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CLINICAL TRIAL

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Effect of prebiotics on gastrointestinal symptoms and quality of life in children with intestinal failure: A pilot study

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Abstract

Objectives: Children with intestinal failure (IF) have a substantial disease burden, with significant gastrointestinal (GI) symptoms, abnormal stool patterns and reduced health-related quality of life (HRQOL). This study examined the effects of prebiotic supplementation on GI symptoms and HRQOL.

Methods: An open-label, randomised controlled trial involving two phases. In Phase 1, children aged 1–18 years with IF received supplementation with a blend of prebiotics for 4 weeks. In Phase 2, participants were randomised to either continue supplementation or cease supplementation for 6 months to evaluate long-term effects. Primary end points included parent-reported GI symptoms and HRQOL, measured by PedsQL™ scales. Secondary end points were stool consistency and frequency, nutritional support and antibiotic use.

Results: Out of 47 children completing Phase 1, 43 completed Phase 2 (24 in the intervention group, 19 in the control group). After 4 weeks, 60% reported reduced GI symptoms. By the end of Phase 2, the intervention group showed no significant changes in HRQOL score, but significant GI symptom improvements compared to controls (mean paediatric quality of life inventory GI score difference of 6.9, $p = 0.01$). Stool frequency decreased (median −1.0 vs. 0 stools/day, $p = 0.003$), and stool consistency normalised more frequently in the intervention group (42% vs. 6%, $p = 0.02$). No significant changes were noted in nutritional support or antibiotic use.

Conclusion: While HRQOL remained unchanged, short- and long-term prebiotic supplementation significantly improved GI symptoms, stool frequency and stool consistency in children with IF, indicating its potential as a therapeutic option in paediatric IF.

Trial Registration: ClinicalTrials.gov ID: NCT04981262 https://clinicaltrials.gov/study/NCT04981262?cond=intestinal%20failure&term=prebiotics&rank=2.

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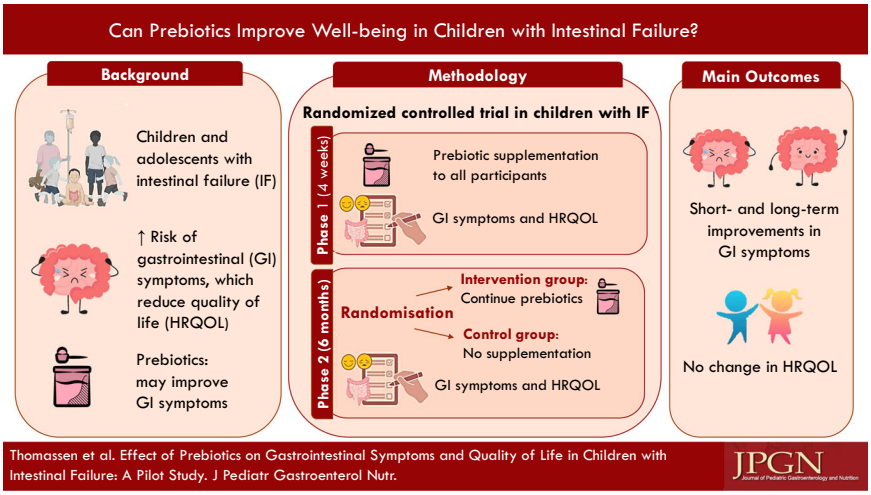

KEYWORDS
enteral nutrition, health-related quality of life, parenteral nutrition

1 | INTRODUCTION

Paediatric intestinal failure (IF) is a condition where the functional intestinal mass is insufficient to absorb enough nutrients to support growth and well-being, requiring extensive nutritional support.[1,2] IF can result from congenital conditions that necessitate substantial bowel resection, such as short bowel syndrome (SBS) or from impairments in bowel motility or epithelial absorption.[1] Patients experience altered gastrointestinal (GI) functioning, GI symptoms and reduced health-related quality of life (HRQOL).[3,4] Challenges include malabsorption and poor tolerance to enteral nutrition, necessitating long-term parenteral nutrition (PN), crucial for survival but depriving the gut of essential nutrients and substrates for the gut flora.[5] The result is enteropathy, poor epithelial barrier function and altered gut microbiota.[6,7]

Studies have shown reduced bacterial diversity and proteobacteria overabundance in children with IF.[8,9] This pro-inflammatory dominance may increase inflammation and reduce gut integrity. PN duration, enteral nutrition tolerance and dietary fibre intake affect microbiota composition.[9] Dysbiosis and bacterial overgrowth may cause symptoms like abdominal pain, nausea, diarrhoea and constipation, further hindering enteral nutrition and prolonging PN dependence.[10,11] Treatment typically involves antibiotics, though they fail to provide long-term relief, necessitating repeated courses and increasing resistance risk.[12,13] Prebiotics, non-digestible components in food, can beneficially impact gut microbes and potentially reduce GI symptoms and complications.[14,15] Positive outcomes on GI symptoms and HRQOL have been observed in patients with various GI complaints using prebiotics.[16–18]

In this study, we explore whether supplementing children with IF with a prebiotic blend can alleviate GI symptoms and, consequently, enhance HRQOL.

