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ORIGINAL ARTICLE

A novel Monash Pouch diet in patients with an ileoanal pouch is tolerable and has favorable metabolic luminal effects

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Abstract

Aims: To evaluate a whole-food diet strategy (the Monash Pouch diet [MPD]) designed based on the interacting roles dietary factors play with pouch health. Specifically, its tolerability and acceptability, whether it achieved its dietary and metabolic goals, and the effects on symptoms and inflammation were examined.

Methods: In a 6-week open-label trial, patients with ileoanal pouches educated on the MPD were assessed regarding diet tolerability and acceptance, food intake (7-day food diaries), pouch-related symptoms (clinical pouchitis disease activity index), and, in 24-h fecal samples, calprotectin, fermentative biomarkers, and volatile organic compounds (VOC).

Results: Of 12 patients, 6 male, mean (SD) age 55 (5) and pouch age 13 (2) years, one withdrew with partial small bowel obstruction. Tolerability was excellent in 9 (75%) and acceptance was high (81%). Targeted changes in dietary intake were achieved. Fecal branched- to short-chain fatty acid ratio increased by median 60 [IQR: 11–80]% ($P = 0.02$). Fecal VOCs for 3 compounds were also increased, 2-methyl-5-propan-2-ylcyclohexa-1,3-diene (Fold-change [FC] 2.08), 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane (FC 3.86), propan-2-ol (FC 2.10). All six symptomatic patients achieved symptomatic remission ($P = 0.03$). Fecal calprotectin at baseline was 292 [176–527] μg/g and at week 5 was 205 [148–310] μg/g ($P = 0.72$).

Conclusion: Well tolerated and accepted, the MPD achieved targeted changes in intakes and fermentation of carbohydrates relative to that of protein. There were signals of improvement in symptoms. These results indicate the need for a randomized-controlled trial. (Trial registration: ACTRN12621000374864; https://www.anzctr.org.au/ACTRN12621000374864.aspx).

financially benefits from the sales of a digital application and booklets on the low FODMAP diet. Funds raised contribute to research of the Department of Gastroenterology and to the University. No author receives personal remuneration.

Author contribution: Zaid S Ardalan, Chu K Yao, Peter R Gibson and Miles P Sparrow conceived the concepts and designed the study. Zaid S Ardalan recruited participants, collected and analyzed data for the study and wrote the manuscript. Chu K Yao designed and administered the diet, was involved in data collection and analysis, and wrote the manuscript. Kraig Green and Chris Probert performed analysis of volatile organic compounds, interpreted the data and contributed to manuscript writing. Paul A Gill conducted analysis of fecal short-chain fatty acids. Sam Rosella helped analyze fecal samples for calprotectin. Jane G Muir was involved in the design of the diet and critically revised the manuscript for important intellectual content. Miles P Sparrow designed the study, critically revised the manuscript for important intellectual content. Peter R Gibson designed the study, critically revised the manuscript for important intellectual content. All authors approved of the final manuscript.

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Introduction

Patients with ulcerative colitis, who undergo restorative proctocolectomy with ileal pouch–anal anastomosis, generally report a good quality of life. However, a proportion experience pouch-related symptoms secondary to pouchitis or non-inflammatory complications, such as irritable pouch syndrome.[1,2]

The pathogenesis of pouchitis results from the interaction of an abnormal pouch mucosal immune system with the microbiota,[3] both of which may potentially be influenced by diet. Dietary factors provide key substrates for bacteria that release putatively pathogenic metabolites such as increased hydrogen sulfide (H_2S),[4] and decreased short-chain fatty acids (SCFA), such as butyrate,[5] functional alterations that likely characterizes the pouch microbiota.[3] Supplementation of fermentable fibers such as oligosaccharides and resistant starch is associated with increased abundances of *Lactobacillus* and *Bifidobacterium* spp. and greater SCFA production.[6,7] However, due to the shorter stasis of luminal pouch contents,[8] oligosaccharides, being rapidly fermentable, are ideal candidates to increase fermentation in the pouch.[9] Increased carbohydrate fermentation also suppresses protein fermentation and, therefore, H_2S production by shifting bacterial use of protein substrates for biosynthetic purposes.[10] This has previously been demonstrated in an *ex vivo* study where fructo-oligosaccharides (FOS) markedly lowered fecal H_2S production by >80%.[11] Additionally, dietary factors, such as osmotically active, slowly absorbed, and rapidly fermentable carbohydrates (e.g., fermentable oligo-, di- and monosaccharides and polyols [FODMAPs]), via their effect on upper gastrointestinal transit, small bowel water content, and fermentation by pouch microbiota, exert effects on the frequency of pouch emptying and fecal characteristics independent of their potential impact on pouchitis pathogenesis.[3]

Despite this, clinical guidelines incorporating dietary recommendations for patients with symptomatic ileoanal pouches or pouchitis are currently non existent. Few studies have explored the utility of whole-diet approaches with equivocal outcomes. One dietary approach called the 'Monash Pouch diet' has been designed to hypothetically minimize H_2S production and correct SCFA deficiency via manipulation of pouch fermentation and dissimilatory sulfate reduction pathways and reduce the free-water content of ileal effluent.[3,12] However, before embarking on more definitive exploration of the clinical efficacy of this diet, three questions need to be addressed. First, are changes to dietary intake tolerated in patients with ileoanal pouches? Secondly, are dietary intake goals achievable? Thirdly, can these dietary changes achieve metabolic goals of increasing fermentation of carbohydrates relative to that of protein?

Hence, the current study aimed primarily to address the tolerability of the Monash Pouch diet (MPD) and to assess how well the diet achieved the dietary and metabolic goals. The study also aimed secondarily to evaluate the effect of the diet on symptoms and markers of inflammation.

