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Ran Yan

r.yan@ecu.edu.au

Edith Cowan University

Amanda Devine

Edith Cowan University

Johnny Lo

Edith Cowan University

Evania Marlow

Edith Cowan University

Ian C Dunican

Edith Cowan University

Kanita Kunaratnam

Edith Cowan University

Lesley Andrew

Edith Cowan University

Claus T Christophersen

Edith Cowan University

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Dietary fibre blend improves gut health in patients with Irritable Bowel Syndrome following a low FODMAP diet: a randomised, double-blind control trial

Authors' names:

Ran Yan ^{1,2}, Amanda Devine ^{1,2}, Johnny Lo ³, Evania Marlow ^{1,2,4}, Ian C Dunican ^{1, 5}, Kanita Kunaratnam ¹, Lesley Andrew ⁶, Claus T Christophersen ^{1,2}

Authors' institutions

1. School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia
2. Nutrition and Health Innovation Research Institute, Edith Cowan University, Joondalup, WA, Australia
3. School of Science, Edith Cowan University, Joondalup, WA, Australia
4. Joondalup Health Campus, Joondalup, WA, Australia
5. Centre for Sleep Science, School of Human Sciences, The University of Western Australia, Crawley, Western Australia, Australia.
6. School of Nursing and Midwifery, Edith Cowan University, Joondalup, WA, Australia

Corresponding Author:

Ran YAN

School of Medical and Health Sciences, Edith Cowan University

270 Joondalup Drive, Joondalup, WA

E: r.yan@ecu.edu.au

Abbreviations:

ASV, Amplicon Sequencing Variant; DASS21, Depression Anxiety Stress Scales; DistLM, Distance-based linear models; FDR, false discovery rate; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI, gastrointestinal; HAMS, high amylose resistant starch; hs-CRP, high-sensitivity C-reactive protein; IBS, irritable bowel syndrome; IBS-SSS, IBS-Symptom Severity Scale; Interleukin, IL; RS, resistant starch; SCFA, short chain fatty acid; TNF- α , Tumour Necrosis Factor alpha; QOL, quality of life; VSI, Visceral Sensitivity Index.

Author contributions

RY, AD and CC contributed to drafting the manuscript; RY, JL, AD, CC contributed to study design and the statistical analysis. All authors contributed to finalising the manuscript.

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ABSTRACT

Purpose:

A diet low in FODMAP negatively affects the gut microbiota of Irritable Bowel Syndrome (IBS) patients, despite alleviation of symptoms. This study examines whether ur gut®, a mix of dietary fibres, when given to patients with stable symptoms on an existing low FODMAP diet, can improve gut microbiota, mental health, sleep and quality of life (QOL) in IBS patients without symptom exacerbation.

Methods:

Adult participants (n=26, 3 males) completed a randomised, double-blind controlled study. Participants were provided with either ur gut® (n=13) or placebo (n=13) for 3 weeks after a 1-week baseline. At baseline and end of intervention, blood, 24-h faecal samples and 3-day weighed-food diaries were collected. Validated questionnaires were used to evaluate mental health, sleep, QOL and gut symptoms. Participants reported daily IBS symptoms and wore a wrist-based actigraphy to capture daily sleep.

Results:

During the intervention, both groups maintained baseline stable gut symptoms and sleep patterns. After the intervention, the ur gut® group had lower energy ($P < 0.05$) and protein ($P < 0.01$) intake compared to the placebo group, and increased resistant starch intake ($P < 0.001$) compared to baseline. Changes in overall genus-level gut microbiota composition ($P < 0.01$), including *Ruminococcus E* (5.5-fold increase, $P < 0.01$), were observed. ur gut® improved GI-specific anxiety ($P = 0.01$) and sexual subscale of QOL ($P = 0.018$).

Conclusion:

A specific mix of fibres can increase fibre intake, improve gut microbiota and gastrointestinal-specific anxiety without impacting sleep and symptoms of IBS patients on a low FODMAP diet as compared with placebo, despite no changes found in faecal and blood biomarkers. This provides a dietary avenue to improve gut health with no exacerbation of symptoms in IBS patients.

Australia and New Zealand Clinical Trial Registry <http://www.anzctr.org.au/>,
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Keywords: Irritable bowel syndrome; Dietary fibre; gut microbiota; Short chain fatty acids; Quality of life

Author Contributions Statement

R.Y. conceived the study, contributed to study design, data collection, data analysis, and drafted the manuscript. A.D. and C.T.C. contributed to study conception and design, supervised the project, and critically revised the manuscript. J.L. contributed to data collection and data analysis. I.C.D. provided expertise in sleep-related measures and contributed to data interpretation and manuscript revision. E.M., L.A. and K.K. provided clinical input and contributed to data interpretation. All authors reviewed and approved the final version of the manuscript.

Conflict of interest statement

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INTRODUCTION

Irritable Bowel Syndrome (IBS) affects around 5% of people globally [1], inflicting mental and life quality loss on individuals and imposing an economic burden on communities [2,3]. A diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) has been demonstrated as efficient in symptom management [4]. As a group of short-chain carbohydrates that occur naturally in varied foods, FODMAP is poorly absorbed in the small intestine and is rapidly fermented in the proximal colon, causing increases in water volume, osmotic activity, fermentation and gas production, which in turn leads to distention and symptom induction [5]. Thus, despite the existence of similar physiological responses for both IBS individuals and healthy people following FODMAP consumption, GI symptoms associated with visceral hypersensitivity can be induced in IBS patients [6,7]. Moreover, IBS patients have been shown to have lower pain thresholds with higher perceptions of gut-related pain than the general population [8].

A low FODMAP diet, however, has been suggested to have unfavourable impacts on gut microbiota, including: a reduction in total bacterial abundance [9]; prebiotic bacteria abundance, such as *Bifidobacteria* [10]; butyrate-producing bacteria (*Faecalibacterium prausnitzii*); and gut health related bacteria (*Akkermansia muciniphila*) [11]. Moreover, despite symptom amelioration [12], low FODMAP diets have not been shown to restore the dysbiotic gut microbiome of IBS, and can negatively impact the gut microbiota of healthy subjects [13,14], while the clinical response can be dependent on the original microbiota signature in IBS patients [15]. This was demonstrated in a longer-term study with 18 IBS patients who had completed a 3-phase FODMAP diet over a 12-month period showed that short chain fatty acid (SCFA) concentration was reduced compared to baseline, despite symptomatic improvement and unchanged *Bifidobacteria* abundance with a relative abundance at 1.2% - 1.3% [13].

