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Gut microbiota in non-hospitalised SARS-CoV-2 infection is compositionally distinct from IBS despite comparable dysbiosis prevalence: a prospective cohort study from acute infection to six months

Birgitte Berentsen

Birgitte.Berentsen.Jacobsen@helse-bergen.no

University of Bergen

Eline MR Hillestad

University of Bergen

Ingeborg Brønstad

University of Bergen

Astri J Lundervold

University of Bergen

Rebecca Jane Cox

Haukeland University Hospital

Nina Langeland

University of Bergen

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Gut microbiota in non-hospitalised SARS-CoV-2 infection is compositionally distinct from IBS despite comparable dysbiosis prevalence: a prospective cohort study from acute infection to six months

Birgitte Berentsen [1,2,] Eline MR Hillestad [1,2,] Ingeborg Brønstad[1, 2,] Astri J Lundervold[3,6], Rebecca Jane Cox[4]#, Nina Langeland[1,2,5]#

[1] Department of Clinical Science, University of Bergen, Bergen, Norway
[2] Department of Medicine, Haukeland University Hospital, Bergen, Norway
[3]Department of Clinical and Biological Psychology, University of Bergen, N-5020 Bergen, Norway.
[4] Influenza Centre, Department of Clinical Science and Department of Microbiology, Haukeland University Hospital, Bergen Norway
[5]Norwegian Institute of Public health, Oslo, Norway.
[6]Department of Geriatric Medicine, Haraldsplass Deaconess Hospital, Bergen, Norway

#Contributed equally

Abstract

Background: Gut dysbiosis has been documented after COVID-19, but whether it occurs and persists after mild to moderate non-hospitalised infection, and how it compares with irritable bowel syndrome (IBS), remains unclear.

Methods: We prospectively followed 31 non-hospitalised patients with mild-to-moderate SARS-CoV-2 infection at acute infection, four weeks and six months using the GA-map® Dysbiosis Test, with healthy controls (n=36) and patients with moderate-to-severe IBS (n=58) as cross-sectional reference groups. Composition was compared by PERMANOVA on Bray-Curtis dissimilarities, individual taxa by Wilcoxon rank-sum tests with false discovery rate (FDR) correction, and within-patient change by linear mixed-effects models. Gastrointestinal symptoms, fatigue and cognitive symptoms were related to the microbiota by Spearman correlation.

Results: Overall composition differed across groups (p=0.001). SARS-CoV-2 patients differed from healthy controls (adjusted p=0.048, 0.005 and 0.007) and from IBS (adjusted p=0.011, 0.004 and 0.004) at all three time points, whereas composition within the SARS-CoV-2 cohort did not change over follow-up and IBS did not differ from healthy controls. Alpha diversity did not differ across groups. Five taxa were altered at every time point against both reference groups, with *Eubacterium rectale*, *Bacteroides stercoris*, *Ruminococcus gnavus* and Proteobacteria depleted and *Shigella* spp. & *Escherichia* spp. elevated.

Følsomhet Intern (gul)

Actinobacteria and *Bifidobacterium* spp. increased within patients by four weeks (both FDR=0.002) and exceeded IBS levels at six months (both FDR<0.001). Dysbiosis was as prevalent as in IBS (8/28, 3/29 and 7/26 versus 15/58) and more prevalent than in healthy controls (2/36) at baseline and six months, but individual trajectories were bidirectional and no patient was dysbiotic throughout. Gastrointestinal symptoms largely resolved, whereas mental fatigue remained at the IBS level and cognitive symptoms were present in 13/26 patients at six months versus 6/35 healthy controls. Neither individual taxa nor the Dysbiosis Index was associated with symptom severity in the SARS-CoV-2 cohort.

Conclusions: Gut microbiota alterations after mild-to-moderate SARS-CoV-2 infection persisted through six months without resembling the microbiota seen in IBS, and were not associated with persistent fatigue or cognitive symptoms.

Corresponding author: birgitte.berentsen.jacobsen@helse-bergen.no

KEYWORDS COVID-19; SARS-CoV-2; gut microbiota; dysbiosis; long COVID; post-infectious IBS; disorders of gut-brain interaction; gut-brain axis; GA-map

Følsomhet Intern (gul)

BACKGROUND

SARS-CoV-2 infection is associated with gastrointestinal involvement (1). The virus infects intestinal epithelial cells via the angiotensin-converting enzyme 2 receptor (2). Faecal viral shedding occurs in ~ 41% of infected individuals, and acute gastrointestinal symptoms including diarrhoea, nausea, and abdominal pain affect approximately 12% of patients (3).