Methods

Participants. Patients with an ileoanal pouch with bowel continuity for at least 12 months, aged ≥18 years, and on stable pouch-directed therapies were consecutively recruited from various outpatient inflammatory bowel disease and surgical clinics in Victoria, Australia, between February and April 2020. Patients were excluded if they had coeliac disease, followed a predominantly plant-based diet, were pregnant or breastfeeding, or took fiber supplements with 4 weeks or probiotics within 2 weeks of entering the study. This study was approved by the Alfred Ethics Committee (HREC 58716) and registered with Australian New Zealand Clinical Trials Registry (ACTRN12621000374864). Written informed consent was obtained from all participants prior to study enrolment.

Study protocol. This was a 6-week pilot dietary advice trial. Eligible patients attended a screening visit where basic demographic data were collected, and history of pouchitis reviewed by an investigator to determine pouch phenotype. They subsequently completed a one-week run-in period where 7-day food records for assessment of habitual diet, daily symptoms, and bowel habits were recorded and a 24-h fecal collection made.

In the second visit, baseline pouch-related clinical assessment was performed. Pouch malodor, health-related quality of life (HRQOL), anthropometry, and psychological status were also assessed.[13] Participants then received a 1-h dietary education with the study dietitian (C.K.Y.) and followed the diet for 5 weeks, during which daily symptom and bowel habits were recorded along with weekly tolerability scores. Seven-day food records were also completed at weeks 2 and 5. At the end of week 5, participants completed another 24-h fecal collection and returned for a final study visit where diet acceptability in addition to pouch-related symptoms, HRQOL, anthropometry, and mental health indices was assessed.

Dietary intervention. The dietary education comprised five different principles: (1) increase oligosaccharide intake to a target of 6–8 g/d[14]; (2) reduce total protein to 75–100 g/day; (3) reduce foods rich in sulfur-containing protein including animal or supplemental protein; (4) reduce osmotically active carbohydrates – fructose occurring in excess of glucose and polyols; and (5) minimize intake of preservatives (sulfites, sulfates, nitrites, and nitrates) and carrageenan, a sulphated polysaccharide. Naturally occurring sulfates such as those present in cruciferous vegetables were not restricted. Additionally, to account for the presence of hypolactasia in some individuals, instructions for a lactose-free diet were provided to all participants. A sample meal of the MPD is outlined in Supplementary Table 1.

Subjects were also provided with comprehensive written resources including recipes and a 7-day meal plan to assist with adherence over the 5 weeks. The 7-day meal plan was designed to optimize gastrointestinal tolerance by gradually increasing daily oligosaccharide to the target intake. Weekly telephone calls by the study doctor (Z.S.A.) or study dietitian (C.K.Y.) were done to assess adherence and to provide adjustments to the diet if there were difficulties with adapting to the diet or if troublesome symptoms were occurring. Patients were also provided with contact details of researchers to allow them to obtain troubleshooting advice during the intervention period.

Analytical methods used to quantify dietary intake, and measures of adherence are described in the Supplementary Methods.

Tolerability and acceptability of the diet. The primary endpoint of the study was tolerability of the MPD at week 5, assessed using a 100-mm visual analogue scale (VAS) where 0 is least tolerable and 100 is highly tolerable. Tolerability was considered 'excellent' if the week-5 VAS score was >75 mm, 'moderate' if 50–75 mm, and 'poor' if <50 mm. Changes in tolerability over the 5 weeks were also assessed. Acceptability of the diet was assessed at the end of the study using a validated 'Diet Satisfaction Score' questionnaire.[15] Responses were recorded on a 5-point Likert scale and the sum of each response yielded a total score of 50. Responses to the individual domains were collapsed into three main responses, 'disagree', 'neutral', or 'agree'.

Fecal indices. All fecal samples passed during the 24-h collection period were immediately placed into −20°C portable freezers and subsequently delivered to the laboratory. The study investigator noted the fecal frequency and, for each fecal sample, recorded the weight and rated it according to a validated King's Stool Chart.[16] A higher score indicates more frequent, looser, and heavier stools. Fecal odor was scored by patients on a 100-mm VAS where 0 = "not troublesome" and 100 = "the worst odor". Methodologies to quantify fecal biochemistry are detailed in the Supplementary information.

Clinical assessment. Pouch-related symptoms of emptying frequency and urgency were assessed using the Pouchitis Disease Activity Index (PDAI)[17] clinical subscore. A PDAI ≥3 was used as the cut-off for a symptomatic pouch. Pouch-related symptoms of incomplete emptying were assessed using an obstructed

Table 1 Baseline demographics and pouch phenotype of the 11 patients who completed 5 weeks of the Monash Pouch diet.

Characteristics		
Age (y), mean (SD)		54 (17)
Male, *n* (%)		7 (64)
Age of pouch (y), mean (SD)		12 (6)
Previous history of pouchitis, *n* (%)		9 (82)
Time to first pouchitis (months), median (IQR)		24 (12–42)
Pouch phenotype, *n* (%)	Normal pouch	2 (18)
	Antibiotic-responsive pouchitis	1 (9)
	Antibiotic-dependent pouchitis	7 (64)
	Antibiotic-refractory pouchitis	1 (9)
	Crohn's-like disease of the pouch	0
Current pouchitis, *n* (%)		5 (45)
Ongoing medications for pouchitis, *n* (%)[‡]		8 (56)
Cigarette smoking status, never/ex/current, *n*		9/1/1
NSAID use status,[†] never/previous/intermittent, *n*		4/3/4

[†]Regular or previous describes taking NSAIDs ≥7 days after pouch creation.

