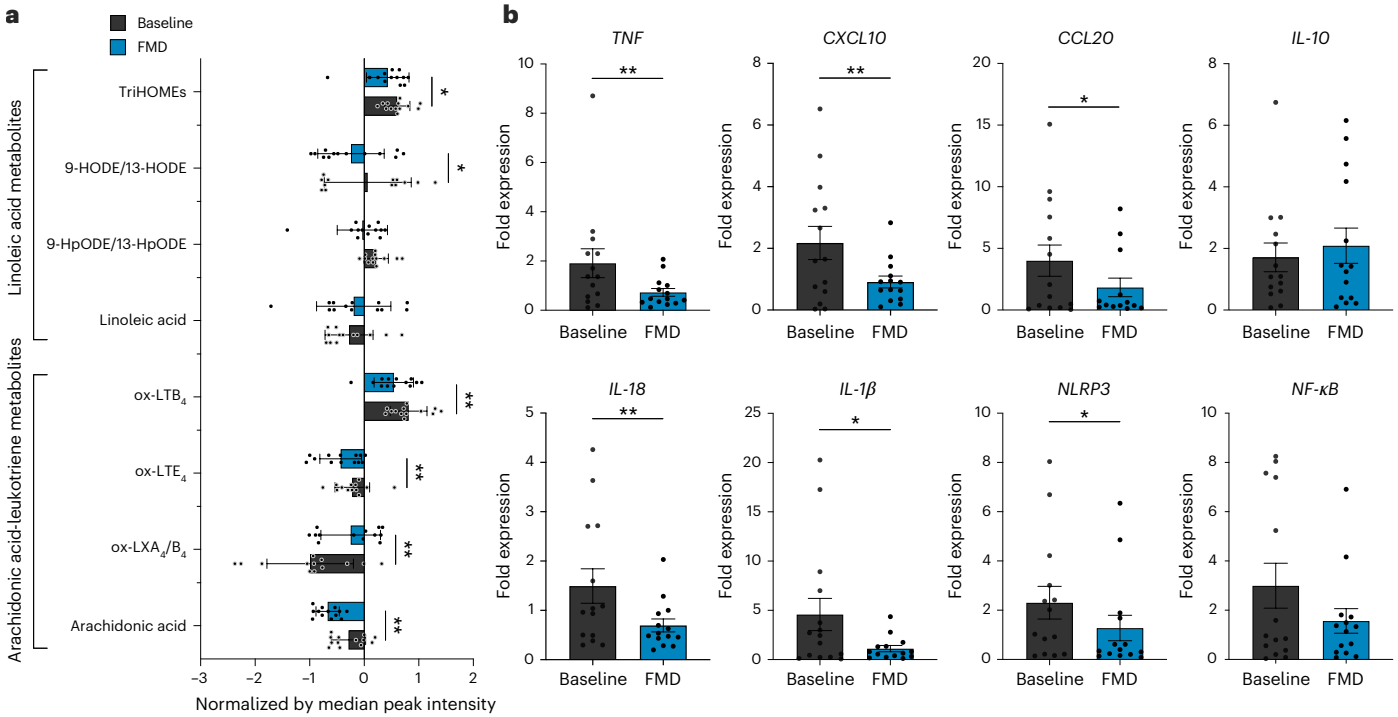

Fig. 4 | FMD attenuates lipid mediators and immune-effector transcripts associated with CD. a, Untargeted plasma metabolomics at baseline ($n = 13$) and after FMD ($n = 13$) showed reductions in pro-inflammatory oxidized LT and linoleic acid metabolites after FMD versus baseline, with a concomitant increase in anti-inflammatory oxo-LXs. These metabolites are represented in the figure as ox-LTB_4, 20-OH-LTB_4; ox-LTE_4, 18-carboxy-dinor-LTE_4; ox-LXA_4/LXB_4, 15-oxo-LXA_4/B_4. **b**, RT–qPCR analysis of PBMCs at baseline ($n = 14$) and after FMD ($n = 14$) demonstrated reduced expression of pro-inflammatory chemokines and cytokines. Blood samples were available only for a subset of the original FMD arm cohort, drawn after one FMD cycle. One patient's plasma samples were excluded due to quality control failure. Statistical significance was assessed by paired two-sided Wilcoxon signed-rank test. Data are presented as mean ± s.e.m. *P* values were FDR-adjusted using the two-stage BKY procedure (adjusted within panel), with significance defined as $q \leq 0.10$. Asterisks denote FDR-adjusted significance (*$q \leq 0.10$; **$q \leq 0.05$). Exact FDR-adjusted *P* values (q) for all results are as follows: (**a**) TriHOMEs, $q = 0.09$; 9-HODE/13-HODE, $q = 0.06$; 9-HpODE/13-HpODE, $q = 0.31$; linoleic acid, $q = 0.59$; ox-LTB_4, $q = 0.02$; ox-LTE_4, $q = 0.02$; ox-LXA_4/B_4, $q = 0.05$; arachidonic acid, $q = 0.02$; (**b**) *TNF*, $q = 0.04$; *CXCL10*, $q = 0.04$; *CCL20*, $q = 0.09$; *IL-10*, $q = 0.43$; *IL-18*, $q = 0.04$; *IL-1β*, $q = 0.01$; *NLRP3*, $q = 0.09$; *NF-κB*, $q = 0.36$. HpODE, hydroperoxyoctadecadienoic acid; CXCL, C-X-C motif chemokine ligand; CCL, C-C motif chemokine ligand; NF-κB, nuclear factor-κ B1.

outcome of clinical response and remission. Furthermore, patients with mild CD (the majority of the trial participants) often do not have notable abnormalities in CRP, which can make it more challenging to assess therapeutic responses. Following emerging evidence after initial study design, such as the STRIDE II guidelines, which linked a 50% reduction in fecal calprotectin to corticosteroid-free remission and endoscopic inactivity, we conducted a post hoc analysis to assess the proportion of patients in each group who met this threshold[32–34]. Significantly more participants in the FMD group had a 50% or greater decline in fecal calprotectin, providing further biochemical support for the favorable changes observed in CDAI in the FMD group. We also observed concordant reductions in inflammatory pathways across both plasma metabolomics and PBMC transcript profiling, as further discussed below, aligning with improvements in clinical biomarkers and disease activity.

These findings highlight the potential of FMD to serve as an effective intervention for mild and moderate CD. This is an unmet clinical need, particularly as mild CD has no FDA-approved therapies apart from corticosteroids. It is notable that we show that FMD was superior to baseline diet for the induction of clinical response and remission even among patients not on CD therapy. In addition, FMD requires dietary changes for only 5 days per month, allowing individuals to maintain their usual eating patterns and making it potentially adaptable across diverse baseline diets.