Persistent symptoms beyond the acute phase are common following SARS-CoV-2 infection. Fatigue and cognitive symptoms are among the most prevalent post-COVID sequelae, reported in approximately one in three and one in five survivors respectively, at twelve weeks or longer, based largely on hospitalised and mixed-severity cohorts (4). However, similar findings have also been demonstrated in non-hospitalised populations, where substantial long-term symptom burden persists even after mild infection (5, 6). Notably, these symptoms frequently co-occur with persistent gastrointestinal symptoms (1).

The intestinal microbiome is central to host immunity and systemic homeostasis, and its disruption after SARS-CoV-2 infection has been implicated in COVID-19 severity, recovery, and neuropsychiatric manifestations via the microbiota–gut–brain axis (7). Commensals such as *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and bifidobacteria are often depleted during infection and remain reduced for up to 30 days after viral clearance, and the degree of dysbiosis correlates with circulating inflammatory markers (8). Longitudinal studies in hospitalised cohorts further demonstrate that microbiota alterations may persist beyond six months and up to a year in patients with post COVID Condition (PCC) (9, 10). In these populations, gut dysbiosis correlates with overall symptom burden, and distinct microbial profiles have been linked to specific symptom clusters (9, 10). However, the persistence, clinical significance, and symptom associations of microbiota alterations following mild non-hospitalised SARS-CoV-2 infection remain incompletely characterised. Persistent gastrointestinal symptoms following SARS-CoV-2 infection may resemble disorders of gut-brain interaction, including irritable bowel syndrome (IBS) (11). Whether SARS-CoV-2 infection leads to a gut microbiota profile resembling IBS, and whether such alterations relate to persistent gastrointestinal, fatigue, and cognitive symptoms, remains unclear. In this study, we hypothesised that gut microbiota composition following mild SARS-CoV-2 infection would remain distinct from healthy controls over six months and would differ from moderate-to-severe IBS despite partially overlapping symptom profiles. To address this, we aimed to i) characterise gut microbiota trajectories and dysbiosis prevalence from acute infection through six months, with comparison to healthy controls and a moderate-to-severe IBS cohort, ii)

Følsomhet Intern (gul)

determine whether post-COVID microbiota composition resembles or differs from IBS at the taxonomic level, and iii) investigate associations between microbiota alterations and gastrointestinal symptoms (IBS-SSS), fatigue, and cognitive impairment (CFQ-11 subscales).

Methods

Study design and participants

This was a prospective observational cohort study of non-hospitalised patients with SARS-CoV-2 infection, with healthy controls and patients with IBS as cross-sectional reference groups. Patients who tested positive for SARS-CoV-2 by RT-PCR between January and April 2021 were recruited through Bergen Municipality Emergency Department, social media, and local television. According to national virological surveillance data during this period, the Alpha (B.1.1.7) variant of SARS-CoV-2 was the dominant circulating lineage, with sporadic detection of the Beta (B.1.351) variant (12). Eligible patients were in the acute phase of infection and isolating either at the designated quarantine facility (Corona Hotel) or at home. Patients requiring hospitalisation were excluded. Recruitment only included 32 assessed for eligibility because the Bergen Accident and Emergency Department, the main recruitment site, was overwhelmed by mass testing during the Alpha wave (January to April 2021). No formal sample size calculation was performed for the present analyses. As reference groups, healthy controls with no gastrointestinal symptoms or known disease, and patients with moderate-to-severe IBS (IBS-SSS >175) fulfilling Rome IV criteria, were drawn from the Bergen Brain-Gut cohort, as described elsewhere (13, 14). Data were collected between May 2019 and December 2021 at Haukeland University Hospital using identical questionnaires and the GA-map® Dysbiosis Test. Both reference groups self-reported to be SARS-CoV-2 negative without formal testing. Community transmission in Norway was low throughout this period, and testing was free, widely available, and recommended for anyone with respiratory symptoms. Undetected prior infection was unlikely, as pre-vaccination seroprevalence in Norway was 0.9% nationally and 1.4% in Vestland county, where the study was conducted, closely matching the cumulative incidence of virologically detected cases and indicating that free, symptom-triggered testing captured most infections (15).