[‡]Treatments included probiotics in 2 (18%), tinidazole in 1 (9%), budesonide in 1 (9%), azathioprine in 3 (27%), and vedolizumab in 2 (18%).

defecation syndrome score (ODS-S)[18] questionnaire. An ODS-S ≥9 was used as the cut-off for obstructed defecation.

HRQOL was assessed with the Cleveland Global Quality of Life (CGQOL) questionnaire.[2] Levels of anxiety, depression and stress were assessed using the validated truncated 21-item Depression, Anxiety and Stress Scale (DASS-21).[13]

Statistical analysis. A sample size of 13 (assuming a 30% dropout rate) was chosen for this pilot, open-label study.

All but the VOC data were analyzed using SPSS v27 statistical analysis software (IBM; New York, USA). Summary statistics were computed and differences pre- and post-intervention compared using paired t-tests or Wilcoxon-signed rank test. Nominal variables were compared using the McNemar's test. In the post hoc analysis, Fisher's exact test was used to analyze differences in proportion of patients. Friedman test was used to see if there was a statistically significant change in tolerability VAS over the course of the study. All tests were two-sided and considered significant at $P \leq 0.05$. Correction for multiple comparisons was not performed for this pilot study.

Fecal VOC data were analyzed using MetaboAnalyst (version 5.0). No filtering was applied to the data. Missing values were replaced by Limits of Detection, 1/5 of the minimum positive value of each variable. Results were log-transformed, normalized by median and scaled according to the mean. Principal Component Analysis (PCA) was computed to clustering between baseline and post-dietary intervention. Significantly altered metabolites were defined by median fold-change value ≥2.

Results

Participants. Thirteen ulcerative colitis patients with ileoanal pouches were screened but one withdrew before starting the diet (Supplementary Fig. 1). One patient withdrew in the second week after developing a partial small bowel obstruction. While this participant's data were included in the tolerability assessment, they were not included in the final analysis of the other endpoints. Baseline characteristics and pouch phenotype of patients are provided in Table 1.

Table 2 Changes in dietary intake of participants with the Monash Pouch diet intervention.

Nutrients		Baseline	Week 5	Percent change at week 5	*P*-value
Energy, MJ/d, mean (SD)		8.5 (1.4)	7.4 (1.1)	−11 (22) %	0.06
Protein g/d, median (IQR)	Total	92 (81–106)	74 (70–87)	−19 (3–28) %	0.05
	Animal	63 (56–70)	38 (33–44)	−38 (5–58) %	0.006
	Plant	29 (27–36)	42 (33–46)	31 (11–44) %	0.01
Carbohydrates g/d, mean (SD)	Total	174 (36)	191 (26)	12 (17) %	0.081
	Starch	116 (27)	105 (21)	−7 (11) %	0.028
Fat g/d, mean (SD)	Total	97 (26)	71 (22)	−22 (35) %	0.79
	Saturated fat	35 (11)	23 (7)	−33 (21) %	0.18
Fiber g/d	Total fiber, mean (SD)	19.9 (5)	30.8 (5.9)	64 (55) %	0.001
	Oligosaccharides, mean (SD)	3.7 (1.3)	5.7 (1.6)	75 (85) %	0.013
	Resistant starch, mean (SD)	2.5 (0.7)	4.6 (1.3)	95 (82) %	0.001
	Non-starch polysaccharides, median (IQR)	7.3 (6.6–11.0)	11.7 (10.0–15.6)	60 (61) %	0.033
FODMAPs g/day, mean (SD)	Fructans	3.1 (1.1)	4.0 (1.1)	49 (68) %	0.047
	Galacto-oligosaccharides	0.7 (0.3)	1.7 (0.8)	197 (163) %	0.003
	Lactose	21.1 (15.6)	1.4 (2.2)	−85 (19) %	0.002
	Excess fructose	1.2 (0.6)	0.6 (0.5)	−37 (56) %	0.014
	Polyols	0.9 (0.6)	0.4 (0.3)	−30 (65) %	0.055
Sulfur-containing amino acids, g/d mean (SD)	Total	2.2 (0.9)	1.6 (0.7)	−17 (47) %	0.119
	Cysteine	0.68 (0.28)	0.57 (0.20)	−1.8 (64) %	0.361
	Methionine	1.55 (0.62)	1.1 (0.43)	−23 (43) %	0.066
Inorganic sulfur mg/d, mean (SD)		157.5 (0.64)	112.8 (0.56)	−22 (38) %	0.08
Micronutrients					
• Thiamine mg/d, median (IQR)		1.4 (1.3–2.3)	1.3 (1.1–1.9)	−4 (37) %	0.59
• Niacin mg/d, mean (SD)		14.3 (4.7)	23.5 (7.8)	81 (84) %	0.01
• Riboflavin mg/d, mean (SD)		2.8 (1.6)	2.3 (1)	−20 (86)	0.49
• Folate μg/d, median (IQR)		327 (257–454)	291 (241–408)	−5.5 (29–52) %	0.72
• Vitamin B12 μg/d, median (IQR)		4.3 (3.4–7.1)	1 (0.7–1.8)	−74 (48–88) %	0.06
• Vitamin C mg/d, mean (SD)		79.5 (53)	96.8 (53)	28 (4–70) %	0.16
• Vitamin A μg/d, median (IQR)		796 (548–1311)	947 (799–1292)	17 (−22–73) %	0.42
• Calcium mg/d, mean (SD)		1036 (376)	675 (218)	−26 (35) %	0.02
• Iron mg/d, mean (SD)		13.5 (2.4)	14.5 (3)	10 (31) %	0.40
• Zinc mg/d, mean (SD)		13.1 (2.8)	11 (2.9)	−13 (30) %	0.13
• Sodium mg/d, mean (SD)		2796 (585)	1672 (587)	−38 (23) %	0.001