FMD likely confers benefit in CD through multiple mechanisms. Caloric restriction suppresses inflammatory pathways, including nuclear factor-κ B, NOD-like receptor family, pyrin domain-containing protein 3 (NLRP3) and TNF—central mediators of mucosal inflammation and tissue damage in CD[35,36]. Our transcriptional profiling of PBMCs demonstrated that FMD reduced expression of key pro-inflammatory mediators, including NLRP3, TNF, IL-1β and IL-18; IL-1β and IL-18 are cytokines released downstream of NLRP3 inflammasome activation, and propagate intestinal inflammation[37–43]. FMD also reduced circulating levels of arachidonic acid-derived LT and linoleic acid oxidized metabolites—pro-inflammatory lipid mediators elevated in CD and linked to epithelial barrier disruption and inflammation[27,28]. Second, FMD and the post-FMD refeeding state activate intestinal stem cells in mouse models, facilitating the replacement of damaged epithelial tissue through various signaling proteins and growth factors, such as increased fibroblast growth factor 2 expression[17,44]. Third, FMD is rich in prebiotic oligofructoses, fructo-oligosaccharides and galactomannan that promote outgrowth of beneficial bacteria, including Lactobacillaceae, a family of bacteria that has been shown to regulate T-cell activity and attenuate colitis symptoms[45]. Fourth, FMD promotes adaptive autophagy, which is an early part of cellular stress response; autophagy, which removes damaged organelles and misfolded proteins, protects host cells from subsequent injury[46]. Finally, in other studies, both fasting and FMD have been shown to increase serum ketones several fold; certain ketones, such as β-hydroxybutyrate, have been shown to modulate intestinal inflammation through direct effects on inflammatory cell profiles[47–49].

FMD was able to rapidly improve symptoms compared with baseline diet, with 66% participants reporting clinical improvement after a single, 5-day cycle of FMD. We also observed loss of clinical

Table 2 | List of adverse events per NCI CTCAE version 5.0 (ref. 62)

Adverse event	Grade 1			Grade 2			Grade 3		
	FMD	Control	*P* value	FMD	Control	*P* value	FMD	Control	*P* value
	n (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)	
Fatigue	26 (40.0)	3 (9.4)	<0.01	8 (12.3)	1 (3.1)	0.26	0 (0.0)	0 (0.0)	1.00
Headache	27 (41.5)	0 (0.0)	<0.01	6 (9.2)	1 (3.1)	0.42	0 (0.0)	0 (0.0)	1.00
Bloating	16 (24.6)	1 (3.1)	<0.01	6 (9.2)	0 (0.0)	0.17	0 (0.0)	0 (0.0)	1.00
Dizziness	12 (18.5)	1 (3.1)	0.06	4 (6.2)	0 (0.0)	0.30	0 (0.0)	0 (0.0)	1.00
Diarrhea	12 (18.5)	11 (34.4)	0.13	3 (4.6)	3 (9.4)	0.39	0 (0.0)	2 (6.3)	0.11
Abdominal pain	13 (20.0)	1 (3.1)	0.03	1 (1.5)	5 (15.6)	0.01	0 (0.0)	6 (18.8)	<0.01
Other complaints	11 (16.9)	3 (9.4)	0.38	2 (3.1)	1 (3.1)	1.00	0 (0.0)	0 (0.0)	1.00
Nausea	9 (13.9)	1 (3.1)	0.16	3 (4.6)	1 (3.1)	1.00	0 (0.0)	0 (0.0)	1.00
Concentration impairment	8 (12.3)	0 (0.0)	0.05	2 (3.1)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00
Malaise	5 (7.7)	0 (0.0)	0.17	3 (4.6)	0 (0.0)	0.55	0 (0.0)	0 (0.0)	1.00
Flatulence	7 (10.8)	0 (0.0)	0.09	0 (0.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00
Irritability	5 (7.7)	0 (0.0)	0.17	0 (0.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00
Constipation	4 (6.2)	0 (0.0)	0.30	0 (0.0)	0 (0.0)	1.00	0 (0.0)	1 (3.1)	1.00
Vomiting	2 (3.1)	3 (9.4)	0.33	0 (0.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	0.33
Dry mouth	0 (0.0)	0 (0.0)	1.00	1 (1.5)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00
Fecal incontinence	0 (0.0)	0 (0.0)	1.00	1 (1.5)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00
Chills	1 (1.5)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00
Tinnitus	1 (1.5)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00

Adverse events are graded according to CTCAE guidelines. Grade 1, mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2, moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (that is, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.). Grade 3, severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (that is, bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden). *P* values were calculated by two-sided Fisher's exact test or chi-square test. CTCAE, Common Terminology Criteria for Adverse Events.

response after a washout period of 3 months. This suggests that the optimal number of FMD cycles required to maintain clinical benefits over extended periods in patients with CD remains unclear, and that continued 5-day cycles per month of diet therapy may be necessary for sustained remission.

Participants with colonic and ileocolonic CD had higher rates of clinical response and remission with FMD compared with control. However, participants with ileal disease alone did not demonstrate the same improvement. We hypothesize that this is due to the distinct immune environments in the large and small bowel. The colonic immune microenvironment is more responsive to luminal antigens, and fasting effectively reduces antigenic stimulation[50,51]. In addition, given the more rapid turnover of enterocytes relative to colonocytes, the autophagy response triggered by fasting may not be as beneficial in the small bowel[52,53].

Blinded endoscopic assessments also showed promising results with FMD—four of five participants with baseline endoscopic disease achieved endoscopic remission by the end of the third diet cycle[17,54]. Patients not receiving any IBD therapy experienced significant improvement with FMD relative to baseline diet alone—an important finding given the limited maintenance treatment options for mild CD.

The trial had a high response rate in the control group, with approximately 40% participants showing clinical improvement or remission. This high response rate was likely multifactorial. First, all participants were allowed to continue standard-of-care medical therapy. Second, as the study population included only patients with mild-to-moderate CD, it is reasonable that some participants had clinical improvement due to fluctuations that may occur in the natural history of the disease.

Adherence to the FMD was high, likely due to the provision of meal kits and the brief, 5-day duration of dietary restrictions. FMD was well-tolerated, with no serious adverse events reported. A total of 17 participants (17.5%) dropped out of the study, and the study was powered a priori to account for dropouts.