Emerging research has shown the link between gut microbiota and IBS comorbidities, including problems in sleep [16] and mental health [17]. Moreover, gut microbiota has been indicated as a potential target for health-related improvement. Previous animal studies have found microbiota-derived butyrate to enhance sleep [18], where butyrate supplementation ameliorated damage in intestinal homeostasis

induced by sleep deprivation [19]. SCFA are rapidly absorbed in the human colon, whereby SCFA levels decline along the large intestine, with approximately 5% of bacteria-derived SCFA being excreted in faeces [20], if excess amount is produced. Butyrate, one of the main SCFA, produced via fermentation of dietary fibre residue that enters the colon by local obligate anaerobic bacteria, is the preferred metabolic fuel for healthy colonocytes, providing approximately two-thirds of their energy (> 60%) [21]. Additionally, butyrate drives the energy metabolism of colonocytes towards mitochondrial beta-oxidation, which in turn consumes oxygen and maintains epithelial hypoxia [22,23]. Butyrate can also modulate microbial tryptophan metabolites that appear to be dysfunctional in IBS patients, which are in turn linked to psychiatric comorbidities [24] and poorer sleep quality [25]. Therefore, existing evidence supports the pivotal role of microbiota-derived butyrate in functions such as sleep and mental health [26]. Notably, a low intake of dietary fibre limits the function of gut microbiota, including producing SCFA, especially butyrate [27]. Longer-term studies of restrictive food patterns, such as a low FODMAP diet, have demonstrated that dieters habitually consume low fibre (10–17g/d) [13,28], which is below Australian dietary recommendations [29]. However, fibre intake has also been positively associated with faecal output and SCFA, whereby reaching a daily faecal output of 150 g may reduce colon cancer risk via improving varied fermentation-derived products, including butyrate [30].

Gut health, according to newest consensus statement from the International Scientific Association for Probiotics and Prebiotics (ISAPP), refers to both subjective experience and objective measures of gut function, and absence of symptoms is not equivalent to good gut health [31]. To date, little research has focused on the triad of gut microbiota, sleep and mental health when identifying the effectiveness of a fibre-related dietary intervention in IBS patients who follow a low FODMAP diet [32]. Research has suggested the inadequate fibre intake in the IBS population [33], and the predominant role of IBS individuals' baseline microbiome composition on the response to fibre consumption [34]. Emerging human studies have evidenced beneficial effects of resistant starch (RS) type 2 via reshaping the gut microbiome, such as managing non-alcoholic fatty liver disease [35], facilitating weight loss [36], reduce inflammatory mediators[37]. However, RS type 2 alone is not well tolerated in patients with IBS as its readily fermentable capacity [38,39]. Nevertheless, animal

studies have shown that psyllium can shift the fermentation of high amylose resistant starch (HAMS) [40] or inulin [41] further distally in the colon, suggesting that the mixture was likely to increase its tolerability. Hence, this study has aimed to identify, in this IBS population, if ur gut®, a mix of dietary fibres (RS and psyllium husk), can increase the intake of fermentable dietary fibre without exacerbation of symptoms, and determine effects on gut health and microbiota, sleep, mental health and quality of life (QOL).

MATERIALS AND METHODS

Participants and Sample Size

Inclusion and exclusion criteria have been included in the protocol paper [42] and are detailed in the supplementary material. In summary, adult IBS patients (18-65 years old) were included if they had stable symptoms (self-reported), a clinical diagnosis of IBS by a gastroenterologist or other medical professional, and had been on a low FODMAP diet for at least one month prior to the intervention. Participants were excluded if they were current smokers or had a known diagnosis of other gastrointestinal illness.

The participant recruitment began in July 2020 in Perth, Western Australia. The initial sample size calculation proposed in the protocol indicated a total of 50 participants was required to detect a change in log SCFA concentration of 0.4, corresponding to a small-to-medium effect size of 0.2. However, the recruitment was significantly impacted by the COVID 19 pandemic, resulting in multiple lockdowns and reduced interest/engagement from the public. As a result, a revised sample size calculation was performed using G*Power version 3.1.9.2 [43]. The calculation was based on a within-between interaction design to minimally detect a medium effect size of 0.3 with 80% power and an α -error at 5%, whereby a minimum sample size of 24 was required. Accounting for a 15% attrition rate, the final minimum required sample size was 28 participants.

Trial Protocol

The study protocol has been published elsewhere [42], and methodological details are outlined in supplementary methods. In summary, this study was designed as a randomised, double-blind, control trial, including a one-week baseline and a

three-week intervention. At baseline (Timepoint 1, T1), participants were assessed for anthropometric measures, such as body weight (kg), waist and hip circumference (cm) and percentage of lean and fat mass (determined by BOD POD, an Air Displacement Plethysmograph). Fasting blood samples were collected to assess blood biomarkers of inflammation including Interleukin-6 (IL-6), IL-1 β , Tumour Necrosis Factor alpha (TNF- α) and high-sensitivity C-reactive protein (hs-CRP). The baseline concentration and excretion amount of SCFA were examined from a 24-h faecal sample (all faecal output within the 24 hours) collected on the last day of a 3-day weighed food diary. This was recorded by each participant for analysing of habitual dietary intake. The general diet quality was assessed using Aussie-Dietary Quality Index [44], detailed in the supplementary material. Varied validated questionnaires were used to assess IBS symptoms [45,46], FODMAP intake [47], sleep[48-52], mental health[53,54], QOL [55,56] and physical activity[57], at T1 and at Timepoint 2 (T2) - the end of the interventional period, as detailed in the study protocol [42]. After the baseline week, participants were randomly assigned to one of two groups, either the ur gut® fibre powder or placebo (maize flour without resistant starch with psyllium husk), for a period of three weeks. The intervention of ur gut® fibre consists of HAMS and psyllium husk (International Patent Application (WO/2025/007187)). To ensure that any observed intervention effects were not due to psyllium husk, the placebo incorporated an identical psyllium husk component in the same amount. Both groups increased their dose from 5 g to 40 g/d over 11 days until the full dose was consumed for a further 10 days (40 g /d), as described in the study protocol [42]. For every 100 g of ur gut®, it provides 67 g carbohydrate consists of 56 g dietary fibre (36 g resistant starch) and 11 g other carbohydrate, as well as 1 g protein and less than 1 g of fat. Education about consumption, calculation of compliance and specimen collection and analysis are detailed in the supplementary material. A wrist-actigraphy monitor, a Readiband™ v5 (Readiband, Fatigue Science Inc., Canada) (validated [58]), was provided to each participant to capture daily sleep data. Throughout the four weeks, participants recorded their daily symptoms via an online checklist. At T2, the assessments conducted at T1 were repeated. The primary outcome was severity of IBS symptoms, with other analyses listed as secondary outcomes.

The study was approved by the Human Research Ethics Committee of Edith Cowan University (2019-00619-YAN). The study was registered with the Australia and

New Zealand Clinical Trial Registry (ACTRN12620000032954). All participants consented before the commencement of the study. All authors had access to the study data and reviewed and approved the final manuscript.