Dietary intake. Eight (73%) of the 11 patients had excellent adherence, two (18%) had partial, and one patient (9%) had poor adherence. Dietary intake during baseline and dietary intervention is shown in Table 2. Changes in intake of the most of the targeted dietary components were successfully achieved. This included significant reductions in intake of excess fructose ($P = 0.01$), total protein ($P = 0.05$), lactose ($P = 0.002$) and a trend for polyols ($P = 0.06$) were achieved whilst total oligosaccharide intake increased compared with habitual intake. Furthermore, the reduction in protein intake was derived from a significant fall in animal protein intake ($P = 0.006$). Only trends for reduced intake of polyol and inorganic sulfur were observed (Supplementary Fig. 2). No changes in sulfur-amino acid intake were achieved. Additional changes were increased intake of total fiber ($P = 0.003$) and resistant starch ($P = 0.001$) and non-starch polysaccharides (NSP) ($P = 0.02$).

Tolerability and acceptability. At the end of the adaptation period, median tolerability scores were high at 78.0 (21.3–93.0) mm and tended to increase over time ($P = 0.08$) with median VAS scores increasing to 92.5 (80.0–95.0) mm by week 5 (Fig. 1). Four patients (33%) required dietary modifications to lower intake of oligosaccharide-rich foods including the patient who withdrew. Overall, nine patients (75%) reported excellent tolerability, two patients (16%) moderate tolerability and one patient (9%), who withdrew, poor tolerability.

Of a total score of 50, mean diet satisfaction scores were 38 (4) at week 5 and were high (≥35) for 9 patients (81%) and moderate in the other 2 (18%). For individual domains, the vast majority did not feel hungry on the diet, found the diet easy to follow at home, offered enough variety, was affordable, felt physically well, was satisfied with its impact on their pouch and could follow the diet long term (Supplementary Table 2). There were no differences between patients with and without pouchitis.

Fecal analyses. Daily fecal weight increased ($P = 0.04$) but no changes in fecal consistency, water content, King's Stool Chart score, or subjective assessment of fecal odor were observed (Supplementary Table 3). There were no differences between patients with and without pouchitis.

Total or individual SCFA concentrations and their relative proportions did not change, but total BCFA fell and the BCFA:SCFA ratios consistently decreased by a median of 60 (11–80)% ($P = 0.03$) at week 5 (Fig. 2). Relative proportions of the main SCFA did not change with diet (Supplementary Fig. 3).

There was no change in the average number of VOCs detected between baseline and at week 5 (53(9) *vs* 55(7); $P = 0.59$). Overall, principal components analysis did not identify distinct clustering between baseline and post-diet intervention for the overall cohort (Fig. 3a) or for those with pouchitis *vs* those without (Fig. 3b). However, comparisons between heatmaps in Figure 3c between individuals with and without pouchitis saw differences in patterns of VOC abundance at baseline but not following the dietary intervention. Median fold-change (FC) identified peak intensities for three metabolites that were altered from pre- to post–intervention—

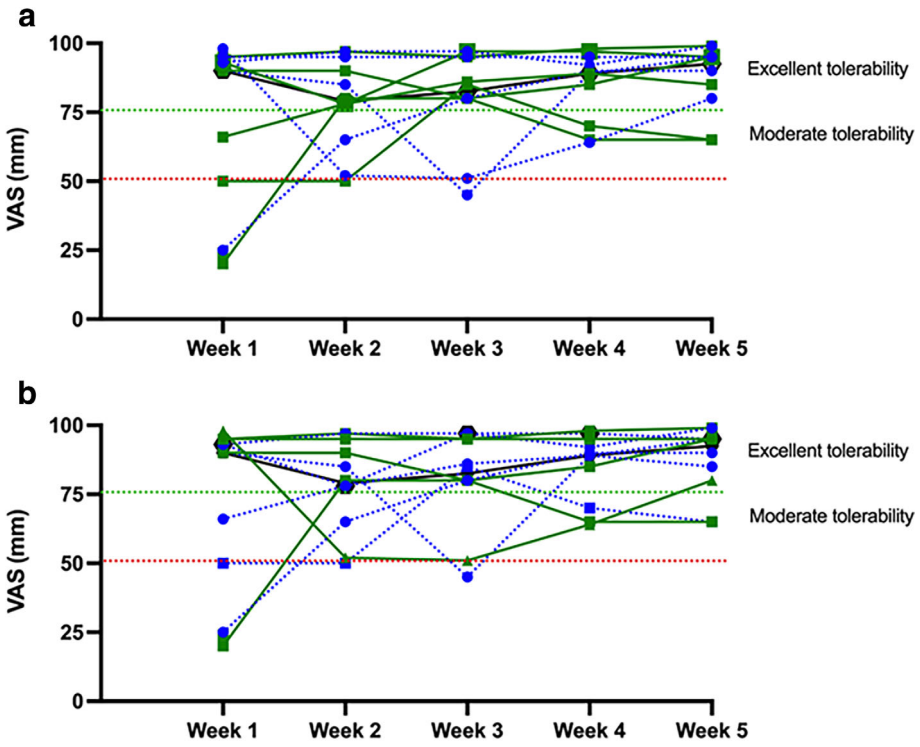

Figure 1 Diet tolerability over the duration of the study in based on (a) pouch symptoms and (b) pouchitis status at entry. (a) —■—, Symptomatic; ···●···, Asymptomatic; —⊗—, Median tolerability. (b) —■—, Pouchitis; ···●···, No pouchitis; —●—, Median tolerability.