Ethics approval and consent to participate

Følsomhet Intern (gul)

All participants provided written informed consent. The SARS-CoV-2 study (REK 187554) and the Bergen Brain-Gut study (REK 2015-01621) was approved by the Regional Committee for Medical and Health Research Ethics.

Questionnaires

Visual analogue scale and initial gastrointestinal complaints

Upon initial SARS-CoV-2 infection patients scored their general condition according to a standardised visual analogue scale (VAS) from 1-10 where 1 = noticed nothing, 3 = mild symptoms, 5 = noticed symptoms in the nose and throat, sore throat, 7 = became ill with a high fever and sore throat and lungs, cough, 10 = became seriously ill/hospitalised. Patients reported whether they suffered nausea, abdominal pain, vomiting or diarrhoea (yes/no).

IBS symptom severity scale

To identify gastrointestinal IBS-like symptoms, patients completed the questionnaire irritable bowel syndrome symptom severity scale (IBS-SSS) 0-500 where <75 remission, 75-175 mild, 176-300 moderate, and > 300 severe cases. A reduction of 50 points indicate improvement of the patient's symptoms (16).

Chalder fatigue scale

The Chalder Fatigue Scale (CFQ-11) is a validated 11-item self-rated instrument measuring physical and mental fatigue (17, 18). Each item is scored 0 to 3 on a Likert scale, and bimodal scoring (0,0,1,1) yields a global fatigue score of 0 to 11, with a score of 4 or higher defining a fatigue case. Its validated two-factor structure comprises a physical fatigue subscale (items Q1 to Q7, range 0 to 21) and a mental fatigue subscale (items Q8 to Q11, range 0 to 12), used here as the primary fatigue outcomes. For comparability with prior Bergen non-hospitalised post-COVID cohorts (5, 6), we additionally derived a combined cognitive-symptom measure from items Q8 (concentration) and Q11 (memory). Patients were classified as having cognitive symptoms if either item scored ≥2 ("more than usual"), and the Q8+Q11 sum was retained as a secondary continuous cognitive-symptom score.

Faecal sampling and analysis

Participants were provided with sampling kits for home collection (GA-map® Sample Collection Kit, Genetic Analysis AS, Oslo, Norway) with written instructions. Faecal samples

Følsomhet Intern (gul)

were collected at baseline, within a few days of the positive test, and at approximately four weeks and six months, frozen immediately at −20°C, and retrieved by research personnel. Questionnaires were completed on the same day as sample collection at all time points. SARS-CoV-2 RNA was extracted and analysed using RT-PCR. Faecal bacterial composition was assessed using the GA-map® Dysbiosis Test (Genetic Analysis AS, Oslo, Norway), a validated CE-marked assay targeting 48 bacterial markers across major taxonomic levels using 16S ribosomal RNA gene amplification (variable regions V3–V9) followed by DNA probe hybridisation on the Luminex® 200 platform. The test provides normalised signal intensities representing semi-quantitative bacterial abundance and generates a Dysbiosis Index on a five-point scale, where Dysbiosis Index 1–2 indicates normobiosis and Dysbiosis Index 3–5 indicates clinically significant dysbiosis (19). Bacterial nomenclature was updated to current taxonomic classifications, including reclassification of *Eubacterium biforme* to *Holdemanella biformis* and *Eubacterium hallii* to *Anaerobutyricum hallii*. Two bacterial markers (*Coprobacillus cateniformis* and *Acinetobacter junii*) were below the detection threshold across all COVID-19 samples and were excluded from all analyses. After exclusions, 46 bacterial taxa were included. For comparative microbiota analyses, healthy controls (HC n=36) and patients with moderate-to-severe IBS (IBS-SSS >175, n=58) from the Bergen Brain-Gut cohort were included as reference groups. Their GA-map Dysbiosis Test data have been reported previously (14).