What is Known

- Children with intestinal failure (IF) have prolonged dependence on parenteral nutrition, which contributes to an altered gut microbiota.
- Microbiota alterations can affect gastrointestinal (GI) functioning in IF patients and, through this, reduce health-related quality of life (HRQOL).
- Prebiotics, natural substances in food, can modify the gut flora composition and improve GI symptoms.
- The potential benefits of prebiotic supplementation are unexplored in children with IF.

What is New

- Prebiotics reduced GI symptoms in children with IF but did not affect HRQOL.
- Prebiotics may be a viable treatment option for children with this condition.

2 | METHODS

2.1 | Ethics statement

The study was approved by the Regional Committees for Medical and Health Research Ethics, Norway (#170851) and data protection authorities and registered in the Clinical Trials registry (ClinicalTrials.gov ID: NCT04981262), June 2021. Informed consent was

obtained from parents and participants aged 16 and older.

2.2 | Trial design

The trial examined the effects of prebiotic supplementation in children with IF. The study was an open-label randomised controlled trial with a two-phase sequential design: a single-group treatment phase (Phase 1) to assess short-term effects, followed by randomisation to evaluate long-term outcomes (Phase 2). Phase 1 (SDC Figure 1) was a 4-week open intervention with prebiotics. In Phase 2, participants were randomised to either continued intervention or no intervention for 6 months. Conducted from September 2021 to December 2023, the study took place at Oslo University Hospital and the University of Oslo, Norway.

2.3 | Study participants

Children aged 1–18 years with IF were enroled from five paediatric centres in Norway. IF was diagnosed according to the ASPEN 2022 criteria[1]; congenital malformations or diseases requiring intestinal surgery leading to SBS; severe dysmotility, like pseudo-obstruction; or severe enteropathy, necessitating PN. Furthermore, a history of at least 60 days of treatment with PN within a 74-day period was required. Exclusion criteria included short-term PN use due to temporary illness (e.g., infections), temporary gut malfunction due to advanced medical treatments like cancer therapy, and inability to tolerate enteral nutrition.

2.4 | Intervention

All participants received a 4-week course of prebiotic supplementation using a commercial fibre product (Stimulance©, Nutricia Norge) containing a blend of prebiotics: soy polysaccharide, cellulose, resistant starch, gum arabic, fructooligosaccharide, and inulin. The daily dosage was based on previous studies on prebiotics in children,[19,20] and adjusted by weight; 6 g for those weighing <15 kg, 10 g for 15–24 kg and 12 g for ≥25 kg. The prescribed dose was divided into two daily doses. Each participant was provided a neutral box containing the product, a measuring spoon, and written instructions for a gradual introduction to the target amount.

2.5 | Randomisation

Participants were allocated 1:1 to the intervention or control group, stratified by PN status (PN or not at randomisation date). The list was created using STATA 17 (StataCorp LP) with random block sizes of 2-10. Concealed envelopes were prepared by a researcher with no clinical involvement in the trial and opened by the clinical researchers upon completion of the 4-week follow-up assessments. A placebo product, like dextrose, was not provided due to potential side effects like D-lactic acidosis.

2.6 | Study visits

The trial included three study visits: at baseline, after 4 weeks and after 7 months (6 months after randomisation).

2.7 | Assessments

Primary end points:

- *GI symptoms*: GI symptoms were collected using electronic versions of PedsQl™ 3.0 GI Symptom Scale parent reports.[21] Scores were transformed from a 5-point Likert scale to a 0–100 scale, where higher scores indicated fewer symptoms. The proportion of participants scoring beyond a minimal important difference value, the smallest change perceived as important by patients or parents, was calculated. Values were derived from Varni et al.'s study on children with GI disorders.[22]
- *HRQOL*: HRQOL was assessed using electronic versions of PedsQl™ 4.0 Generic Model parent report[23] and the Infant scale for children under 2 years, and transformed as above.

Secondary end points:

- *Stool pattern*: At each study visit and subsequent 24-h recalls, stool frequency was recorded as the number of stools per day, while stool consistency was assessed using the Bristol Stool Scale (BSS),[24] with scores <3 indicating constipation, 3–4 normal stools, 5 loose stools and 6–7 diarrhoea. Stoma output was recorded for patients with a stoma.
- *Clinical data*: medical information, including use of antibiotics, was obtained from electronic patient records.
- *Nutritional information*: Two 24-h dietary recalls were conducted around the three study visits by a registered dietitian, including details on parenteral and enteral nutrition support.

2.8 | Adherence

Participants and carers reported the amount of product used daily and the method of administration at each study visit. After study completion, all participants could choose to continue supplementation, irrespective of the allocated group.