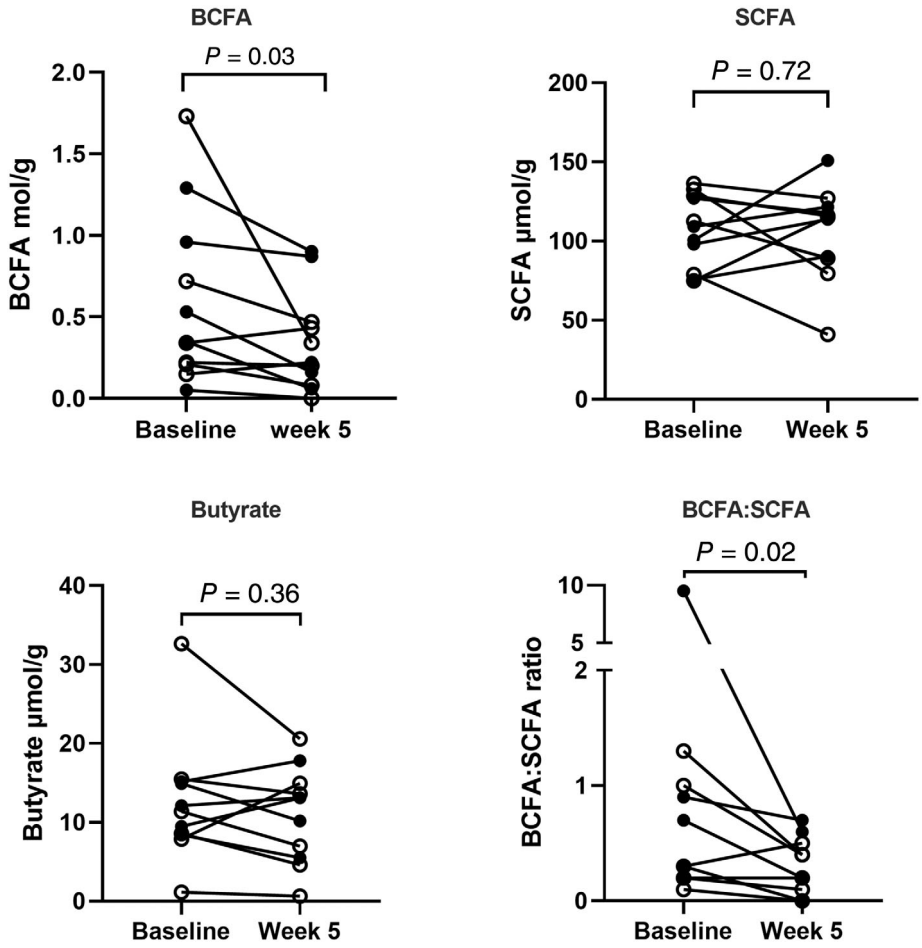

Figure 2 Fecal metabolite concentrations during the baseline period and after 5 weeks of the Monash Pouch diet. ●, Pouchitis; ○, No pouchitis.

IUPAC name: 2-methyl-5-propan-2-ylcyclohexa-1,3-diene (common name: alpha-Phellandrene), (1,3,3-trimethyl-2-oxabicyclo [2.2.2]octane (common name: Eucalyptol) and propan-2-ol (common name: isopropanol) were all increased (Fig. 3d).

Clinical response. Symptoms of obstructed defecation (ODS-S scores) fell during the MPD ($P = 0.04$), and the clinical PDAI scores and degree of seepage tended to fall (both $P = 0.06$) (Fig. 4). The proportion of patients with a symptomatic pouch fell from 55% at baseline to 9% with the diet ($P = 0.12$). All six symptomatic patients achieved symptomatic remission (clinical PDAI <3) with median clinical PDAI dropping from 3 to 1 ($P = 0.03$) (Table 3). Of the five asymptomatic patients, two had a lower clinical PDAI, two had no change in their clinical PDAI, and one patient had worsened clinical PDAI scores. Of the individual components of the clinical PDAI, seven patients (63%) reduced the frequency of pouch emptying from 7 [5–8] to 5 [5, 6] ($P = 0.09$). A small reduction in weight was documented at week 5 (72.2(17) *vs* baseline: 73.5(17) kg; $P = 0.021$). Fecal calprotectin at baseline was 292 [176–527] µg/g and at week 5 was 205 [148–310] µg/g ($P = 0.72$) (Fig. 4).

Health-related quality of life and levels of depression, anxiety and stress. No changes in CGQOL or in depression or anxiety scores were associated with the MPD, but stress scores were reduced ($P = 0.04$) at the end of the study (Table 3).

Analysis of study outcomes according to pouch phenotype. Comparisons between patients with and without pouchitis showed no differences in dietary intake, fecal characteristics including pH, water content, and weight as well as fecal short- and branched-chain fatty acids between patients with and without pouchitis. Diet satisfaction scores were also similar according to pouch symptoms at entry (symptomatic 83% *vs* asymptomatic group 80%) or to recent pouchitis (80%) or not (83%).