Statistical analysis

Analyses were performed in R 4.4.1 using packages vegan, lme4, and lmerTest, with $p<0.05$ considered significant. IBS-SSS was compared across groups using a Kruskal-Wallis test followed by pairwise Wilcoxon rank-sum post-hoc tests within pre-specified families (SARS-CoV-2 time points versus HC and versus IBS), with Bonferroni correction. The physical and mental fatigue subscales and the combined cognitive-symptom score (Q8+Q11 sum) were compared by pairwise Wilcoxon rank-sum tests within the same families, with Benjamini-Hochberg (BH) false discovery rate (FDR) correction. Within-COVID longitudinal change in the fatigue subscales was assessed on the complete-case subset by the Friedman test. Baseline characteristics were compared by Kruskal-Wallis tests for continuous variables and Fisher's exact tests for categorical variables. VAS scores, gastrointestinal symptom frequencies, faecal SARS-CoV-2 RNA detection, and the cognitive-symptom and fatigue-caseness prevalences are reported descriptively. For microbiota analyses, BH-FDR correction was applied across the 46 taxa within each comparison. Alpha diversity was compared using Kruskal-Wallis tests

Følsomhet Intern (gul)

with pairwise Wilcoxon post-hoc tests. Beta diversity was assessed on Bray-Curtis dissimilarities by PERMANOVA (adonis2, 999 permutations under a fixed seed), with BH-FDR correction. Dysbiosis prevalence was compared by Fisher's exact test, with BH-FDR correction within two pre-specified families (SARS-CoV-2 time points versus HC and versus IBS), with Wilson 95% confidence intervals for group prevalences. Differential abundance was tested by Wilcoxon rank-sum at each timepoint, and taxa were classified as persistently altered when FDR<0.05 at all three time points. Longitudinal within-patient change in log-abundance was modelled by linear mixed-effects models with a per-participant random intercept and a linear trend across time points, using Satterthwaite degrees of freedom, with a sensitivity analysis adding age and sex. Spearman rank correlations related the Dysbiosis Index and individual taxa to clinical outcomes, BH-FDR-corrected within each timepoint and symptom-variable family.

Use of Artificial Intelligence

The authors used Claude (Anthropic) to assist with manuscript preparation, including literature searching, reference verification, and editing for clarity and consistency. Claude was also used to assist in the development and debugging of R code for statistical analyses and data visualisation. All scientific content, data interpretation, conclusions, and analytical decisions were generated, verified, and approved by the authors. The AI assistant did not contribute to study design, data collection, or intellectual content.

Results

Study population and follow-up

Of 32 patients with SARS-CoV-2 assessed for eligibility, one was excluded after hospital admission and 31 were enrolled, as shown in the study flow chart (**Supplementary Figure S1**). The cohort was 61% female with a mean age of 39 ± 11 years. Reference groups comprised 36 healthy controls (67% female, mean age 36 ± 13 years) and 58 patients with moderate to severe IBS (79% female, mean age 38 ± 11 years). Demographic and clinical cohort details are listed in **Supplementary Table S1.**

Disease severity, gastrointestinal symptoms and faecal viral shedding

At the time of acute SARS-CoV-2 infection, patients reported moderate impairment in general health (VAS general condition mean 4.8 ± 1.8, n=24; **Figure 1A**). Acute gastrointestinal

Følsomhet Intern (gul)

symptoms were reported by 9 of 24 patients (38%) during acute infection. The most frequently reported symptom was diarrhoea (7/23, 30.4%), followed by nausea (4/23, 17.4%) and abdominal pain (2/20, 10.0%), while no patients reported vomiting (**Figure 1B**). Faecal SARS-CoV-2 RNA was detected in 19/26 patients (73.1%) at baseline, declining to 2/27 (7.4%) at four weeks and reaching complete clearance by six months (**Figure 1C**).