2.9 | Adverse events

Adverse events were documented by the principal investigator and dosage was reduced or discontinued if needed.

2.10 | Power calculation

The sample size calculation was based on unpublished data comparing HRQOL scores of children with IF with or without daily abdominal pain (mean score 67 vs. 84). Using a paired *t* test, with a standard deviation of 20 points, 80% power, and a significance level of 0.05, 22 participants per group were required.

2.11 | Statistical analysis

We analysed the data using IBM SPSS for Windows, version 29 and STATA 18.0. Categorical values and proportions were compared using Chi-square or Fisher's test, with the effect sizes reported as Cramer's *V* ($V = 0.1$–0.2 small effect, $V = 0.3$–0.4 medium effect, $V \geq 0.5$ large effect). For normally distributed continuous variables, we used independent sample *t*-tests to compare mean scores between groups. Changes in GI symptoms and HRQOL after Phase 1 were assessed using paired sample *t* tests. Effect sizes were reported as Cohen's *d* ($d = 0.1$–0.4, small effect; $d = 0.5$–0.7, medium effect; ≥0.8, large effect). For non-normally distributed data, we compared median values using the Mann–Whitney *U* test, differences between groups and the Wilcoxon test to test changes over time in Phase 1. Effect sizes were reported as *r* (0.1–0.2 = small, 0.3–0.4 = medium, ≥0.5 = large effect). To test between-group differences and the effectiveness of the intervention after Phase 2, we used a one-way analysis of covariance (ANCOVA), adjusted for baseline and effect size reported as partial squared eta (η^2) ($\eta^2 = 0.01$–0.05, small effect; $\eta^2 = 0.06$–0.13, medium effect; $\eta^2 \geq 0.14$, large effect). All assumptions for ANCOVA were met. Missing data were excluded pairwise, and the significance level was set to 0.05.

3 | RESULTS

Eighty patients were assessed for eligibility, with 55 included in Phase 1 and 47 randomised in Phase 2 of the study (Figure 1; CONSORT diagram).

Seven participants discontinued the intervention in Phase 1; three due to the palatability of the product, two had severe constipation needing treatment, partly due to reduced fluid intake and two experienced increased abdominal pain. One withdrew without explanation. Three participants reduced the dose by half; two due to constipation tendencies and one because of abdominal pain. Only three reported brief intervals of not taking the supplement, lasting 1–4 days.

Patient characteristics are detailed in Table 1. The mean age was 7.5 years, and there were more boys (73%) than girls. The intervention and control groups were generally comparable, except for a higher prevalence of SBS in the intervention group (88%) compared to the control group (50%) ($X^2 = 9.1$, $p = 0.01$) and a younger age at resection (median 0 days vs. 28 days, $p = 0.04$). Baseline median stool frequency was also higher in the intervention group (3.5 vs. 2.0, $p = 0.04$).

3.1 | Results at 4 weeks (end of Phase 1)

After 4 weeks of supplementation, there was a significant improvement in parent-reported scores for abdominal pain (difference = 8.1, $p = 0.01$, $d = 0.5$), nausea and vomiting (difference = 6.1, $p = 0.04$, $d = 0.4$) and diarrhoea (difference = 6.7, $p = 0.01$, $d = 0.5$) with small to medium effect sizes. A trend towards higher total GI score was observed (difference = 3.0, $p = 0.054$, $d = 0.4$).

Sixty per cent had a positive response to the intervention (responders) defined by a positive change in total GI score, and in 44% the improvement exceeded the minimal important difference threshold (SDC, Table 1). Responders had a significantly lower baseline GI score (i.e., more GI symptoms) than non-responders, with a large effect size (mean 68.8 vs. 79.7, $p = 0.02$, $d = 0.9$) (Figure 2A,B). Mean HRQOL scores showed no significant change (mean difference = −1.4, $p = 0.43$, $d = 0.1$).

Stool consistency (BSS) changed during Phase 1; constipation decreased from 13% to 0%, normal stools increased from 24% to 47%, loose stools rose from 16% to 29% and diarrhoea decreased from 47% to 24% (SDC, Figure 2). The overall change in stool consistency was not significant ($Z = -1.6$, $p = 0.11$, $r = 0.3$). Median daily stool frequency decreased from 2.8 to 2.0 stools ($Z = -3.2$, $p = 0.002$, $r = 0.5$) (SDC, Figure 2), and median stoma losses reduced from 900 to 750 mL per day ($Z = -1.7$, $p = 0.07$, $r = 0.6$).

3.2 | Results of the randomised trial at 7 months (end of Phase 2)

After 7 months (1 + 6 months) of prebiotic supplementation, 70% of the intervention group had a positive change in total GI scores from baseline (i.e., fewer symptoms), compared to 35% in the control group (SDC, Table 2). In terms of minimal important

difference, 65% of the parents in the intervention group reported symptom improvement compared to 14% in the control group. The difference was significant, with a large effect size ($X^2 = 9.0$, $p = 0.01$, $V = 0.5$).