Adverse effects. One patient had a serious adverse event. At the beginning of week 2, she developed a transient episode of partial small bowel obstruction. This occurred on a background of a previous history of adhesive small bowel obstructions and of anal stenosis managed with regular dilatation. Five patients reported bloating and/or abdominal cramps after

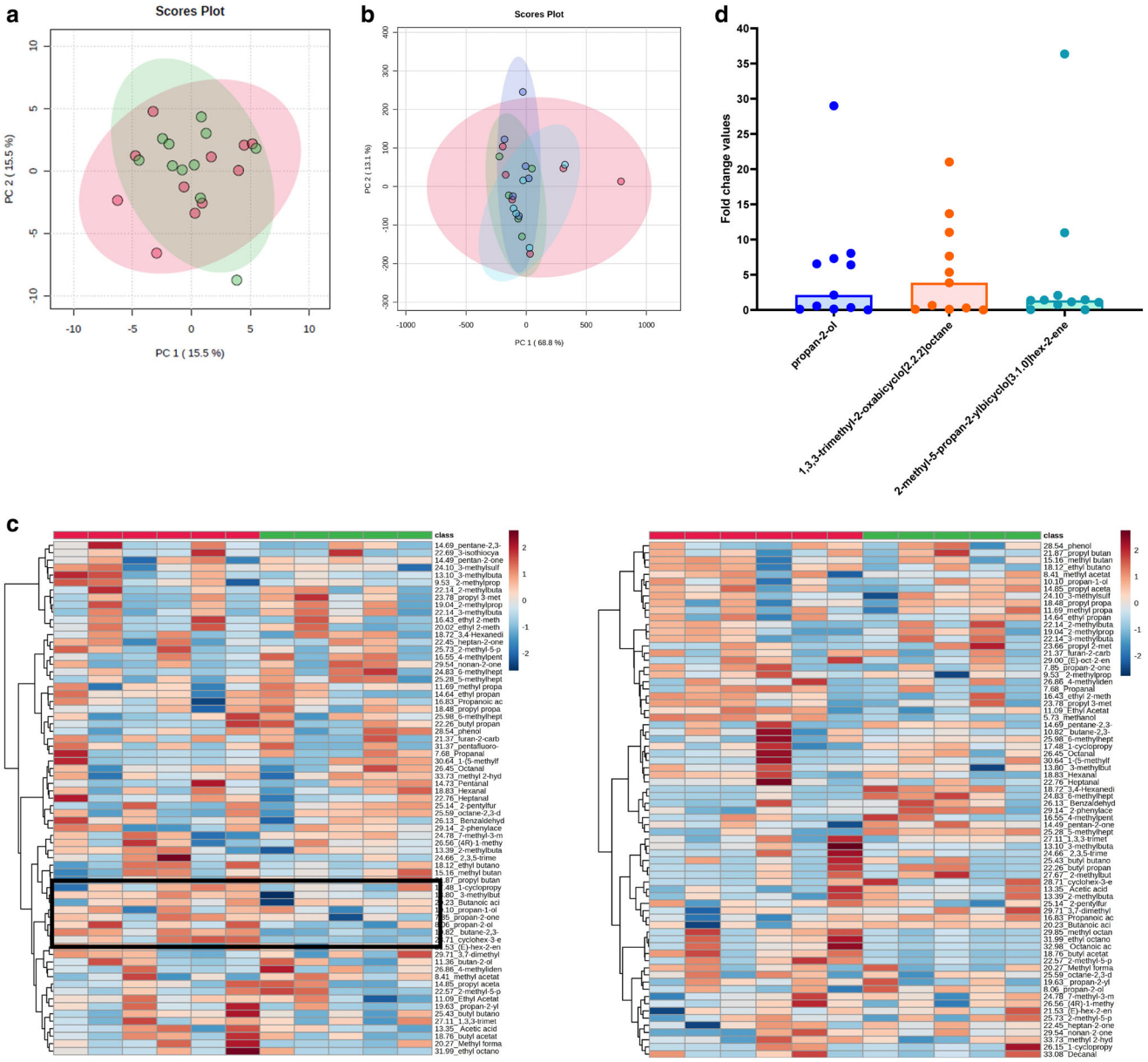

Figure 3 Principal components analysis plot of VOC patterns between (a) baseline and following 5 weeks of the Monash Pouch diet as well as (b) between patients with pouchitis and without pouchitis at baseline and post-dietary intervention. The explained variance are in brackets. (c) Heatmaps showing differences in VOC patterns between patients with and without pouchitis at baseline and following dietary intervention. (d) Graph showing fold changes of key volatile organic compounds identified to be altered from pre- to post-dietary intervention. Each dot represents an individual patient. BL = Baseline; FU = week 5 of dietary intervention. (a) ●, Baseline; ●, Week 5 diet intervention; (b) ○, BL no pouchitis; ○, BL pouchitis; ○, FU no pouchitis; ○, FU pouchitis; (c) **Class**—■, BL no pouchitis; ■, BL pouchitis; **Class**—■, FU no pouchitis; ■, FU pouchitis.

commencing the diet. These symptoms resolved spontaneously in one and with reduction of oligosaccharide intake in three patients. The symptoms persisted in one patient despite partial adherence to the diet.

Discussion

The novel MPD strategy is a whole diet approach that was well tolerated and acceptable to the majority of patients with an ileoanal pouch. Dietetic advice on principles of the diet achieved the desired dietary changes and resulted in a favorable fecal metabolite profile with enhanced carbohydrate relative to protein fermentation. There were signals to suggest that it improved pouch function in symptomatic patients.