Statistical Methods

The per-protocol analysis was undertaken using data from participants who completed the study, whereby non-compliant participants were excluded. Linear Mixed Modelling was used to determine both within- and between-group differences in health outcomes via the group x time interaction effect and the main effects (if the interaction is not significant), with BMI and age included as covariates. Gender was not included due to the small number of male participants (n=3). Post-hoc tests were conducted if a significant effect was detected. The significance level was set at $P \leq 0.05$. Furthermore, false discovery rate (FDR) correction was performed on all raw P-values to minimise false positive results, and an effect was noted as marginal when the raw $P \leq 0.05$, but the FDR $P > 0.05$. For gut microbiota, a combination of R, Primer 7 and Permutation Multivariate Analysis of Variance (PERMANOVA) + (PRIMER-E, Plymouth), was used to analyse bacterial community structure at three taxonomic levels; phylum, genus and Amplicon Sequencing Variant (ASV). The relative abundance data were square root transformed and a Bray-Curtis dissimilarity matrix was calculated, followed by the deployment of Principal Coordinates Analysis (PCoA) to visualise findings of the three taxonomic levels at T1 and T2. For determination of significant associations at baseline and longitudinal dissimilarities between the two groups, PERMANOVA and dissimilarity percentage (SIMPER) were conducted. Distance-based linear models (DistLM) and distance-based redundancy analysis (dbRDA) were used to integrate gut microbial findings with all other relevant aspects. Further details of the statistical analyses are provided in the supplementary methods.

RESULTS

Participants

Overall, 30 participants consented to the study. In the placebo group, one female withdrew before being provided with the placebo. Another female withdrew on day 8 of placebo administration due to self-reported feelings of unwell, and one was lost to follow-up after administration. In the ur gut® group, one female participant stopped consuming the supplement on day 8 due to self-reported nausea. These data

162 were not included in any of the analyses. Therefore, a total of 26 participants (87%)
 163 completed the study and were included in the analysis (Supplementary results,
 164 Supplementary Figure 1), which fulfilled the minimum required sample size of 24
 165 participants. The mean age of participants was 37 ± 13 years, whereby 88% ($n = 23$)
 166 were female, with no between-group difference in demographic characteristics and
 167 IBS subtypes (Table 1). Compliance for the placebo group ($94.8 \pm 5.5\%$) was
 168 significantly higher than the ur gut® group ($89.0 \pm 6.5\%$) ($P = 0.022$), and both groups
 169 met the *a priori* compliance criteria ($> 80\%$). No significant change was noted in
 170 anthropometrics and physical activity between T1 and T2 (Supplementary Table 1).

171 Table 1. Results of anthropometry and physical activity by group and timepoint

Anthropometry and physical activity	Group × Time Interaction P	ur gut® Group, n=13 Mean (SE)			Placebo Group, n=13 Mean (SE)			Between-group P
		T1	T2	T2-T1	T1	T2	T2-T1	
Bodyweight, kg	0.057	65.0 (3.5)	64.9 (3.5)	-0.1 (0.3)	62.9 (3.5)	63.6 (3.5)	0.7 (0.3) ¹	0.735
BMI, kg/m ²	0.058	23.0 (0.9)	22.9 (0.9)	0.0 (0.1)	22.8 (0.9)	23.1 (0.9)	0.2 (0.1) ²	0.995
Waist circumference, cm	0.629	74.3 (2.8)	74.6 (2.8)	0.3 (0.5)	76.2 (2.8)	76.9 (2.8)	0.7 (0.5)	0.600
Hip circumference, cm	0.203	99.2 (2.2)	99.0 (2.2)	-0.2 (0.5)	98.7 (2.2)	99.4 (2.2)	0.8 (0.5)	0.974
Waist/Hip ratio	0.359	0.7 (0.0)	0.8 (0.0)	0.0 (0)	0.8 (0.0)	0.8 (0.0)	0.0 (0.0)	0.496
Fat percent, %	0.610	24.9 (2.4)	24.4 (2.4)	-0.5 (0.5)	29.3 (2.4)	29.2 (2.4)	-0.1 (0.5)	0.180
Fat-free mass percent, %	0.610	75.1 (2.4)	75.6 (2.4)	0.5 (0.5)	70.7 (2.4)	70.8 (2.4)	0.1 (0.5)	0.180
Fat mass, kg	0.333	16.3 (2.1)	16.0 (2.1)	-0.3 (0.4)	18.7 (2.1)	18.9 (2.1)	0.2 (0.4)	0.371
Fat-free mass, kg	0.421	48.6 (2.8)	48.9 (2.8)	0.3 (0.4)	44.1 (2.8)	44.9 (2.8)	0.8 (0.4)	0.300
Body volume, L	0.236	62.3 (3.5)	62.5 (3.5)	0.1 (0.4)	60.9 (3.5)	61.6 (3.5)	0.7 (0.4)	0.817
Body density, kg/L	0.751	1.0 (0)	1.0 (0)	0.0 (0)	1.0 (0)	1.0 (0)	0.0 (0)	0.189
Systolic blood pressure, mm Hg	0.897	105 (4)	102 (4)	-3 (2)	109 (4)	107 (4)	-2 (2)	0.357
Diastolic blood pressure, mm Hg	0.416	70 (3)	69 (3)	0 (2)	74 (3)	71 (3)	-3 (2)	0.314
Heart rate, beats per minute	0.326	61 (3)	64 (3)	3 (2)	67 (3)	67 (3)	1 (2)	0.164
International Physical Activity Questionnaire								
Total MET ³ , min/w	0.887	3477 (936)	3772 (954)	295 (-708)	2103 (936)	2257 (936)	153 (-684)	0.255
Vigorous intensity MET, min/w	0.069	1359 (406)	875 (417)	-484 (-398)	487 (406)	1059 (406)	572 (-385)	0.505

Moderate intensity MET, min/w	0.442	959 (371)	1613 (385)	654 (-427)	436 (371)	624 (371)	188 (-415)	0.099
Walking, min/w	0.242	1159 (444)	1362 (459)	203 (-484)	1180 (444)	574 (444)	-607 (470)	0.482

Note: T: Timepoint. SE = Standard Error. BMI: Body mass index. Fat-Free Mass: Fat-free mass is everything except fat, including muscle, water, bone, and internal organs. For the anthropometric data, Linear Mixed Modelling (LMM) was used to assess differences between- and within-groups, without any adjustment. For physical activity data, LMM was used to assess differences between- and within-groups with BMI = 22.9049, and age = 37.27 included as covariates in the model.

¹ P=0.017. ² P= 0.019, Both > 0.05 after False discovery rate adjustment.