A significant positive treatment effect on parent-reported GI symptoms was observed in the intervention group, with a large effect size (6.9 point difference, $p = 0.01$, $\eta^2 = 0.17$) (Table 2). While improvements were observed across all GI symptom scale dimensions, only 'discomfort when eating and drinking' reached statistical significance. There were no differences in improvements across different symptom dimensions, though gas and abdominal pain were the most frequently reported to both improve and worsen. Total GI symptoms had exacerbated in 17% of the intervention group compared to 43% in the control group at Phase 2 follow-up, and constipation worsened in 10% of the intervention group versus 31% of the control group during this period.

There were no differences in parent-reported HRQOL between the two groups at 7 months (Table 2), and changes in scores of the different dimensions of HRQOL were overall small in both groups.

Stool consistency normalised in 43% of the intervention group versus 6% of the control group ($p = 0.02$) (SDC, Figure 2). The intervention group's median BSS went from 6 (diarrhoea) to 4 (normal stools) while the control group remained at a median BSS of 5. The intervention group also showed a significant reduction in median daily stool frequency (−1.0 stool per day vs. 0.0, $Z = 3.0$, $p = 0.003$, $r = 0.5$) compared to the control group (SDC, Figure 2). Reduction in median stoma losses was not statistically different between the two groups (225 mL vs. 0 mL, $Z = -1.2$, $p = 0.25$, $r = 0.5$).

At baseline, nine children (38%) in the intervention group and four (22%) in the control group used intermittent antibiotics for bacterial overgrowth. At the end of the study, four (16%) patients in the intervention

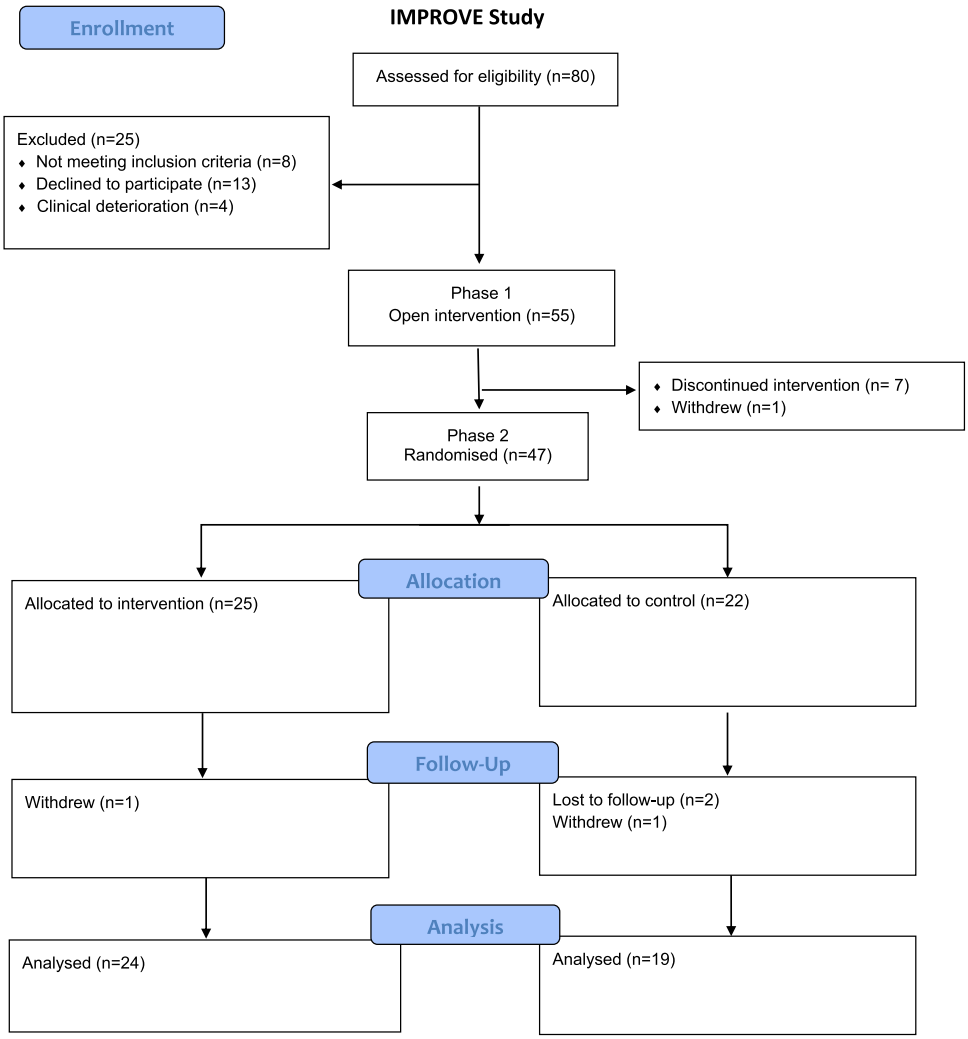

FIGURE 1 Consort flow diagram.