Despite targeting foods naturally high in oligosaccharides in a population with high rates of food intolerances,[3] tolerability scores were rated highly as was acceptability, with all but two patients interested in implementing the diet long term. Factors contributing

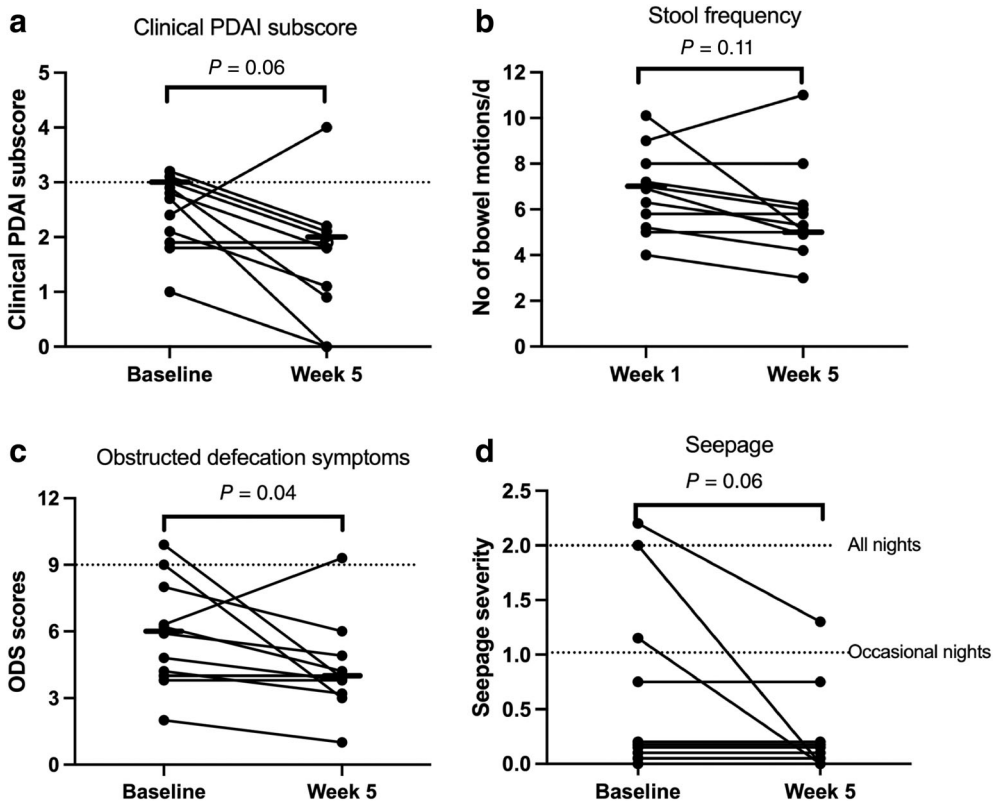

Figure 4 Clinical and fecal indices during the baseline period and after 5 weeks of the Monash Pouch diet. PDAI, pouch disease activity index; ODS, obstructive defecatory symptom; FC, fecal calprotectin.

Table 3 Comparison of pouch-related symptoms, HRQOL, and DASS21 from baseline to week-5 on the Monash Pouch diet

		Baseline	Week 5	*P*-value
Clinical Pouch Disease Activity Index (PDAI), median (IQR)	All	3 (1)	2 (1)	0.06[a]
	Symptomatic (≥ 3)	3 (3–3)	2 (0.75–2)	0.03[a]
	Asymptomatic	2 (1.5–2)	2 (0.5–3)	1[a]
	Pouchitis	3 (2–3)	2 (0.5–3)	0.35[a]
	No pouchitis	2.5 (2–3)	2 (1.5–2.5)	0.025[a]
Specific symptoms	Pouch emptying frequency, median (IQR)	7 (5–8)	5 (5–6)	0.09[a]
	Abdominal cramps, *n* (%)	7 (63%)	3 (27%)	0.37[b]
	Seepage, *n* (%)	4 (36%)	1 (9%)	0.12[b]
	Incomplete evacuation, *n* (%)	7 (63%)	4 (36%)	0.20[b]
	Excessive straining, *n* (%)	8 (72%)	4 (36%)	0.12[b]
Pouch Obstructed Defecation Symptom Score, median (IQR)		6 (4–8)	3.9 (3–4)	0.04[a]
Cleveland Global Quality of Life, mean (SD)		0.71 (0.16)	0.77 (0.15)	0.15[c]
Depression, Anxiety and Stress Scale-21 mean (SD)	Depression subscale	5.3 (8.8)	5.5 (8.1)	0.89[c]
	Anxiety subscale	6.0 (6.8)	4.7 (6.7)	0.17[c]
	Stress subscale	11.3 (9.5)	7.1 (8.2)	0.04[c]

Statistical analysis was computed using [a]Wilcoxon-signed rank test, [b]McNemar's test, and [c]Paired *t*-test. None of the *P* values remained significant following FDR corrections (adjusted *P*-value ≤0.01).
DASS21, Depression Anxiety Stress Scores; HRQOL, health-related quality of life.

to the good tolerability are likely to include the net reduction of FODMAP intake on the diet as increases in oligosaccharide were offset by the reduction in excess fructose, polyols and lactose, the initial gradual adaptation period,[19,20] and the sufficient variety for flexibility of food choice, as reflected in the participants' acceptability responses of finding the diet having good variety.

The diet was designed to achieve five changes to the participants' habitual diet. First, the delivery of fermentable fiber to the pouch was achieved via a 75% increase in oligosaccharides compared with that in the habitual diet. There was also a non-targeted doubling in resistant starch and a 64% increase in total fiber intake, by virtue of incorporating foods such as grains, legumes, and certain starchy vegetables. While less efficiently fermented in ileal pouches,[9] the increased resistant starch delivery favorably contributed to the first goal. Secondly, intake of osmotically active FODMAPs was reduced by 50%. Reduction in lactose intake may have been an important part of reducing osmotically active FODMAPs in at least some patients, as lactose malabsorption may be common in those with ileoanal pouches.[21] Thirdly, protein intake was reduced, but only modestly mainly due to the majority of the participants having habitual intake <100 g/d. Fourthly, there was a 30% reduction in intake of animal protein, a rich source of sulfur-amino acids. Interestingly, this also resulted in a trend for lower intake of vitamin B12, a potential concern for patients with an ileoanal pouch who may have reduced ability for its absorption post-pouch construction. Finally, good adherence to the avoidance of processed foods containing sulfur additives were reflected by the lowered inorganic sulfur intake. However, no food composition data were available to document quantitative changes in sulfites or carrageenan intake. Concomitantly, sodium intake was reduced following the dietary education and may reflect a reduction in ultra-processed foods, although this was not directly assessed in this study. Thus, the dietary teaching succeeded in achieving majority of the desired changes in a large proportion of participants, supporting feasibility of the diet.