³ Results reported as MET, unit was minutes per week, exercise equivalent minutes (MET minutes) weekly

IBS Symptoms and Bowel Habits

The severity of symptoms was assessed by two questionnaires: the Gastrointestinal Symptom Rating Scale for IBS [45] and the Irritable Bowel Syndrome-Symptom Severity Scale (IBS-SSS) [46]. Both groups had a moderate level of symptoms and did not change over the intervention (Table 2). Likewise, no significant interaction effect was found in daily GI symptom scores throughout the 4-week study (Supplementary Table 2).

Whilst the effect of intervention/placebo on bowel habits were examined longitudinally, no significant interaction effects were observed for stool weight and type (self-rated using Bristol Stool Chart [59]) or the number of bowel movements (an average of the last three days of each timepoint, same period as the 3-day food diary) (Supplementary Table 3).

Table 2 Results of IBS symptom questionnaires by group and timepoint.

Questionnaire	Group × Time Interaction P	ur gut® Group, n=13 Mean (SE)			Placebo Group, n=13 Mean (SE)			Between-group P
		T1	T2	T2-T1	T1	T2	T2-T1	
IBS-SSS	0.941	238.5 (22.7)	232.1 (22.7)	-6.4 (27.8)	272.9 (20.9)	265.0 (20.9)	-7.9 (25.6)	0.321
GSRS-IBS	0.599	49.2 (3.4)	45.0 (3.5)	-4.2 (3.9)	51.2 (3.4)	44.1 (3.4)	-7.1 (3.8)	0.891
Pain	0.892	7.5 (0.7)	6.7 (0.7)	-0.8 (0.8)	8.3 (0.7)	7.7 (0.7)	-0.6 (0.7)	0.296
Bloating	0.455	13.8 (1.1)	12.7 (1.2)	-1.1 (1.2)	14.3 (1.1)	12.0 (1.1)	-2.3 (1.1)	0.946
Constipation	0.876	6.5 (0.9)	5.9 (0.9)	-0.6 (0.8)	6.7 (0.9)	6.0 (0.9)	-0.8 (0.8)	0.878
Diarrhoea	0.327	14.0 (1.4)	12.8 (1.5)	-1.1 (1.8)	16.4 (1.4)	12.7 (1.4)	-3.7 (1.8) ¹	0.458
Early satiety*	0.536	7.5 (0.9)	7.0 (0.9)	-0.5 (0.9)	5.4 (0.9)	5.7 (0.9)	0.3 (0.9)	0.130

Notes: T: Timepoint; SE: Standard error; IBS-SSS: Irritable Bowel Syndrome-Symptom Severity Scale. GSRS-IBS: Gastrointestinal Symptom Rating Scale for IBS; Linear Mixed Modelling was used to assess differences between- and within-groups with BMI = 22.9049, and age = 37.27 included as covariates in the model. P-values reported are unadjusted.

¹ P = 0.05, False Discovery Rate P > 0.05.

*Early satiety refers to if the fullness feeling appears shortly after meal and long after eating

Dietary outcomes (FODMAP, Macronutrients)

At T1, no significant between-group difference was noted for all dietary outcomes, except for energy from carbohydrate (in percentage), which was higher in the placebo group than the ur gut® group ($40.6 \pm 8.9\%$ vs $31.5 \pm 7.2\%$, $P = 0.009$, $FDR-P = 0.045$).

Across the whole study period, there was no significant Group x Time interaction effect for any dietary outcomes, including Dietary Quality Index (DQI), or FODMAP intake, where these dietary markers remained stable in the respective groups (Supplementary Table 4). However, a significant interaction effect was observed for intakes of energy and protein ($P = 0.032$ and $P = 0.004$ respectively; both $FDR P < 0.05$). Both showed lower intakes in the ur gut® group at T2* (T2* indicates values from both diet and supplement) in contrast to increases in the placebo group (Figure 1A and B, Supplementary Table 4).

A marginal interaction effect ($P = 0.016$, $FDR P > 0.05$) was observed in habitual dietary fibre derived from diet only, with a decrease in the ur gut® group at T2 compared to the habitual intake at T1; however, this reduction was offset by the ur gut® supplement, leading to an overall increase in fibre intake at a total of 33.1 ± 2.4 g/d at T2 (Figure 1C, Supplementary Table 4), which met daily Australian recommended levels for males (30 g/d) and females (25 g/d). A significant Group x Time interaction effect for RS was noted ($P < 0.001$, $FDR P < 0.05$), with the ur gut® group significantly increased their intake of resistant starch to 9.5 ± 0.3 g/d at T2* from their T1 level at 2.0 ± 0.3 g/d ($P < 0.001$) (Figure 1D, Supplementary Table 4). This reached the average intake level of Australian adults at 9.5 g/d [60], although only half of the suggested amount of 20 g/d [61]. Supplementary Figure 2A–D shows individual participant changes in intake between T1 and T2 across each group, corresponding to Figure 1A–D.

Sleep

Participants exhibited normal sleep duration, sleep latency and sleep efficiency measured daily across the baseline week, according to the National Sleep Foundation's recommendations [62], whereby no significant change was observed during the intervention in either group in relation to objective sleep measures (Supplementary Figure 3). A marginal interaction effect was observed for Time at Sleep Onset ($P = 0.031$, FDR $P > 0.05$), where the placebo group delayed their sleep onset time, whilst the ur gut® group maintained their sleep onset time throughout the study (Supplementary Figure 3B). Similarly, no significant effects were observed in sleep questionnaires (Supplementary Table 5). These sleep outcomes indicated that sleep patterns and behaviours were stable in the ur gut® group over the duration of the study.

Mental Health and Quality of Life

Suggestive evidence of an interaction effect was observed for the Visceral Sensitivity Index (VSI) [54] ($P = 0.034$, FDR-adjusted $P > 0.05$), where the ur gut® group had a reduction of 7.4 ± 2.6 units at T2, whilst VSI remained steady for the placebo group (Supplementary Table 6). No significant interaction effects occurred on measures of the Depression Anxiety Stress Scales (DASS21) [53] (Supplementary Table 6). Two genera, *Alistipes* and *Coprococcus*, showed a significant positive correlation with VSI score ($r_p = 0.750$ and 0.743 , $P < 0.001$, respectively).

A marginal interaction effect was found on the sexual subscale of the IBS- QOL [55] ($P = 0.019$, FDR-adjusted $P > 0.05$), where the ur gut® group had a within-group increase of 12.5 ± 4.9 ($P = 0.018$), whilst there was no notable change for the placebo group (Supplementary Table 7). No significance was noted for all remaining seven subscales of IBS-QOL (Supplementary Table 7).