This study has several key strengths. To our knowledge, this is the largest randomized, controlled trial of a solid, nonexclusion diet in adults with CD[55–59]. While exclusive and partial enteral nutrition are effective, their limited palatability and high cost currently hinder broad adoption[60,61]. In contrast, FMD is compatible with a wide range of dietary patterns and does not require complete change in diet—an important advantage as the global prevalence of IBD rises, particularly outside Europe and North America. This study identifies a dietary intervention that is not only effective at controlling clinical disease activity but also effective for inducing biochemical response in patients with mild-to-moderate CD. Notably, there were no differences between FMD and control in starting corticosteroids or advanced therapy during the trial. Furthermore, there was no difference in the recent start of advanced therapy (defined as less than or equal to 2 months) or median duration of advanced therapy. While we believe that FMD is best used as an adjunctive treatment along with conventional therapy, our data suggest that it may be effective as monotherapy in patients with mild disease. In addition, the concordant metabolomic and transcriptional signatures from analysis of biological samples provide alignment with the clinical benefit, indicating that FMD modulates known metabolic pathways and associated cytokine-chemokine networks implicated in CD. Finally, the trial also enrolled participants from diverse geographic regions across the United States, adding to the generalizability of the findings.

Our study has some limitations. Similar to virtually all diet studies, we were unable to blind patients to the group to which they were randomized. In addition, while we enrolled patients with mild-to-moderate disease, nearly two-thirds of the cohort had mild disease, limiting our

ability to understand the impact on patients with moderate-to-severe disease. Patients with mild disease may be more prone to assessor bias when reporting symptoms, particularly in diet studies. Furthermore, the study could not assess the effect of FMD on endoscopic healing because the number of participants who underwent colonoscopy was too small to permit quantitative analyses of this outcome. Given the small and open-label nature of this study and limited endoscopic data, findings should be interpreted with care. Also, the study population was predominantly white, which may impact the generalizability of the results to other races and ethnic groups. In addition, despite collecting blood samples within 24 h of completing FMD, this duration and variability, along with the lack of specialized stabilization in our metabolomics, detection of labile metabolites, such certain eicosanoids, may be attenuated. For these reasons, we view these findings as hypothesis-generating at the species level; targeted workflows in a follow-up cohort can further delineate the principal mediators. While there are several mechanisms of action by which FMD exerts its anti-inflammatory effect, it is notable that the majority of downregulated pathways in the pathway enrichment comparing FMD to control mapped predominantly to arachidonic and linoleic acid metabolism, indicating that attenuation of inflammatory lipid mediators occurs at the pathway level rather than being driven by a single species.

In conclusion, our study demonstrates that FMD is a clinically effective and feasible intervention for inducing clinical response and remission in mild-to-moderate CD. While additional investigation is necessary, its adaptability and short duration of dietary restriction make it a promising adjunct to pharmacologic therapy.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-04173-w.

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Methods

Study design and patient population

The 'effects of an intermittent reduced-calorie diet on CD' study was an open-label, randomized, controlled, clinical trial (NCT04147585) conducted at Stanford University that compared the effectiveness of FMD versus baseline diet to reduce clinical disease activity in patients with mild-to-moderate CD. The study protocol was approved by the Stanford University Institutional Review Board (IRB), and complied with all federal regulations, state laws, local policies and established ethical practices. For more information, the study protocol and statistical analysis plan are included in Supplementary Note.

Enrollment occurred between 2019 and 2023 in the United States. We screened 279 potential participants, who were identified from a national recruiting campaign. A total of 119 participants were recruited. Twenty-two participants, although eligible, decided not to participate before randomization. The 97 enrolled patients were block randomized 2:1 (block size of 6) such that 65 participants were assigned to FMD and 32 to control. The random allocation sequence was sequentially numbered. Thirty-eight of these patients were recruited from Stanford University, and the remaining patients were recruited nationally from 59 institutions. During the trial, 14 participants in the FMD group and 3 in the control group withdrew (Supplementary Table 4).

Sample size determination

The study was powered for the primary outcome assuming an α of 0.05, power of 90% and a dropout rate of 30%. For sample size determination, the enrollment ratio was assumed to be 2:1. The effect size was estimated from the proportion of healthy control patients who normalized CRP during FMD in a study of healthy participants[8].

Inclusion and exclusion criteria

Adult patients (male or female) between the ages of 18 and 70 years with CD were eligible for inclusion in the study. Male or female sex was self-reported by patients at the time of screening; information was not collected regarding sex identity. Participants were also required to have mild-to-moderate symptoms, defined by a CDAI score above 150 and no greater than 450. A diagnosis of CD was established by each patient's gastroenterologist based on usual clinical, radiographic, endoscopic and histologic criteria.

Patients were excluded from the study based on several criteria. Women who were pregnant, nursing or planning to become pregnant were not eligible. In addition, individuals with a known nut allergy or a BMI below 18 were excluded. Patients who were severely weakened by disease or medical procedures, or who were taking medications that may not be safely combined with a calorie-restricted diet, were not allowed to participate. Patients with diabetes who used antidiabetic drugs associated with the risk of hypoglycemia were similarly excluded. Furthermore, individuals with more than mild-to-moderate cardiovascular disease or life-threatening cancer were not eligible unless approved by a physician. This also applied to patients with a history of severe cardiac disease, particularly uncompensated congestive heart failure (NYHA grade 2 or higher) or a left ventricular ejection fraction of less than 40%, as well as those with a history of syncope. Patients with dietary requirements incompatible with the FMD meal plan were excluded, along with those with liver or kidney disorders that could be adversely affected by a low-glucose and protein diet. Patients already on a calorie-restricted diet, those with short bowel syndrome and individuals with a history of relevant gastrointestinal surgeries, including ostomy of the small or large intestine, total colectomy, proctocolectomy or ileoanal pouch, were also excluded from the study. Patients who had undergone resection of the terminal ileum, resection of short strictures of the small intestine or hemicolectomy were not excluded.

Intervention

Participants randomized to the intervention arm consumed the FMD for five consecutive days per month for three consecutive months. Participants resumed their normal diet during the remaining approximately 25 days in each month.

Ahead of the start date for each FMD cycle, participants received a commercially available diet box, which was purchased by the research team from L-Nutra. Each box contained all the meals for each day of the 5-day FMD cycles. The foods for each day consisted of soups, nutrition bars, snacks and supplements. During the FMD, participants' daily calorie intake was limited to 1,090 calories (10% protein, 56% fat, 34% carbohydrates) on day 1, and 725 calories (9% protein, 44% fat, 47% carbohydrates) on days 2–5. Participants were encouraged to follow the diet exactly and consume only and all of what was provided in the box for each day. In the rare cases where a particular food or ingredient was poorly tolerated, participants were allowed to substitute that item using a recipe with matching macronutrients developed by the research dietitian. Any substitution requests or needs were overseen by the research dietician to ensure the nutritional consistency with the FMD.