In comparison to other diets that have been investigated in patients with ulcerative colitis and pouchitis, the MPD partially overlaps with the 4-strategies to a SUlphide Reducing (4-SURE) and a Mediterranean diet. Specifically, both the 4-SURE and MPDs target H_2S reduction[22] and, therefore, incorporate an increase in fermentable fiber and reduce total and sulfur-containing protein and sulfite-containing food additives. Furthermore, the increase in legumes and grains high in oligosaccharides and reduction in processed meat reflect the Mediterranean diet pattern reported by Haskey et al.[23] However, key differences of the MPD are the higher targets for oligosaccharides and the additional focus on reducing osmotically active FODMAPs compared with the 4-SURE and Mediterranean diet.

Unfortunately, there is currently no reliable and practical way of directly measuring pouch H_2S production. An alternate way was to examine protein fermentation, shown to be the major source of H_2S.[11] Fecal BCFA, a highly specific marker of protein fermentation, fell significantly by 14%. Likewise, quantification of carbohydrate fermentation is challenging. A commonly applied method is to determine concentrations or output of major SCFAs in the pouch effluent, but this is an insensitive measure[24] since SCFAs are rapidly taken up by the epithelium. Furthermore, measurement of fecal SCFA concentrations is subject to artefactual increases due to continuation of fermentation ex vivo,[25] which will be exaggerated in the presence of residual (unfermented) substrate. In the current study, the feces were frozen immediately after their passage to stop further fermentation. Because of the inverse relationship between carbohydrate and protein fermentation, it may be that the BCFA:SCFA ratio is a more sensitive marker of increased carbohydrate fermentation. Indeed, in the current study, BCFA:SCFA ratios were consistently reduced by the MPD. However, its change relative to protein fermentation can be assessed by the ratio of BCFA (metabolites of protein fermentation) to SCFA. Indeed, BCFA:SCFA ratios were consistently reduced by the MPD. Analysis of VOC revealed limited information regarding the metabolic activities of the pouch microbiota. The diet had limited impact on changes in the VOC milieu in the pouch. Abundances of 2-methyl-5-propan-2-ylcyclohexa-1,3-diene (alpha-Phellandrene), 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane (eucalyptol) are flavoring agents[26] but their role is uncertain. Therefore, the significance of increased abundances of these compounds are unknown. What was interesting however were the signals for differences in patterns of VOC produced in patients with and without pouchitis prior to dietary intervention. Such differences were not detected in heatmaps for the same participants at follow-up, suggesting that the diet may be effective in restoring the metabolome to a more normal state. These observations should be interpreted with caution given the small sample size and further analysis of stool VOC as well as metagenomics sequencing of the microbes in a larger cohort of pouch patients, including those with and without pouchitis is warranted.

A signal of clinical benefit of the diet was the improvement in symptoms that seemed greater than might be anticipated from placebo rates of 24% (95% CI: 14%–37%) reported in pouchitis trials.[27] If this represented cause and effect, it might be associated with restricting osmotically active FODMAPs by virtue of reducing the volume of water entering the pouch[28] as inferred from the effects of low FODMAP in two studies where frequency of pouch emptying and ileostomy output were reduced by 20%.[29] In this study, however, fecal output increased but no changes in measured water content or consistency of the pouch effluent occurred. Whether changes in the microbiota and/or its metabolites influenced pouch inflammation or irritability could not be validly assessed given the small number of patients studied and the heterogeneity of the inflammatory state of the pouches. It is possible that the reduction in protein fermentation metabolites, reflected by the decrease in BCFA:SCFA ratio, led to decreased exposure of the pouch wall to other potentially toxic metabolites that are injurious and may modulate pouch 'irritability'. There is currently very limited knowledge regarding the role of BCFA in the pouch lumen or its effects on the pouch epithelium. The other mechanistic effect of the diet may be in its effect of shifting the pouch metabolome via VOC production to resemble those without pouchitis as discussed earlier. There were variable effects on fecal calprotectin and ascribing functional significance of calprotectin changes to the profile of VOCs observed is not feasible. These mechanisms deserve further study via a targeted controlled study.

The only unanticipated adverse event was an episode of partial small bowel obstruction. The reduced delivery of osmotic agents may have led to marked reduction in small bowel water content, and its ability to 'flush' luminal contents into the pouch, as had previously been proposed in a previous study.[29] An additional factor may have been an increase in fermentable fiber intake that potentially may increase the bulk of small bowel contents. Hence, the diet might not be suitable for patients prone to small bowel obstruction.

The strengths of this study centered on the scientific rationale underpinning the design of the diet and the subsequent

assessment of biomarkers that reflected the success (or otherwise) of the diet in changing the pouch luminal microenvironment. However, the study was limited by its pilot nature with a small sample size, heterogeneity of the patient cohort and lack of a control group, together with the methodological inability of measuring the effect on H_2S production.

In conclusion, this pilot study has demonstrated the high patient tolerance and acceptability of the MPD and that, within the methodological limitations, the pouch luminal metabolite goals were fulfilled. There were signals that the diet might improve patient symptoms. A well-powered, randomized-controlled trial of the MPD in more homogeneous cohorts of patients with symptomatic pouches is feasible and indicated.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Data S1. Supporting Information.