Faecal SCFA and Blood Biomarkers

No significant interaction effects were shown on the concentration and excretion amount of SCFA in 24-hour stool samples (Supplementary Table 8). However, significant changes in faecal output and SCFA were found, when dividing the ur gut® group according to their T1 faecal output lower or greater than 150 g/d, a faecal index associated with improving fermentation products in relation to colon cancer risk [30]. At T2, the ur gut® LOW subgroup ($n = 5$, T1 faecal output < 150 g/d)

significantly increased the faecal butyrate concentrations and excretion by 51% and 289% of their T1 level (both $P < 0.05$, FDR $P > 0.05$), where their mean faecal output also increased from 78 to 162 g/d (detailed in the Supplementary Results and Supplementary Table 9 and 10).

Blood biomarkers of inflammation status were collected, but most of the results for IL-1 β and TNF- α were below detection limits, leading to insufficient sample sizes for further analysis. For IL-6 and hs-CRP, no significant changes were observed (Supplementary Table 11).

Gut Microbiota

PERMANOVA analysis did not show significant microbial composition changes at the phylum level ($P = 0.610$). However, overall microbial composition significantly altered at the genus level ($P = 0.003$), where between-group differences were not significant at T1 ($P = 0.262$, Figure 2A), but were significant at T2 ($P = 0.008$, Figure 2B), despite no Group $\times$ Time interaction effect. Similarly, at ASV level, no significant between-group difference at T1 ($P = 0.275$) was observed; however, after the intervention, the microbial composition of the two groups significantly differed ($P = 0.002$) (Supplementary Figure 4A and B).

The genus of *Ruminococcus E* significantly increased to a relative abundance of 11.33% at T2 with a fold change (fc) of 5.5 ($P < 0.01$) in the ur gut® group, where 92.3% ($n=12$) of participants recorded an increase (Figure 3A, Supplementary Table 12). This relative abundance was greater than that of the placebo group at T2 ($P < 0.001$, FDR $P = 0.0037$) (Supplementary Table 12). Similarly, ur gut® enriched *Prevotella*, $fc = 5.9$ ($P > 0.05$), which was significantly more abundant at T2 compared to the placebo where the relative abundance of *Prevotella* remained unchanged (Figure 3B, Supplementary Table 12). A similar but insignificant trend was found in *Akkermansia*, with $fc = 2.6$ in the ur gut® group compared to a $fc = -1.8$ in the placebo group (Supplementary Table 12). Among all classified genera, a total of three genera significantly changed within the ur gut® group, including *Ruminococcus E* (increased), *Anaerobutyricum* (decreased) and *Catenibacterium* (decreased), with none occurring in the placebo group (Supplementary Table 13, also showing between-group difference at T1 and T2).

Within the ur gut® group, ASV 14 *Ruminococcus E* was marginally enriched, 1.6% (T1) vs 6.7% (T2), $fc = 4.3$ ($P = 0.010$, $FDR.P > 0.05$) (Figure 3C, Supplementary Table 14). Other enriched ASVs included ASV 12 *Akkermansia muciniphila* (Figure 3D), ASV 21 *Ruminococcus E bromii A sp003526955* (Figure 3E), ASV 11 *Prevotella copri A* (Figure 3F), ASV 18 *Prevotella copri A sp900546535* and with respective fcs of 32.9, 9.7, 8.8 and 9.1, despite their statistical insignificance (Supplementary Table 14)

Gut Microbiota- Gut Diversity

Regarding gut diversity indices, the placebo group was observed to have a significantly lower diversity at baseline than the ur gut® group, including Chao1 index, Shannon index and Fisher index (Supplementary Table 15). No significant interaction effects were noted after the intervention, where the indices remained stable in the ur gut® group at T2 (Supplementary Table 15).

Gut Microbiota - DistLM

DistLM analysis showed that eight variables individually explained a significant proportion of the variability of gut microbial composition at the three taxonomic levels of gut microbiota (phylum, genus and ASV) (Table 3). The Epworth Sleepiness Scale [52], indicating the daytime sleepiness contributed significantly at all three levels, together with the Pittsburgh Sleep Quality Index [48] at two levels, suggesting the influence of sleep on the gut microbiota composition (Table 3). Daily intake of resistant starch and was found to significantly account for 7.4% ($P < 0.01$) of the total gut microbial variation at genus level (Table 3). At ASV level, starch intake and IBS-SSS explained 5.6% ($P < 0.05$) and 6.2% ($P < 0.01$), respectively; daily dairy intake accounted for 13.3% ($P < 0.05$) at phylum level variation (Table 3).

Table 3. Summary of variables explained significant individual proportion (%) of total gut microbial variation at three taxonomic levels at T2.

Significant Variables	Individual Proportion (%) explained the total microbial composition variation in		
	Phylum level	Genus level	ASV level
ESS	9.8%	7.7%	5.4%
PSQI	9.8%		5.4%
Dairy, serve/d	13.3%		
# of Bowel Movement	6.7%		
Resistant starch, g/d		7.4%	
Age		5.5 %	

Starch, g/d	5.6%
IBS-SSS	6.2%

Note: The data was derived from 25 participants at T2. Only significant proportion was listed in the table ($P < 0.05$), and figures in bold indicate the variable's $P < 0.01$. Acronym: ESS: The Epworth Sleepiness Scale; PSQI: The Pittsburgh Sleep Quality Index; # of bowel movement: mean of the number of bowel movements of the last three days which covered the dietary records period; IBS-SSS: Irritable Bowel Syndrome-Symptom Severity Scale. The sequential test variable order for each level is provided in supplemental Table 16-18.

DISCUSSION

This randomised trial is the first study to comprehensively explore the effects of a mixed fermentable dietary fibre powder (ur gut®) on gut microbiota, sleep, mental health and QOL in IBS patients who are following a low FODMAP diet. The study outcomes showed that ur gut® increased in fermentable fibre intake, benefited overall gut microbial composition, selectively promoted gut microbes, and improved GI-specific anxiety and QOL (sexual subscale), without symptomatic exacerbation or impacts on participants' habitual sleep throughout the study. Moreover, ur gut® boosted participants' fibre intake above Australian dietary recommendations and helped maintain overall diet quality and pattern. The presence of fibre is crucial to protect the intestinal barrier integrity and to balance microbial metabolic networks, whereby fibre-supplemented/fibre-rich diets can maintain the balance between mucin-degrading microbes and fibre-degrading microbes [63].