Outcome measures

The primary outcome was defined as a reduction in CDAI of at least 70 points from baseline or CDAI ≤ 150 (clinical response 70) after the third 5-day diet cycle[63,64]. For the primary analysis, data were obtained within 1 week, starting immediately after the completion of the third FMD cycle when participants had resumed their baseline diet. The CDAI score was calculated at the end of the 1-week period. Secondary outcomes were measured at three time points—after the first cycle of FMD, after the third cycle of FMD and after a 3-month washout period following the third cycle of FMD. The secondary outcomes measured were clinical remission (CDAI ≤ 150), clinical response 100 (reduction in CDAI of at least 100 points from baseline or CDAI ≤ 150), percentage change from baseline CRP, percentage change from baseline erythrocyte sedimentation rate, percentage change from baseline fecal calprotectin, remission per PRO (defined as fewer than four loose or watery (Bristol type 6 or 7) stools per day and minimal abdominal pain (severity rated less than or equal to 1 on a 0–3 Likert scale), PGA of symptoms, effect of FMD on patient quality of life measured by SIBDQ and the effect of FMD on endoscopic healing as measured by the SES-CD. Participants were considered to have achieved PGA remission if they perceived their CD symptoms to be in remission at the time of the assessment. All labs were performed at the Stanford Clinical Lab or at commercial labs. All participants continued to receive standard-of-care medical therapy under the direction of their gastroenterologist.

Additional post hoc analyses were performed. First, after observing that many enrolled patients were not receiving advanced therapy, we evaluated the efficacy of FMD compared with baseline diet in a subgroup of patients who were off advanced therapy. Second, after observing a clinically significant difference in some baseline characteristics (defined by SMD difference of ≥0.20), we performed multivariable logistic regression analyses to estimate the treatment effect while adjusting for imbalanced baseline variables (Supplementary Table 1). Third, we adjusted the inflammatory markers for multiple comparisons (Supplementary Table 5). Finally, we determined what percentage of patients had a 50% or greater decline in fecal calprotectin from baseline, consistent with a clinically meaningful decline previously described in multiple other studies and the STRIDE II guidelines, which were released after the initial study design[32].

For all binary outcomes, any participant who withdrew from the study before the relevant endpoint was categorized as FMD treatment failure. Missing continuous outcomes were imputed by carrying forward the baseline measurement.

Protocol modifications

Our study faced substantial delays in recruitment due to the SARS-CoV-2 pandemic. In response, we modified our protocol to allow any participants who withdrew from the study before the third FMD cycle due to the pandemic to re-enroll after a washout period of 3 months; ultimately, this accommodation allowed for the re-enrollment of four participants.

We also expanded our recruitment from Stanford clinics to nationwide in February 2021. This modification enabled screening of participants from outside Stanford. Local participants continued to have study visits and labs at Stanford clinics; however, for participants living outside of the Stanford area, study visits were conducted through phone or video call and labs were completed at local facilities.

Dietary adherence assessments

Participants reported adherence by completing online questionnaires (weekly during the baseline diet and daily during the FMD cycles) and phone calls from the research team. The daily surveys during FMD cycles asked participants to self-report adherence and any deviations from the FMD. Participants also received two scheduled calls from the research dietitian during the baseline diet period, and three calls from the research team (including at least one call from the study dietitian) during each FMD cycle.

Participants in the FMD arm were considered adherent during FMD cycles if they did not consume more than 400 additional calories beyond what was provided in the meal kit on any given day of the cycle and completed all 5 days of each cycle. Participants were considered adherent to their regular diet if they did not have any self-described changes in diet or exclusion of foods (for example, new start of an MD) during the periods between FMD cycles (for FMD participants) or throughout the study period (for control participants).

Adverse events

Adverse events were assessed at each study visit for all participants and during each diet cycle for the FMD group. Adverse events were self-reported and subsequently graded according to the Common Terminology Criteria for Adverse Events version 5.

Ethics

The protocol was reviewed and approved by the Stanford University IRB (IRB-53161) in 2019. All patients provided written informed consent to participate before proceeding with any study-specific procedures. The study adhered to the Consolidated Standards of Reporting Trials guidelines.

Participants received a $200 reimbursement to offset time and parking-related expenses and the inconvenience/personal costs associated with attending multiple study visits. Participants who agreed to undergo endoscopy as part of the study received an additional $200, bringing the total payment to $400. Payments were made to each participant after completion of all study activities.

Statistical analysis

Sample size was determined a priori by standard power calculations. All analyses of clinical data presented in the main body of the paper were conducted by intention-to-treat analysis. We have also included per-protocol analysis for the following endpoints that were measured after the third cycle of FMD in the supplement: clinical response 70, clinical response 100, clinical remission, remission by PRO and SIBDQ, CRP and calprotectin changes (Extended Data Fig. 4). All endpoints and analyses were prespecified unless otherwise stated. Descriptive data are reported with median and IQR or counts and percentages. Continuous data were analyzed using a two-sided *t* test. For *t* tests, normality was verified using the D'Agostino–Pearson test and homogeneity of variance was verified by Levene's test. Categorical data were analyzed using a chi-square test or Fisher's exact test, as appropriate. All tests were two-sided ($\alpha = 0.05$). *P* values were adjusted for multiplicity using the two-stage Benjamini–Krieger–Yekutieli (BKY) procedure due to positive dependence among tests within a panel; FDR-adjusted *P* values are reported with a prespecified FDR threshold of 10% ($q \leq 0.10$), defining significant results[65]. Adjustments were applied within each prespecified panel, namely the clinical inflammatory biomarker panel (Supplementary Table 5), lipid mediator families (specifically, arachidonic acid-derived LT and linoleic acid-derived metabolite pathways; Fig. 4a and Extended Data Fig. 5), and the cytokine/chemokine RT–qPCR transcripts (Fig. 4b). Additional data analysis methodology for metabolomics and RT–qPCR is described below in their respective sections.

Subgroup analyses were performed to understand the impact of the following variables: mild versus moderate disease, IBD therapy, disease location (L1–L3) and disease behavior. We also assessed the impact of residual confounding using multivariable logistic regression, including the following variables that had baseline imbalances (SMD > 0.20) after randomization: sex, race, ethnicity, smoking status, BMI and use of advanced IBD therapy. The adjusted odds ratios are presented in Supplementary Table 1.

Demographic data are reported as median and IQR or counts and percentages (Table 1 and Supplementary Tables 4, 6 and 7). SMDs were calculated to measure effect size[66,67] (Table 1). SMD is a measure of effect size that quantifies the difference in proportion between two groups. Typically, an SMD of 0.20–0.49 is considered small, 0.50–0.79 is medium and >0.79 is large[66,67]. All clinical data analyses were conducted using R (version 4.3). Data visualization was done using GraphPad.