TABLE 1 Baseline characteristics of patients.

	Phase 1 (*n* = 55)	Phase 2 (*n* = 47)	Intervention (*n* = 25)	Control (*n* = 22)
Age, years, mean (SD)	7.5 (5.0)	7.8 (4.9)	8.2 (4.9)	7.3 (4.9)
Sex, male, *n* (%)	40 (73)	34 (72)	19 (76)	15 (68)
IF diagnosed in infancy, *n* (%)	41 (75)	37 (79)	22 (88)	15 (68)
Prematurity, *n* (%)	28 (51)	24 (51)	13 (52)	11 (50)
Moderate/late (GA 32–37)	14 (26)	12 (26)	8 (32)	4 (18)
Very preterm (GA 28–32)	1 (2)	1 (2)	0	1 (5)
Extreme preterm (GA < 28)	13 (24)	11 (23)	5 (20)	6 (27)
Aetiology, *n* (%)*				
Surgical (SBS)	37 (67)	33 (70)	22 (88)	11 (50)
Motility disorder	13 (24)	10 (21)	3 (12)	7 (32)
Other	5 (9)	4 (9)	0	4 (18)
Comorbidities, *n* (%)				
None	30 (55)	27 (57)	16 (64)	11 (50)
1–2	14 (25)	13 (28)	7 (28)	6 (27)
3 or more	11 (20)	7 (15)	2 (8)	5 (23)
Underlying diagnosis for surgery, *n* (%)				
NEC	11 (30)	9 (27)	5 (23)	4 (37)
Midgut volvulus	7 (19)	7 (21)	6 (27)	1 (9)
Hirschsprung	5 (14)	4 (12)	2 (9)	2 (18)
Intestinal atresia	6 (16)	6 (18)	5 (23)	1 (9)
Abdominal wall defects	6 (16)	6 (18)	4 (18)	2 (18)
Other surgical	2 (5)	1 (3)	0	1 (9)
Type of/surgical details of SBS, *n* (%)				
Type 1	6 (16)	5 (15)	3 (14)	2 (18)
Type 2	12 (32)	10 (30)	7 (32)	3 (27)
Type 3	19 (51)	18 (55)	12 (54)	6 (55)
Age at resection, days, median (range)*	5 (1460)	5 (1460)	0 (881)	28 (1460)
% remaining small intestine,[a] median (range)	25 (80)	25 (79)	24 (79)	28 (60)
Gut lengthening procedure	6 (16)	6 (18)	6 (27)	0
GLP 2, *n* (%)	10 (28)	10 (30)	6 (27)	4 (36)
Antibiotics, *n* (%)	19 (35)	17 (36)	10 (40)	7 (32)
For bacterial overgrowth	16 (29)	15 (32)	10 (40)	5 (23)
Enterostomy, *n* (%)	10 (18)	7 (15)	4 (16)	3 (13)
Stoma output, mL, median (range)	775 (1900)	900 (1650)	1075 (1650)	900 (400)
Stool frequency, median (range)*,[g]	2.5 (9.0)	2.5 (9.0)	3.5 (9.0)	2.0 (9.0)

TABLE 1 (Continued)

	Phase 1 ($n = 55$)	Phase 2 ($n = 47$)	Intervention ($n = 25$)	Control ($n = 22$)
Bristol Stool Scale, (%)[g]				
1–2	7 (16)	5 (13)	2 (10)	3 (16)
3–4	10 (23)	10 (25)	6 (29)	4 (21)
5	7 (16)	7 (18)	1 (5)	6 (32)
6–7	20 (46)	18 (45)	12 (57)	6 (32)
Baseline GI scores[b,g]	71.0 (14.6)	71.4 (14.5)	70.6 (13.6)	72.5 (16.4)
Baseline HRQOL scores[b,g]	70.6 (17.6)	72.6 (15.6)	74.6 (15.4)	69.9 (15.8)
Nutrition, *n* (%)				
Feeding tube	27 (49)	22 (47)	12 (48)	10 (46)
Eating and drinking	49 (89)	43 (92)	24 (96)	19 (86)
EN	23 (42)	20 (43)	11 (44)	9 (41)
PN	29 (53)	23 (49)	12 (48)	11 (50)
Infusions per week (median)	7	7	7	6
PN dependence,[c] mean (SD)	63 (35)	60 (37)	59 (34)	61 (41)
Time dependent on PN, years, median (range)	1.9 (17.7)	2.0 (17.7)	1.9 (14.1)	2.3 (17.7)
Growth				
Weight SDS, mean (SD)	−1.10 (1.11)	−1.06 (1.17)	−0.81 (1.11)	−1.34 (1.19)
Height SDS, mean (SD)	−1.08 (1.55)	−1.05 (1.62)	−0.77 (1.53)	−1.36 (1.69)
BMI SDS, mean (SD)	−0.51 (0.93)	−0.47 (0.85)	−0.38 (0.71)	−0.57 (1.00)
Underweight,[d] *n* (%)	10 (18)	8 (17)	3 (12)	5 (23)
Stunting,[e] *n* (%)	14 (26)	12 (26)	4 (16)	8 (36)
Undernutrition,[f] *n* (%)	3 (6)	2 (4)	1 (4)	1 (5)