- *Insert Figure 1* -

Persistent microbiota divergence from healthy controls and distinction from IBS

To assess whether SARS-CoV-2 infection altered overall gut microbiota composition and whether this persisted over time, we compared beta diversity across SARS-CoV-2 patients at baseline (n=28), four weeks (n=29), and six months (n=26) post-infection with healthy controls (n=36), and patients with IBS (n=58) as a reference group (**Table 1**). Overall gut microbiota composition differed significantly across groups (PERMANOVA R^2=0.053, p=0.001). SARS-CoV-2 patients showed significant separation from healthy controls at baseline (R^2=0.030, adj. p=0.048), four weeks (R^2=0.042, adj. p=0.005) and six months (R^2=0.050, adj. p=0.007) (**Figure 2A**). Notably, microbiota composition within the SARS-CoV-2 cohort was stable from acute infection through six months (R^2=0.013, p=0.397). SARS-CoV-2 patients also differed from IBS patients at all three time points (baseline R^2=0.028, adj. p=0.011; four weeks R^2=0.047, adj. p=0.004; six months R^2=0.048, adj. p=0.004; **Figure 2B-D**), whereas IBS and healthy controls did not differ (R^2=0.017, adj. p=0.093; **Figure 2E**). Moreover, within the predefined panel, alpha diversity did not differ significantly across groups (Kruskal-Wallis, Shannon: p=0.443; Observed Richness: p=0.066; Evenness: p=0.498, **Supplementary Figure S2** and **Supplementary Table S2**).

- *Insert Figure 2* -

Table 1. PERMANOVA beta diversity across cohorts and timepoints

Comparison	R^2	F	*p*	Adj. *p*
All groups	0.053	2.429	0.001	-
COVID timepoints only	0.013	1.033	0.397	-
COVID BL vs HC	0.030	1.935	0.041	**0.048**
COVID 4W vs HC	0.042	2.784	0.002	**0.005**
COVID 6M vs HC	0.050	3.166	0.004	**0.007**
IBS vs HC	0.017	1.626	0.093	0.093

Følsomhet Intern (gul)

COVID BL vs IBS	0.028	2.401	0.008	**0.011**
COVID 4W vs IBS	0.047	4.234	0.001	**0.004**
COVID 6M vs IBS	0.048	4.121	0.001	**0.004**

Bray-Curtis dissimilarities, adonis2, 999 permutations, fixed seed. Adjusted p-values are Benjamini-Hochberg FDR across the seven pairwise contrasts. Bold indicates p<0.05 after adjustment. BL: baseline. HC: healthy controls

Dysbiosis prevalence and individual trajectories

Clinically significant dysbiosis (DI ≥3) was present in 8/28 (28.6%) of SARS-CoV-2 patients at baseline, 3/29 (10.3%) at four weeks, and 7/26 (26.9%) at six months, compared with 2/36 (5.6%) in healthy controls. Prevalence was higher than in healthy controls at baseline (OR=6.60, adjusted p=0.042) and at six months (OR=6.08, adjusted p=0.042), but not at four weeks (OR=1.94, adjusted p=0.649). Prevalence in SARS-CoV-2 patients did not differ from that in moderate-to-severe IBS at any time point (15/58, 25.9%, all adj. p>0.4). IBS patients had a higher prevalence than healthy controls (OR=5.84, p=0.014) (**Figure 3**, **Supplementary Table S3**). Among the 23 SARS-CoV-2 patients with samples at all three time points, six were dysbiotic at baseline, and individual trajectories were heterogeneous. All six had transitioned to normobiosis by six months, while six previously normobiotic patients developed dysbiosis at six months. No patient was dysbiotic at all three time points. Thus, the stable group-level prevalence at six months was sustained by patients newly entering the dysbiotic category rather than by persistent cases.

- *Insert Figure 3* -

Differential abundance

To identify which taxa were altered following SARS-CoV-2 infection, we compared 46 GA-map taxa between SARS-CoV-2 patients and each reference group at every time point using Wilcoxon rank-sum tests, with Benjamini-Hochberg correction applied across the 46 taxa within each comparison. Five taxa were significantly altered (FDR<0.05) at all three time points relative to both healthy controls and IBS, in the same direction against each (**Table 2**). Proteobacteria, *Ruminococcus gnavus*, *Bacteroides stercoris* and *Eubacterium rectale* were depleted, while *Shigella* spp. & *Escherichia* spp. were elevated. *Holdemanella biformis* was elevated relative to healthy controls at all three time points and relative to IBS at six months. Five taxa differed from IBS at all three time points, with *Bacteroides fragilis*, *Streptococcus* spp. and *Streptococcus salivarius* ssp. *thermophilus* & *S. sanguinis* depleted and Clostridia