Pathway analysis directed plasma metabolomics sample preparation and data acquisition

Blood was centrifuged at 800*g* for 10 min. Plasma and PBMCs were isolated and stored as previously described[68]. Plasma samples were thawed on ice and mixed with prechilled 100% methanol at a 1:4 ratio, followed by 30 min of shaking in a sonicator bath. Samples were then kept on ice for an additional 30 min and centrifuged at 4 °C for 15 min. A 150-µl aliquot of the supernatant was transferred into liquid chromatography–mass spectrometry (LC–MS) vials containing 150-µl inserts. Quality control samples were prepared by pooling 10 µl of supernatant from each individual sample.

Untargeted metabolomic profiling was performed on an Agilent 1290 Infinity LC system coupled to an Agilent 6545 time-of-flight mass spectrometer. A reverse-phase (RP) column (Agilent Technologies, part 959758-902) was used in positive and negative ion electrospray ionization (ESI^+ and ESI^-) modes. Briefly, 5-µl supernatant was injected into the system. Mobile phases for ESI^+-included 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B)[69]. Mobile phases for ESI^--included 5-mM ammonium acetate in water (A) and 100% acetonitrile (B)[70]. Gradient settings of RP-ESI^+ were as follows: 0–2.5 min, 5% B; 2.5–9.5 min, 5–95% B; 9.5–12 min, 95% B; 12–12.1 min, 95–5% B; and 12.1–15 min, 5% B. Gradient settings of RP-ESI^- were as follows: 0–2.5 min, 2% B; 2.5–9.5 min, 2–80% B; 9.5–12 min, 80% B; 12–12.1 min, 80–2% B; and 12.1–15 min, 2% B. The flow rate was maintained at 0.4 ml min^{-1}. Dual Agilent Jet Stream ESI parameters are as follows: gas temperature, 300 °C; drying gas, 11 l min^{-1}, nebulizer, 35 psi; sheath gas temperature, 275 °C, sheath gas flow, 11 l min^{-1}; VCap, 3,500 V. MS/time-of-flight was set as follows: fragmentor, 120 V; skimmer, 65 V. The scanning range was set to m/z 100–1,700, and the acquisition rate was 2 spectra per scan. High-resolution, accurate-mass full-scan MS was performed to capture all detectable ions.

Metabolomic annotation and data analysis

Raw data were converted to MS markup language format using MSConvert (version 2.1, ProteoWizard) and processed through MetaboanalystR. A noise threshold of 1,000 was used when constructing isolated chromatograms for each mass. The locally estimated scatterplot smoothing regression method was applied to correct retention times, and missing values were imputed using local chromatographic signals. MS1 annotation used CompoundDB with Human Metabolome Database (version 5.0), applying a 10 ppm mass tolerance. Raw metabolite intensities were normalized to the median peak intensity of each sample to reduce variation arising from sample loading and instrument drift, and then $\log_{10}$ transformed to improve normality. To investigate pathway-level metabolic alterations associated with FMD, metabolites exhibiting a fold change ≥1.5 or ≤1/1.5 were selected for enrichment analysis using MetaboAnalystR. Overrepresentation

analysis was performed leveraging the Reactome pathway database to identify significantly enriched pathways within this subset. Pathways passing FDR correction using the BKY two-step method with an FDR threshold set at 10% ($q \leq 0.10$) were considered significant. We then focused on a subset of FDR-significant pathways of interest and analyzed the corresponding metabolites. Longitudinal within-participant changes in these metabolites were evaluated using paired, two-tailed *t* tests or Wilcoxon signed-rank tests, depending on data distribution[71].

RNA isolation and RT–qPCR

PBMCs were thawed on ice. RNA was extracted using RNeasy Mini (74104, Qiagen). Complementary DNA synthesis was performed using the QuantiNova Reverse Transcription Kit (205411, Qiagen). qPCR was performed on Applied Biosystems StepOnePlus Real Time-PCR System Thermal Cycling Block (Thermo Fisher Scientific) using SYBR Green fluorescence dye (Q712, Vazyme) expression assays, following the manufacturer's instructions. Primers were designed using the Primer-BLAST tool at the National Center for Biotechnology Information and made by the Stanford Protein and Nucleic Acid Facility. For analysis, each gene was normalized to the housekeeping gene, hypoxanthine phosphoribosyltransferase 1. mRNA levels were quantified using the difference in C_t values and calculated using the $2^{-\Delta\Delta Ct}$ method. A list of the qPCR primers used is provided in Supplementary Table 3. For RT–qPCR analysis, statistical significance was assessed using a two-sided ($\alpha = 0.05$) Wilcoxon signed-rank test for paired samples. *P* values were adjusted for multiple comparisons in GraphPad Prism using the two-stage linear step-up BKY across the prespecified transcript panel, which were considered positively dependent. Analysis of inflammatory gene expression using qPCR was conducted using GraphPad Prism 10. FDR correction of *P* values was performed using GraphPad Prism and verified in R.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

We have deposited metabolomics raw data on figshare (https://figshare.com/s/5ef87ff3127d0aad5a5a). Anonymized clinical data may be made available upon reasonable request with at least 4 weeks' notice. Data access requests should contact the corresponding author. Approval of such requests is at the PI's and sponsor's discretion and depends on the nature of the request, the merit of the research proposed, the availability of the data and the intended use of the data.

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Acknowledgements

This work was supported by a grant from The Leona M. and Harry B. Helmsley Charitable Trust to Stanford University (to S.R.S., C.G., J.L.S. and A.H.). We specifically acknowledge Helmsley's S. Soni for her overall support. Additional funding support was provided by NIH–NCATS–CTSA (grant UM1TR004921 to S.R.S. and J.Y.), the Plant Based Diet Initiative at Stanford University (to C.K. and S.R.S.), Kenneth Rainin Foundation (to S.R.S., J.L.S. and S.P.S.), the Doris Duke Foundation Physician Scientist Fellowship Award (2021091 to J.G.), CZ Biohub Physician-Scientist Scholar Award (to J.G.), NIH-NIDDK LRP Award (2L30 DK126220 to J.G., NIH-T32DK007056 to S.P.S. and NIH-K08DK134856 to S.P.S.), Colleen and Robert D. Hass Fund (to S.P.S.), UCSF Center for the Rheumatic Diseases (to J.F.A.), Nora Eccles Treadwell Foundation (to J.F.A.), Arthritis Research Coalition (to J.F.A.), Chan Zuckerberg Biohub Investigator Program (to J.L.S.) and NIH-NIDDK (R01DK085025 to J.L.S.).