The demonstrated effect of ur gut® is due to the unique blend of HAMS and psyllium. Rat studies have shown that the fermentation was shifted further distally when HAMS was mixed with psyllium [40]. Rats fed with HAMS + psyllium demonstrated a higher butyrate concentration, which was maintained throughout the colon; however, for rats taking HAMS only, their butyrate concentration decreased along the colon, with the concentration in the cecum being threefold of that in the faeces [40]. The fibre mix in ur gut® is believed to slow proximal fermentability, where psyllium, with its strong gel-forming and water-holding capacity [64] can positively trap RS granules. It prevents or slows proximal colonic fermentation, preventing or reducing gas-production and related symptom-causing responses, and delivering RS further distally in the colon where it is better tolerated. previous research has shown that RS alone is not tolerated by IBS sufferers [39]. Gut microbes are highly dependent on their substrate preference [65], and as such, we found bacteria were selectively promoted in response to ur gut®. Our results showed that ur gut® consistently

enriched the genus *Ruminococcus E* and ASVs within this genus across participants. Compared to the negative change seen within the placebo group of that genus, this suggests ur gut® provided a substrate for *Ruminococcus E*. As a primary RS degrader, *Ruminococcus.bromii*, a species within the genus *Ruminococcus*, can cross-feed other butyrogenic bacteria by increasing the concentration of acetate, which involves the carbohydrate-fuelled acetyl-CoA pathway - the primary pathway of butyrate generation in the colon [66,67]. Despite not registering statistically significant changes in faecal SCFA concentration, they are influenced by both production and absorption. Notably >95% of SCFA are absorbed by colonocytes, and this absorption in the human colon create a negative concentration gradient throughout the [20]. Our findings of a significant increase in butyrate concentration and excretion in the ur gut® LOW subgroup suggest that IBS patients with a lower baseline faecal output (< 150 g/d) may respond better to the ur gut® supplement.

Our results also showed that ur gut® enriched the genus *Prevotella*, which in turn can reflect long-term dietary patterns, where individuals with a diet based on carbohydrates and low in animal products feature a *Prevotella* enterotype [68]. In comparison to healthy subjects where the *Prevotella* enterotype is more prevalent, IBS patients commonly possess the *Bacteroides* enterotype, and symptom severity, as assessed by IBS-SSS, has been found to worsen as the prevalence of the *Prevotella* enterotype decreases [69]. Research has demonstrated a positive correlation between *Prevotella copri* and a fibre-rich diet [70], where those with non-Western lifestyles (including dietary factors) showed a higher prevalence of *Prevotella copri* compared to those with Western lifestyles (95% vs 30%) [71]. Our study showed an upward trend in *Akkermansia* genus abundance (fc 2.6) and ASV *Akkermansia muciniphila* (fc 32.9) within the ur gut® group. As a mucin degrader with SCFA-producing capabilities, *Akkermansia muciniphila* has been identified as a next-generation probiotic [71], suggesting potential benefits to the gut microenvironment.

The improvement in participants' mental health (GI-specific anxiety assessed by VSI) and QOL (the sexual subscale of IBS-QOL) may be related to gut microbial alteration in relation to fibre supplementation. This study showed a greater abundance of *Alistipes* and *Coprococcus*, to be associated with more severe anxiety (VSI score). Moreover, *Alistipes* and *Coprococcus* had a non-significant fc of -1.2 and -1.3,

respectively, in the ur gut® group at T2, yet participants had a significant reduction of VSI. Other studies have reported higher *Alistipes* abundance in IBS patients with comorbidity of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome [72], and in patients with major depressive disorder compared to healthy controls [73]; however, dietary analysis was not available for these studies. An elevated level of *Alistipes* was also exhibited in those consuming an animal-based diet both in the short term (5 days) [74] and longer term [75], likely related to a lower fibre intake, whereas a diet based on inulin-rich vegetables lowered *Alistipes* abundance in a healthy population [76]. In practical terms, GI-specific anxiety is the most influential factor affecting IBS-specific QOL, whereby psychological distress is also associated with overall QOL [73]. A 2-3 year follow-up study in females with IBS suggested that a high-fibre diet was associated with a significant decrease in anxiety and depression [77]. Regarding fibre supplements, however, its effects on mental health remain unclear, few recent IBS-related studies have included mental health measurements [75]. Although some prebiotic fibres have demonstrated potential to improve mood, they may be poorly tolerated in individuals with IBS as they are fall within the FODMAP category [78]. Research has shown the microbiota-derived SCFA to directly or indirectly modulate signals between gut and brain, affecting brain and behaviour such as stress response, mood and appetite regulation [26,79]. Accordingly, our outcomes suggest that ur gut® may be a promising fibre supplement for mental health benefits.

When ur gut® was introduced to participants' background low FODMAP diet, the stability of symptoms and sleep throughout the study did not change, nor did DQI and FODMAP intakes. ur gut® was well tolerated and accepted by participants, resulting in their continued compliance. Notably, ur gut® was introduced over 11 days, increasing from 5 g/d to 40 g/d, taken as a 20 g dose twice a day, which is aligned with current recommendations of an adaption period for most fibre supplements [80]. Additionally, the effect of ur gut® on reducing energy intake was aligned with participant anecdotal feedback of 'feeling fuller after taking the supplement' on the final clinic visit. This was not an anticipated outcome of this study but is an important consideration for those living with overweight/obesity. Research has indicated that an intake of 8 g/d viscous fibre for 8 weeks can lead to a significant reduction in body weight for the general population and those with diabetes/obesity/overweight [81],

although a longer supplementation period with isolated soluble fibre may be needed for those with overweight/obesity [82].

Limitations

Limitations include a small sample size, dominance of female participants and differing IBS subtypes. IBS is more prevalent in women than men with females accounting for approximately 60–70% of diagnosed cases in Western populations. Gender differences are also evident across IBS subtypes, with IBS-C predominating in women, while IBS-D is more commonly reported in men. Several results showed marginal significances (namely raw $P \leq 0.05$, but FDR-adjusted $P > 0.05$), which could be attributed to our relatively small sample size, especially in gut microbial analysis. Gut transit time and faecal pH were not assessed in the present study, which should be incorporated in future research to strengthen methodological completeness. Further research needs to identify effects or impacts of long-term intake of ur gut® fibre on weight management and metabolic health.

CONCLUSION

In conclusion, this study comprehensively explored the effects of 3-week ur gut® supplementation on gut microbiota, gut health, dietary intake, sleep, mental health and QOL in participants living with IBS and following a low FODMAP diet. Despite no change found in faecal SCFA level between groups, adding ur gut® to this group's habitual low FODMAP diet increased fibre intake, improved GI-specific anxiety and benefited gut microbial composition, without impacting participants symptoms severity, sleep and dietary quality and patterns.