Følsomhet Intern (gul)

elevated. For *Lactobacillus ruminis & Pediococcus acidilactici* the median abundance did not differ between groups, thus, no direction is reported. The number of taxa altered at FDR<0.05 was 8, 16 and 11 against healthy controls and 12, 19 and 18 against IBS, at baseline, four weeks and six months respectively. Actinobacteria and Bacilli were elevated relative to healthy controls at four weeks and six months but not at baseline. No taxon differed between IBS and healthy controls after correction. Full results for all 46 taxa are provided in **Supplementary Table S4.**

Table 2. Bacterial taxa altered at all three time points following SARS-CoV-2 infection, compared with healthy controls and IBS

Taxon	Direction	HC BL	HC 4W	HC 6M	IBS BL	IBS 4W	IBS 6M
Altered versus both reference groups							
Proteobacteria	depleted	<0.001	<0.001	0.001	<0.001	<0.001	<0.001
Ruminococcus gnavus	depleted	0.038	<0.001	<0.001	0.002	<0.001	<0.001
Bacteroides stercoris	depleted	0.006	0.003	0.002	0.001	<0.001	<0.001
Eubacterium rectale	depleted	0.006	0.020	0.031	0.001	0.006	0.008
Shigella spp. & Escherichia spp.	elevated	0.003	0.002	0.002	0.002	0.001	0.002
Altered versus healthy controls							
Holdemanella biformis	elevated	0.027	0.034	0.015	ns	ns	0.044
Altered versus IBS							
Streptococcus spp.	#	0.003	0.006	ns	<0.001	<0.001	0.039
Bacteroides fragilis	depleted	ns	0.003	ns	0.008	<0.001	0.011
Streptococcus salivarius ssp. thermophilus & S. sanguinis	depleted	ns	0.012	ns	0.017	<0.001	0.020
Clostridia	elevated	ns	0.022	ns	0.037	0.006	0.020
Lactobacillus ruminis & Pediococcus acidilactici	¤	ns	0.034	0.049	0.032	0.017	0.023

Benjamini-Hochberg adjusted p-values from Wilcoxon rank-sum tests. Complete list of results see **Supplementary Table S4**. # Streptococcus spp. was depleted relative to IBS but had same median as HC. ¤ *Lactobacillus ruminis & Pediococcus acidilactici* had same median in every comparison. Ns, not significant after correction. BL, baseline. HC, healthy controls.

To characterise within-patient change in bacterial abundance over follow-up, linear mixed-effects models were fitted to all 46 taxa across the SARS-CoV-2 cohort. Actinobacteria and *Bifidobacterium* spp. increased over follow-up (both FDR=0.002), and both effects strengthened after adjustment for age and sex (both FDR<0.001; **Supplementary Table S5**). Most of the increase was already present at four weeks and was maintained at six months, rather than being transient. No other taxon survived FDR correction, and overall community composition within the cohort was unchanged across time points (PERMANOVA p=0.397), indicating that the change was confined to these taxa rather than reflecting a shift in the community as a whole. Neither taxon differed from healthy controls at acute infection. *Bifidobacterium* spp. did not differ from healthy controls at any time point, whereas Actinobacteria abundance was higher than in healthy controls at four weeks and six months

Følsomhet Intern (gul)

(FDR=0.040 and FDR=0.033). By six months both exceeded IBS levels (both FDR<0.001; **Supplementary Table S4**).

Gastrointestinal, mental and physical fatigues symptoms

Median IBS symptom severity (IBS-SSS) in the SARS-CoV-2 cohort was 62 at baseline, decreasing to 50 at four weeks and 36 at six months, compared with 29 in healthy controls and 258 in the IBS cohort (**Supplementary Figure S3** and **Supplementary Table S6).** Compared with healthy controls, IBS-SSS was higher at baseline ($p = 0.036$), but did not differ at four weeks ($p = 0.051$) or six months ($p = 1.00$). In contrast, IBS cohort exhibited significantly higher IBS-SSS scores than SARS-CoV-2 at all time points (all adjusted $p < 0.001$). At six months, 8 of 25 patients with SARS-CoV-2 (32%) had IBS-SSS scores exceeding the threshold for mild IBS, indicating that a clinically meaningful minority presented persistent IBS-like symptoms despite the overall low cohort median.