Author contributions

S.R.S. conceptualized the study and acquired funding. S.R.S., C.G., A.H., J.L.S., J.F.A., V.D.L., D.P., L.B., M.M.D., V.C., J.Y., T.F., C.K. and K.J. developed the methodology. C.K., T.F., J.Y., K.J., E.D., H.J., S.R.S. and V.C. performed the formal analysis and visualization. T.F., C.K., K.J., K.K., S. Streett, E.H., G.B., S. Singh, D.L., N.A., J.G., E.D., H.J., M.T., A.P., Y.J., L.B., S.P.S., D.M., S.R.S. and D.P. helped with patient recruitment and data collection. T.F., C.K., J.Y., E.D., H.J., M.T. and K.J. conducted data curation. S.R.S., A.H., J.L.S., M.M.D. and C.G. were responsible for supervision. C.K., T.F. and S.R.S. contributed to writing the original draft of the paper. All authors were involved in writing, reviewing and editing the paper, and provided the final approval.

Competing interests

V.D.L. has equity interest in L-Nutra and has filed patents related to the FMD. V.D.L. does not receive consulting fees from L-Nutra and has committed his shares of the company to charitable organizations. The authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-025-04173-w.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-04173-w.

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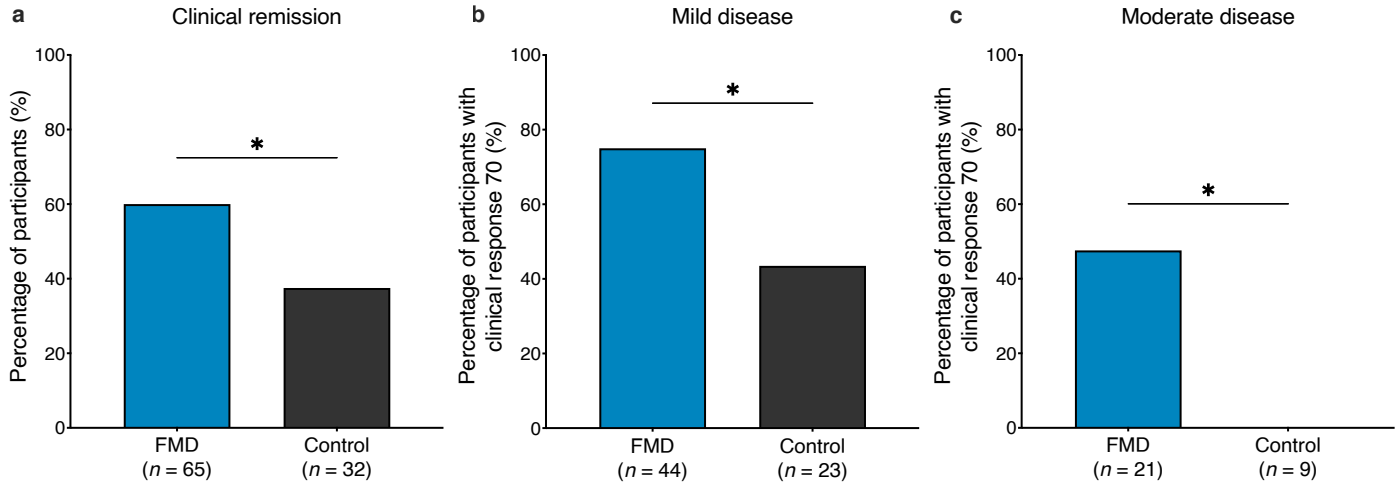
Peer review information *Nature Medicine* thanks Qiwei Li, Nicholas Powell and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Ashley Castellanos-Jankiewicz, in collaboration with the *Nature Medicine* team.

https://doi.org/10.1038/s41591-025-04173-w



Extended Data Fig. 1 | Clinical outcomes after the first FMD cycle. CDAI score significantly decreased among participants with mild-to-moderately active CD after completing the first cycle of the FMD compared to control. **a**, After completing the first 5-day FMD, more participants achieved clinical remission compared to participants who made no diet changes (60.0% versus 37.5%, $P = 0.04$). **b**,**c**, This difference in clinical response after a single cycle of FMD was also observed when patients were stratified into mild (**b**, 75.0% versus 43.5%, $P = 0.02$) and moderate (**c**, 47.6% versus 0.0%, $P = 0.01$) disease. Results are shown as percentages of participants meeting the criteria for response. P values were calculated by Fisher's exact test or chi-square test; NS: $P \geq 0.05$, $^*P < 0.05$. FMD, fasting-mimicking diet.

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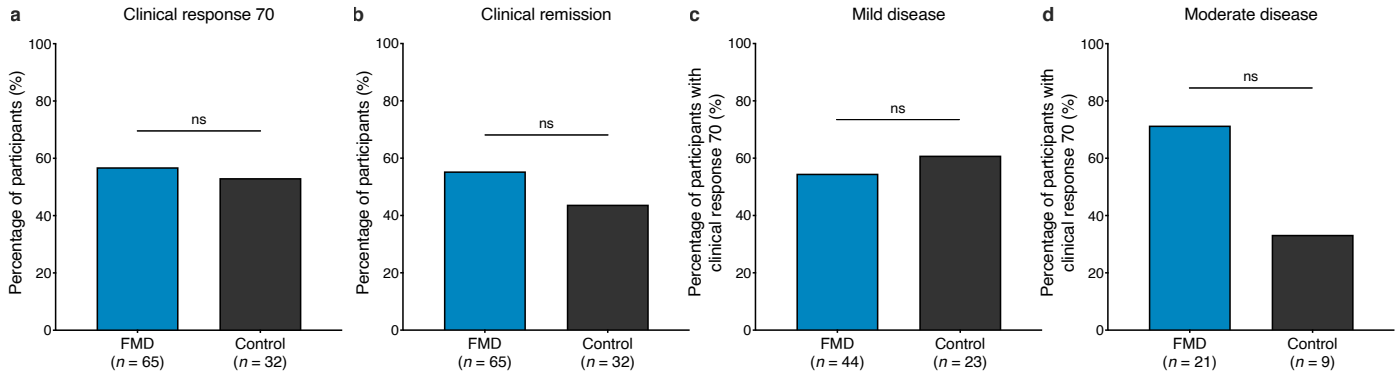

Extended Data Fig. 2 | Clinical outcomes 3 months after the third FMD cycle. CDAI score assessment at the end of the study (week 24); for participants in the FMD group, this corresponded to approximately 3 months after completion of the third FMD cycle. **a**–**d**, No significant differences were observed in the percentages of participants achieving clinical response (**a**, 56.9% versus 53.1%, $P = 0.83$) or clinical remission (**b**, 55.4% versus 43.8%, $P = 0.39$) between FMD and control groups after 3-month washout, regardless of mild (**c**, 54.6% versus 60.9%, $P = 0.79$) or moderate (**d**, 71.4% versus 33.3%, $P = 0.10$) disease severity. Results are shown as percentages of participants meeting the criteria for response. *P* values were calculated by Fisher's exact test or chi-square test; NS: $P \geq 0.05$. FMD, fasting-mimicking diet.