FIGURES

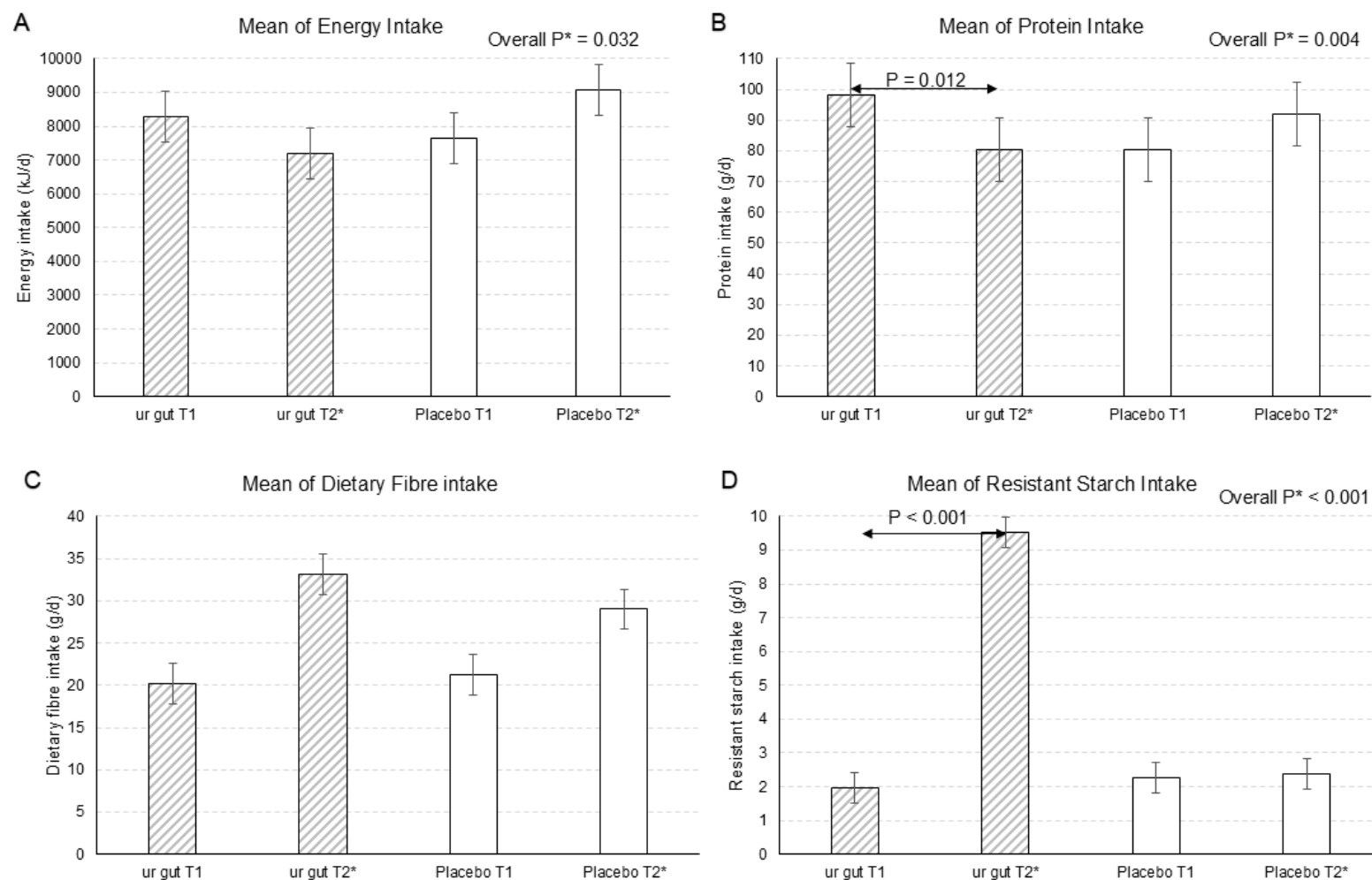


Figure 1 Comparison of intake of nutrients (energy, protein, fibre and resistant starch) by group and timepoint

A. Overall energy intake; B. Protein intake; C. Dietary fibre intake (Dietary fibre intake exclusive of Resistant Starch intake); D. Resistant starch intake. T, Timepoint. * indicates nutrients from both diet and supplement

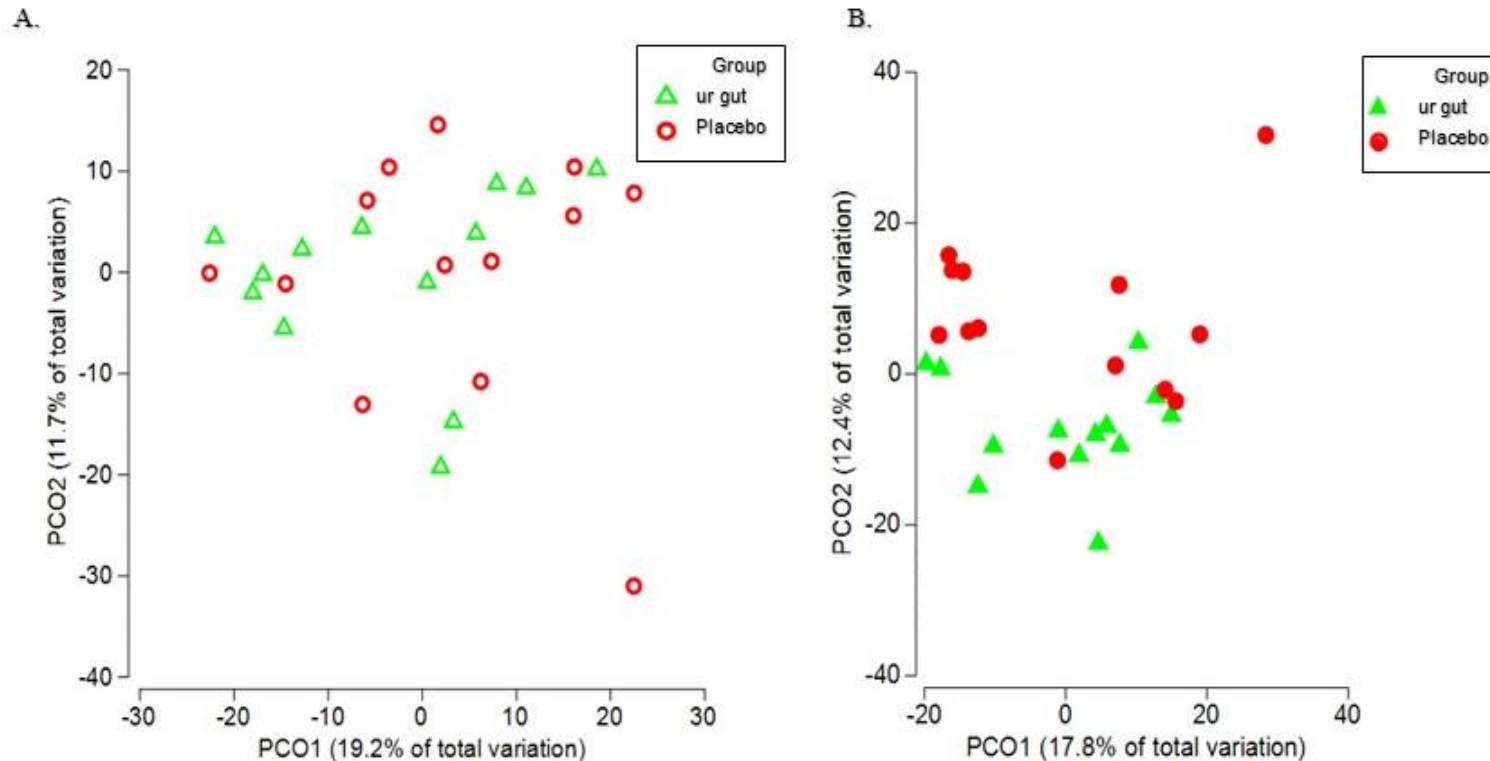


Figure 2 Principal coordinate analysis (PCoA) at the genus level of gut microbiota by group and timepoint

A. PCoA of gut microbiota at the genus-level at T1. The variation in the genus community is best captured by the first two dimensions, PCO axes 1 & 2, which explain 30.9% of the variability between groups. **B.** Genus-level gut microbiota of the two groups was significantly different at T2 ($P = 0.0082$). PCO plot suggests the variation in the genus community structure is best captured by the two dimensions, PCO axe 1 & 2 which explains 30.2% of the variability between groups at T2.