Abbreviations: EN, enteral nutrition; GA, gestational age; GI, gastrointestinal; GLP2, glucagon-like peptide-2; HRQOL, health-related quality of life; IF, intestinal failure; NEC, necrotising enterocolitis; PN, parenteral nutrition; SBS, short bowel syndrome, SBS type 1, end-jejunostomy, SBS type 2, jejunocolic anastomosis, SBS type 3, jejunoileal anastomosis; SDS, standard deviation score.

[a]Based on values from Strujis et al.

[b]Parent reported.

[c]Proportion (%) of estimated energy requirement covered by PN.

[d]Weight ≤ 2 SD.

[e]Height ≤ 2 SD.

[f]BMI ≤ 2 SD.

[g]Stool frequency and BSS $n = 40$, HRQOL score $n = 44$, GI score $n = 42$.

*$p \leq 0.05$ between intervention and control.

group had discontinued the antibiotics, while none in the control group had. The difference was not statistically significant ($p = 0.19$).

Two patients in the intervention group and one in the control group reduced weekly PN infusions, but the median number of infusions per week remained unchanged in both groups ($Z = 0.4$, $p = 0.69$, $r = 0.1$). One patient in each group stopped PN during the study. Mean PN dependence decreased by 14.6% in the intervention group and 15.3% in the control group (difference = 0.7%, $p = 0.97$, $d = 0.02$). At the study conclusion, 79% of the intervention group and 38% of the control group chose to continue with the prebiotic supplement.

In patients with SBS, 60% of the intervention group showed improvement in parent-reported GI symptoms (adjusted for minimal important difference) compared to none in the control group ($X^2 = 6.38$, $p = 0.04$, $V = 0.5$). The intervention group more frequently experienced a reduction in daily