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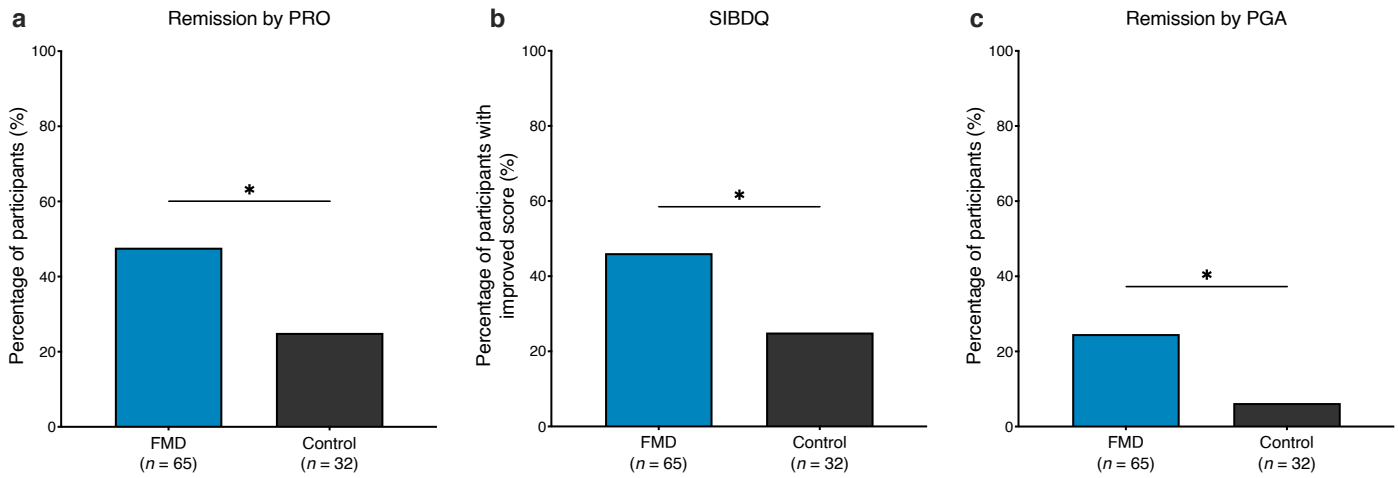

Extended Data Fig. 3 | PRO and quality of life after the third FMD cycle. **a**, Remission by PRO was achieved by 47.7% of FMD versus 25.0% ($P < 0.05$). **b**, Improvement in SIBDQ by more than 50 points was observed in 46.2% of FMD versus 25.0% of control participants ($P < 0.05$)[15,16]. **c**, Remission by PGA was observed in 24.6% of FMD versus 6.3% of control participants ($P = 0.03$). FMD, fasting-mimicking diet; PRO, patient-reported outcomes; SIBDQ, short inflammatory bowel disease questionnaire; PGA, patient global assessment. Results are shown as percentages of participants meeting the criteria for response. *P* values were calculated by two-sided Fisher's exact test or chi-square test; *$P < 0.05$.

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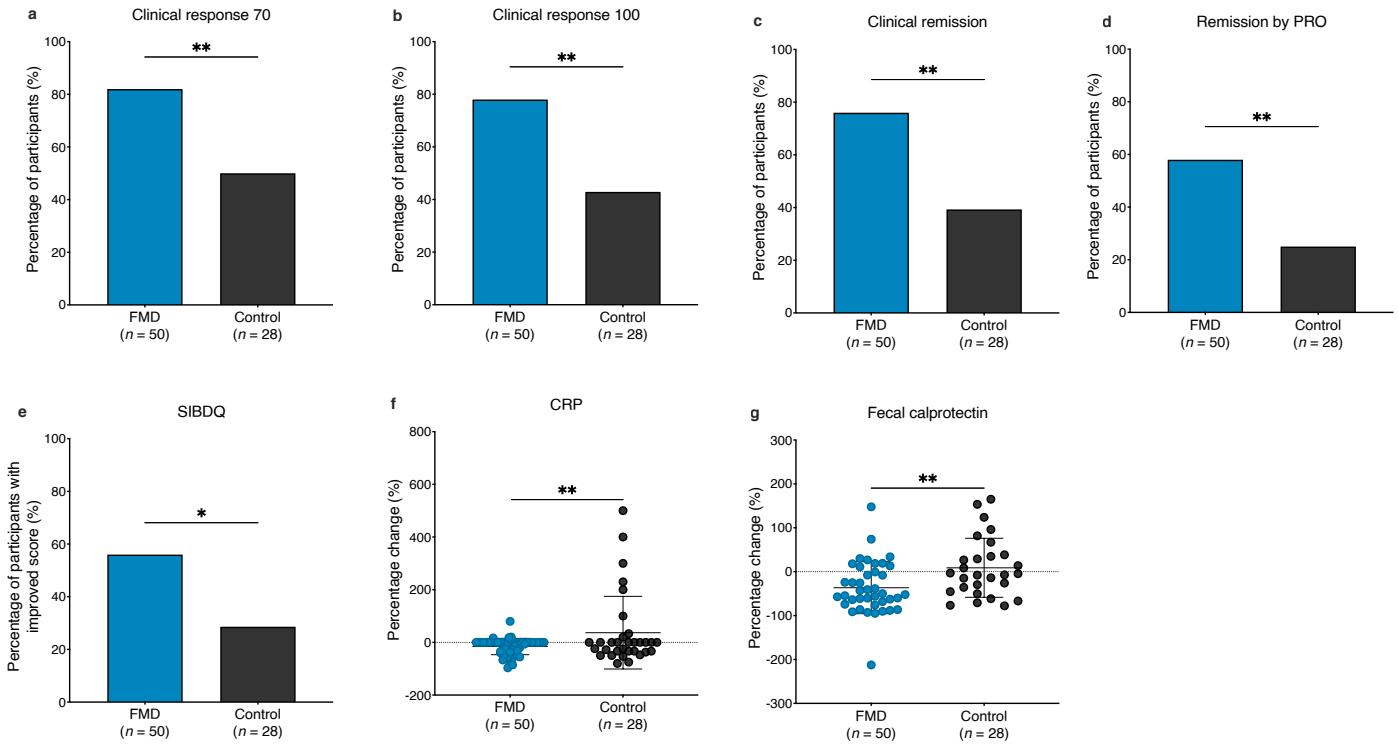