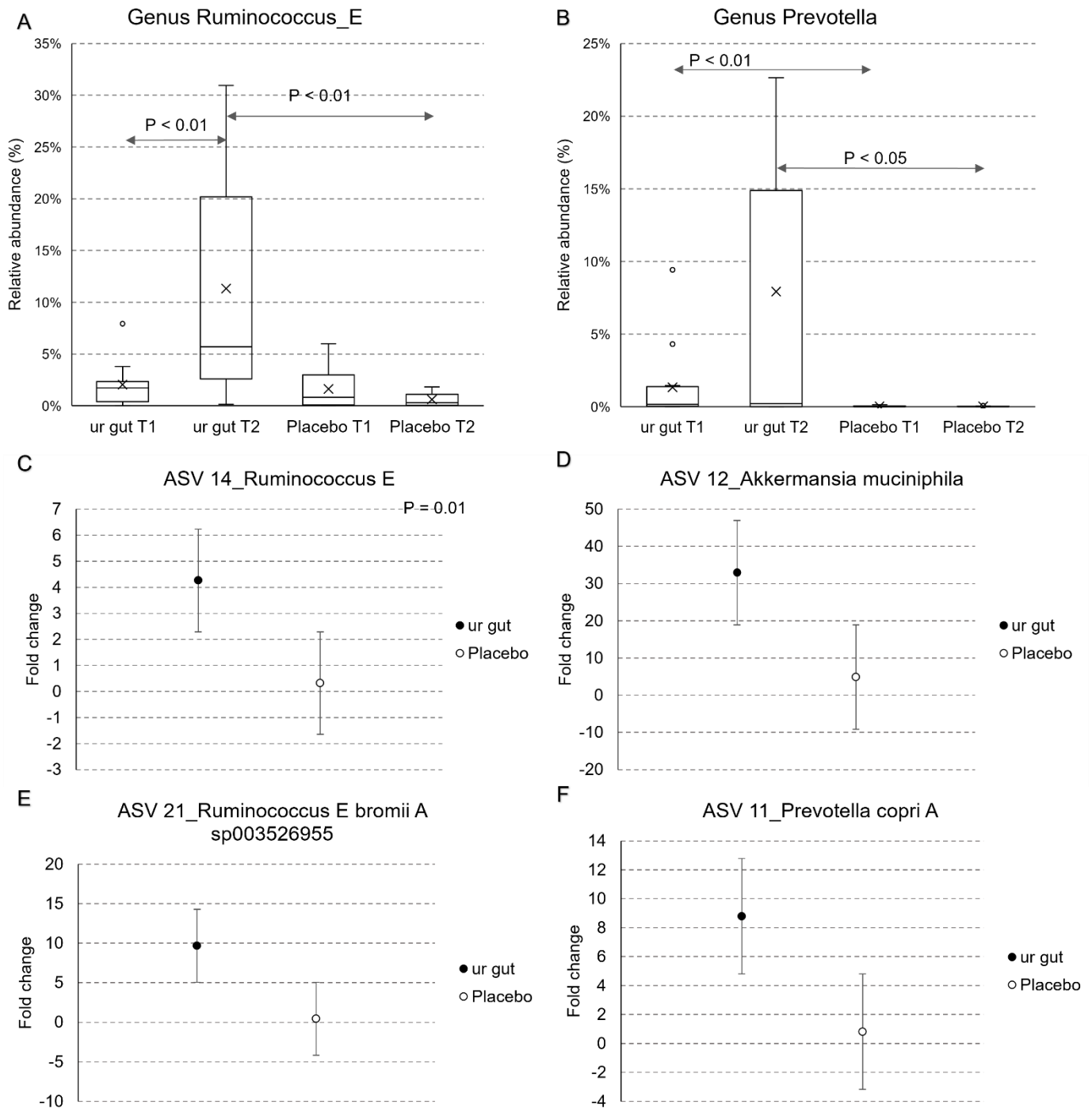


Figure 3 Changes in gut microbes

A: The relative abundance of genus *Ruminococcus E* by group and timepoint. **B:** The relative abundance of genus *Prevotella* by group and timepoint. **C:** Fold change of ASV 14 *Ruminococcus E* within each group. **D:** Fold change of ASV 12 *Akkermansia muciniphila* each group. **E:** Fold change of ASV 21 *Ruminococcus E bromii A sp003526955* each group. **F:** Fold change of ASV 11 *Prevotella copri A* each group.

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FIGURE LEGENDS

Figure 1. Comparison of intake of nutrients (energy, protein, fibre and resistant starch) by group and timepoint.

A. Overall energy intake; B. Protein intake; C. Dietary fibre intake (Dietary fibre intake exclusive of Resistant Starch intake); D. Resistant starch intake. T, Timepoint. * indicates nutrients from both diet and supplement

Figure 2. Principal coordinate analysis (PCoA) at the genus level of gut microbiota by group and timepoint.

A. PCoA of gut microbiota at the genus-level at T1. The variation in the genus community is best captured by the first two dimensions, PCO axes 1 & 2, which explain 30.9% of the variability between groups. B. Genus-level gut microbiota of the two groups was significantly different at T2 ($P = 0.0082$). PCO plot suggests the variation in the genus community structure is best captured by the two dimensions, PCO axe 1 & 2 which explains 30.2% of the variability between groups at T2.

Figure 3. Changes in gut microbes. **A:** The relative abundance of genus *Ruminococcus E* by group and timepoint. **B:** The relative abundance of genus *Prevotella* by group and timepoint. **C:** Fold change of ASV 14 *Ruminococcus E* within each group. **D:** Fold change of ASV 12 *Akkermansia muciniphila* each group. **E:** Fold change of ASV 21 *Ruminococcus E bromii A sp003526955* each group. **F:** Fold change of ASV 11 *Prevotella copri A* each group.

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