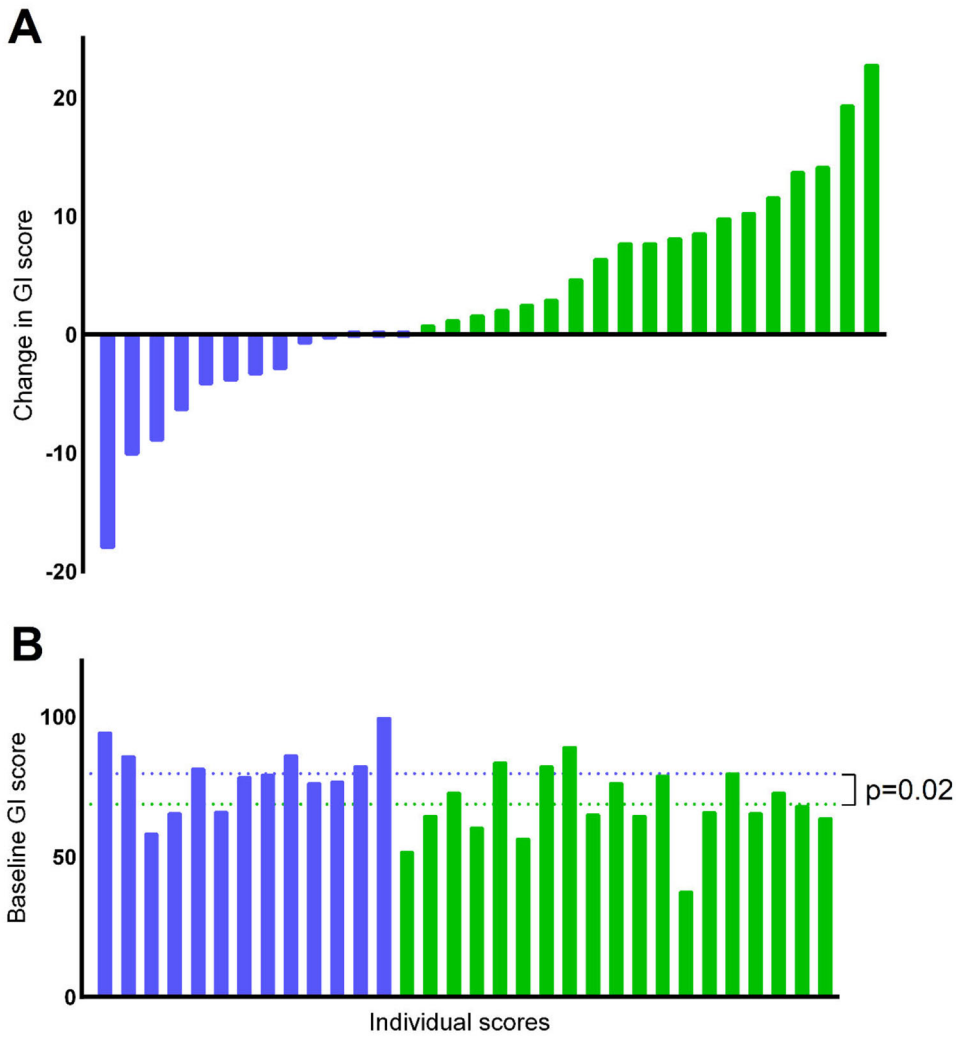

FIGURE 2 (A) Change in parent-reported GI score after Phase 1 short-term prebiotic intervention and baseline values in responders and non-responders. A display of the change in individual parent-reported GI scores ($n = 32$) after 4 weeks of prebiotic supplementation, with responders represented by green bars and non-responders by blue bars. (B) shows the individual parent-reported GI scores at baseline for both groups. The dotted lines indicate the mean scores at baseline for both groups, with the blue line representing non-responders and the green line representing responders. GI, gastrointestinal.

bowel movements (79% vs. 17%, $p = 0.01$) and a greater tendency for stool consistency to normalise (48% vs. 0%, $p = 0.06$). SBS-type sub-analysis showed no significant differences (results not shown).

4 | DISCUSSION

This trial investigated the effect of supplementation with a blend of prebiotics in children with IF and found a significant improvement in parent-reported GI symptoms, stool consistency and frequency, but not in HRQOL. Children with a higher baseline burden of GI symptoms were more responsive, suggesting a potential clinical indicator for treatment candidacy. However, further research is required to establish potential cut-off scores.

This is the first randomised controlled trial to examine the impact of prebiotic intervention on GI symptoms and HRQOL in children with IF. Therefore, explicit comparisons to other trials are not possible. Parents reported a significant reduction in GI symptoms in both the short term and long term, with 60% of the children showing improvement after 4 weeks of treatment, particularly in those with an initial high burden of symptoms (i.e., low baseline GI scores). After 7 months, the intervention group showed sustained positive effects of prebiotics on GI symptoms, suggesting their potential as a therapeutic option for children with IF. In contrast, the control group had a higher frequency of worsening GI symptoms. Although

TABLE 2 Treatment effects of prebiotic supplement on GI symptom scale and HRQOL after Phase 2.[a]

Mean change from baseline			Treatment effect[b]			Effect size
Variable	**Control**	**Intervention**		**(95% CI)**	***p***	
Treatment effect on GI symptoms at 7 months						
PedsQL GI symptom scale 3.0, parent scores	$n = 14$	$n = 23$				
Total score	−2.0	4.9	**6.9**	(1.6–12.2)	***0.01***	0.17
Abdominal pain	2.5	11.0	**8.5**	(−3.1 to 20.2)	0.15	0.06
Discomfort when eating/drinking	−5.1	8.1	***13.3***	(−1.5 to 25.0)	***0.03***	0.13
Eating and drinking limits	−0.4	9.9	**10.3**	(−1.9 to 22.4)	0.09	0.08
Swallow difficulties	−1.5	3.1	**4.6**	(−2.8 to 12.0)	0.22	0.04
Heartburn/reflux	0.0	3.8	**3.8**	(−2.6 to 10.1)	0.24	0.04
Nausea/vomiting	−0.9	3.8	**4.7**	(−5.6 to 15.1)	0.36	0.03
Gas/bloating	−0.9	2.4	**3.3**	(−10.8 to 17.4)	0.64	0.01
Constipation	−4.8	3.4	**8.1**	(−1.1 to 17.3)	0.08	0.08
Bloody stools	0.0	0.3	**0.9**	(−4.6 to 6.3)	0.78	0.00
Diarrhoea	−2.6	3.8	**6.5**	(−3.3 to 16.3)	0.19	0.05
Treatment effect on HRQOL at 7 months						
PedsQL 4.0, parent scores	$n = 16$	$n = 24$				
Total score	0.8	0.7	**−0.1**	(−7.2 to 7.1)	0.98	0.00
Psychosocial	0.6	0.5	**−0.2**	(−7.6 to 7.3)	0.97	0.00
Physical	0.2	1.1	**0.9**	(−9.8 to 11.6)	0.86	0.00
Emotional	−1.4	−0.6	**0.8**	(−8.7 to 10.3)	0.87	0.00
Social	−0.4	−0.1	**0.2**	(−8.8 to 9.3)	0.96	0.00
School	7.6	0.8	**−6.8**	(−17.9 to 4.4)	0.23	0.04

Note: Treatment effects are denoted in bold, significant effects and p values are presented in bold and italic.