Extended Data Fig. 4 | Per-protocol analysis of clinical, patient-reported, and laboratory outcomes after the third FMD cycle. Data from participants who completed the study were assessed after the third FMD cycle; for participants in the control group, this corresponded to approximately 12 weeks after baseline. **a**–**c**, Significantly more participants met criteria for clinical response 70 (**a**, 82.0% versus 50.0%, $P < 0.01$), clinical response 100 (**b**, 78.0% versus 42.9%, $P < 0.01$), and clinical remission (**c**, 76.0% versus 39.3%, $P < 0.01$) after completing the three FMD cycles compared to participants who made no dietary changes. **d**,**e**, Compared to baseline, a significantly higher percentage of participants reported remission by PRO (**d**, 58.0% versus 25.0%, $P < 0.01$) and improvement in SIBDQ score (**e**, 56.0% versus 28.6%, $P = 0.02$) after the third FMD cycle compared to participants in the control arm. **f**,**g**, There were significant differences in mean percentage change in CRP (**f**, −15.7% versus 36.9%, $P < 0.01$) and fecal calprotectin (**g**, −36.5% versus 8.9%, $P < 0.01$) between the FMD and control arms. **a**–**e**, Percentages of participants meeting the criteria for response. **f**,**g**, Mean percentage change measured from baseline to after the third FMD cycle; error bars represent standard error of the mean (s.e.m.). *P* values were calculated by Fisher's exact test or chi-square test (**a**–**e**) or t-test (**f**,**g**); $^{*}P < 0.05$, $^{**}P < 0.01$. FMD, fasting-mimicking diet; PRO, patient-reported outcomes; SIBDQ, short inflammatory bowel disease questionnaire; CRP, C-reactive protein.

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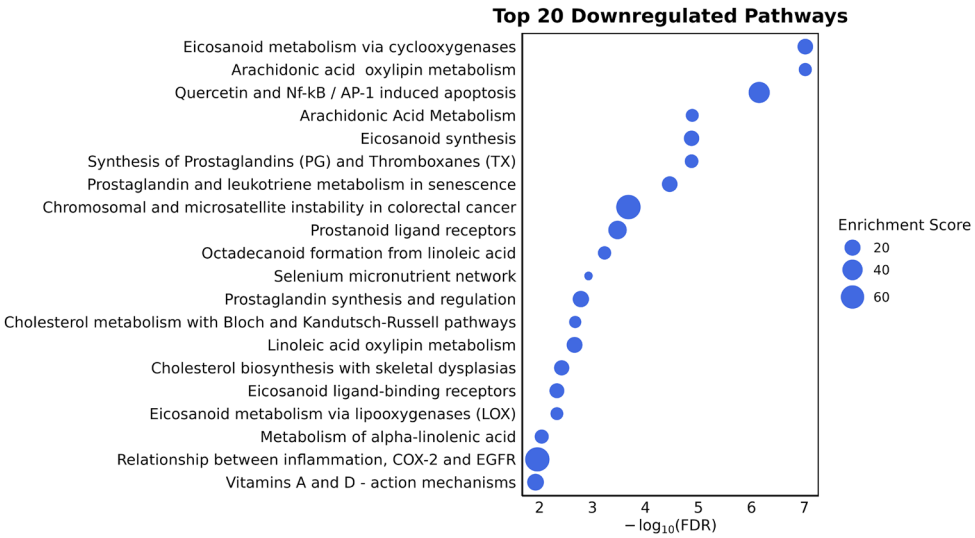

Extended Data Fig. 5 | Downregulated pathways in FMD compared to control. Features with fold change ≤1/1.5 (FMD versus control) underwent pathway enrichment analysis using Reactome in MetaboAnalyst. Figure shows the top 20 downregulated pathways. Two-sided tests as implemented in MetaboAnalyst; P values were FDR-adjusted using the two-stage Benjamini-Krieger-Yekutieli (BKY) procedure, with significance defined as q ≤ 0.10. All pathways shown have FDR-adjusted $P < 0.10$. Dot size indicates the enrichment score, and the x-axis represents statistical significance as $-\log_{10}$(FDR). FMD, fasting-mimicking diet; RAMD, random accelerator molecular dynamics; FDR, false discovery rate; NF-κB, nuclear factor-κ B; AP-1, activator protein 1; PG, prostaglandins; TX, thromboxanes; LOX, lipooxygenases; COX-2, cyclooxygenase-2; EGFR, epidermal growth factor receptor.

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☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
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☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Self-reports on consumed diet, quality of life, and clinical symptoms were recorded in REDCap electronic data capture tool.
Data analysis	Data was analyzed using R version 4.3. Nearly all analyses were pre-specified and any post-hoc analysis is clearly labeled. Continuous data was analyzed using 2-sided tests.Categorical data were analyzed using a chi-square test or Fisher's exact test, as appropriate. All tests were two-sided (α=0.05). When appropriate, P values were adjusted for multiplicity using the two-stage Benjamini-Krieger-Yekutieli (BKY) procedure.

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- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

We have deposited metabolomics raw data on Figshare. In order to best secure patient data, clinical data can be shared upon reasonable request to the corresponding author.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Data on sex are reported in aggregate. Data was self-reported. It was tracked as a baseline demographic characteristic in both the FMD group and control group. Baseline characteristics are reported in aggregate and by sex. The results are applicable to both sexes.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were self-reported for all participants in the trial. Both are reported in aggregate by group.
Population characteristics	Age, sex, ethnicity, BMI, alcohol use, smoking status, Crohn's disease phenotype, Crohn's disease activity index, medications, and inflammatory markers were recorded for all participants
Recruitment	Participants were recruited nationally, via referral from treating physician, or via self-referral. All participants provided informed consent prior to enrollment. Please see manuscript for more details on recruiting.
Ethics oversight	The Institutional Review Board (IRB) at Stanford University approved our study protocol (IRB-53161) in 2019.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size was determined through power calculation. The final sample size was 97 patients. Please see the study protocol for greater detail
Data exclusions	Analyses were done by intention-to-treat. The manuscript includes a CONSORT flow diagram detailing how data were handled
Replication	The study was randomized, and blinding was done where possible (such as blinding the endoscopist). Given the trial involved comparing a calorie-restricted diet to continuation of baseline, it was not possible to blind the participants.
Randomization	We performed block randomization, 2:1 into the FMD and control groups.
Blinding	Blinding was done where possible (such as blinding the endoscopist). Given the trial involved comparing a calorie-restricted diet to continuation of baseline, it was not possible to blind the patients.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov registration: NCT04147585.
Study protocol	Full study protocol is submitted along with the original submission.
Data collection	First patient was recruited in early 2020, and terminated in 2024.. Please see manuscript for details
Outcomes	All outcomes and analyses are pre-specifed unless otherwise specified. Please see manuscript for details.

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a