Abbreviations: GI, gastrointestinal; HRQOL, health-related quality of life; PedsQL, paediatric quality of life inventory.

[a]Values are mean changes from baseline adjusted for the baseline value of the outcome variable using a one-way analysis of covariance model.

[b]Treatment effect refers to the difference in adjusted mean change between the control and intervention groups.

constipation was a key reason for drop-out and dose reduction, it was not found to be the main cause of GI symptom exacerbation in the intervention group. The specific symptoms contributing to the changes in GI complaints remain unclear.

IF is a heterogeneous condition with varying aetiologies that influence symptoms, treatment options, prospects of enteral tolerance and prognosis. Our study reflects this variability. Changes in GI symptom scores varied greatly among patients. In some patients, symptoms of gas and bloating or constipation worsened, while others reported major improvements in the same symptoms. This underscores the need for personalised assessments to determine who might benefit most from prebiotic supplementation. Children with SBS in the intervention group exhibited substantial improvement compared to those with SBS in the control group, which could suggest a condition-specific response to treatment. However, the study was not designed to draw firm conclusions about response differences among IF aetiologies.

Prebiotics appear to be safer and potentially more effective for improving gut function compared to probiotic interventions, which have shown limited efficacy and raised safety concerns in SBS.[11,25] This aligns with studies in other populations, such as autistic children and adults with chronic constipation, where prebiotics reduced GI symptoms and improved HRQOL.[17,18]

The trial also found significant improvements in stool consistency towards normal levels, despite baseline differences between groups. The intervention group had a reduction in stool frequency, indicating positive GI regulation rather than increased constipation, as there was a low occurrence of constipation aggravation in this group.

However, we found no effect on HRQOL. We have previously shown an association between GI symptoms and HRQOL in children with IF.[26] The observed

changes in GI symptoms in our study might not have been significant enough to impact HRQOL. Additionally, improvements in HRQOL could be slow, and the follow-up period might have been too brief to detect differences. Parent-reported HRQOL scores may also be influenced by various factors beyond GI symptoms, such as parent-child dynamics and individual parent factors, such as stress and mental health.[27]

Child self-reports are widely accepted as the gold standard for assessing quality of life in paediatric populations, and we aimed to collect such data in this trial. Despite our efforts, the number of participants providing self-reports was low, with only 10 in the intervention group and 6 in the control group completing the forms. Children in the IF population are particularly at risk for delayed psychomotor and cognitive development,[28] which may have contributed to the low response rate, as cognitive ability often has a greater impact than chronological age.[29] Furthermore, one third of the study population was below the age of 5, the youngest age for which the PedsQL™ self-report form is designed. Given these limitations, we decided to rely exclusively on parent-proxy reports to ensure comprehensive data collection across the participant group.

Different prebiotics are degraded by various species of gut bacteria, thereby promoting the growth of different bacterial phyla.[15] Consequently, using a diverse blend of prebiotics may be preferred when studying their effects on gut health and overall well-being. Our study used a combination of different prebiotics known to affect the microbiota. However, the supplement contained insoluble fibres that have other properties, such as bulking and stool softening, in addition to prebiotic effects. This may contribute to changes observed in stool consistency and frequency. In addition, optimal dosage remains undetermined, warranting further investigation into effective yet non-disruptive supplementation.

A trial strength includes testing prebiotics on all available subjects to improve power in the Phase 1 4-week trial and the randomised, stratified design of the Phase 2 follow-up study. Stratifying on PN dependency was done to minimise bias in relation to tolerance to enteral nutrition, which affects the gut microbiota. However, the higher representation of SBS children in the intervention group, by chance, limits generalisability to other aetiologies of IF. Moreover, a higher drop-out rate in the control group decreased study power. Future research should ensure aetiological stratification beyond PN dependence and consider excluding patients with low GI burden to prevent dilution of effects. Furthermore, some secondary end points of the trial suffered from low power. For example, assessing the effect on antibiotic dependency would require a sample size of 77 children per group to detect a statistically significant difference.

The study primarily uses subjective by-proxy reported outcomes. Although we aimed to validate these with quantifiable measures like stool frequency and consistency, and data on PN dependency, the absence of more standardised measures and a placebo arm constitutes limitations that may introduce bias in interpreting the effectiveness of the intervention.

5 | CONCLUSION

This trial demonstrated that prebiotic supplementation in children with IF improves GI symptoms, stool consistency and stool frequency, in both the short term and long term, indicating potential as a therapeutic option in paediatric IF patients with persistent gastrointestinal symptoms. Effects on HRQOL were, however, not observed. Future large-scale, stratified studies are essential to confirm these findings and optimise prebiotic treatment strategies.

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CONFLICT OF INTEREST STATEMENT

Rut Anne Thomassen and Dr. Anne Charlotte Brun have participated as consultants and speakers for Takeda. The remaining authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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