Symptoms of physical and mental fatigue followed distinct trajectories in patients with SARS-CoV-2 (**Supplementary Figure S4**, **Supplementary Table S7**). Physical fatigue (Q1–Q7) was higher than in healthy controls at baseline (median 12 vs 7; FDR p<0.001), four weeks (median 11; FDR p<0.001) and six months (median 9; FDR p=0.007). It did not differ from IBS at baseline (FDR p=0.50) or four weeks (FDR p=0.17) but was lower than IBS by six months (FDR p=0.006). The within-patient change across time points was not significant (Friedman p=0.10, n=23). In contrast, mental fatigue (Q8–Q11) remained stable. Scores were consistently higher than in healthy controls (medians 5, 5 and 5 vs 4; FDR p=0.006–0.008) and did not differ from IBS at any time point (median 6; all FDR p=0.23), with no within-cohort change over follow-up (Friedman p=0.28, n=24). The combined cognitive-symptom construct (Q8 or Q11 ≥2), retained for comparability with prior Bergen non-hospitalised post-COVID cohorts (5, 6) was present in 13/26 (50%) SARS-CoV-2 patients at six months. Corresponding prevalences were 6/35 (17.1%) in healthy controls and 40/56 (71.4%) in IBS patients (**Supplementary Figure S4C**), placing the SARS-CoV-2 group between the two reference groups.

Symptom correlations

To examine whether the observed microbiota changes were associated with the persistent symptoms experienced by SARS-CoV-2 patients, we performed a Spearman correlation analysis between bacterial taxa and symptom scores in all three cohorts. No taxon-symptom association survived correction in the SARS-CoV-2 cohort, and healthy controls showed the

Følsomhet Intern (gul)

same pattern. In the IBS reference cohort, a single association survived correction, *Ruminococcus gnavus* with the Cognitive symptoms score (rho +0.44, n=56, FDR p=0.029**,** **Supplementary Table S8**), which persisted after adjustment for age and sex. The GA-map Dysbiosis Index was not associated with any symptom score in any cohort at any time point (**Supplementary Table S9**).

Discussion

This prospective study followed gut microbiota composition alongside self-reported gastrointestinal symptoms, fatigue, and cognitive symptoms in non-hospitalised patients with mild-to-moderate SARS-CoV-2 infection from acute illness through six months, with comparison to healthy controls and patients with moderate-to-severe IBS. Four principal findings emerged. First, the gut microbiota of SARS-CoV-2 patients remained compositionally distinct from both healthy controls and IBS throughout follow-up. Second, global microbiota composition did not change across follow-up, and the only within-patient changes at taxon level were increases in Actinobacteria and *Bifidobacterium spp.* Third, gastrointestinal symptoms largely resolved, whereas fatigue and cognitive symptoms persisted, with mental fatigue remaining at IBS levels, and half of patients reporting cognitive symptoms at six months. Fourth, no association was detected between individual taxa or the Dysbiosis Index and gastrointestinal symptoms, fatigue, or cognitive symptoms in the SARS-CoV-2 cohort.

Persistent microbiota alteration after mild to moderate SARS-CoV-2 infection

Beta diversity separated SARS-CoV-2 patients from both healthy controls and IBS at all three time points, whereas alpha diversity remained unchanged. Thus, mild-to-moderate infection was associated with a persistent alteration in microbial composition rather than a loss of overall diversity. Similar long-term alterations have been reported in COVID-19 and PCC cohorts, where deviations may persist for at least six months post-recovery (9, 10, 20-22). Reduced alpha diversity, frequently reported in severe and hospitalised populations, was absent in our cohort, perhaps reflecting a milder disease course (23, 24). However, unchanged Shannon diversity has also been reported in sequencing-based cohorts from both non-hospitalised and hospitalised cohorts spanning a range of disease severities (8, 20, 25), highlighting heterogeneity across reports.

Følsomhet Intern (gul)

The longitudinal within-patient modelling identified sustained increases in Actinobacteria and *Bifidobacterium spp.* (both FDR = 0.002), that persisted throughout follow-up. These are unlikely to represent recovery from an infection-related depletion, since neither was reduced relative to healthy controls during acute infection. Actinobacteria is one of the major phyla of the human gut, and *Bifidobacterium* is among the best-characterised beneficial commensal genera (26). By six months, Actinobacteria abundance was higher than in healthy controls, and both taxa were higher than in IBS. This difference may be explained by the reduced levels often reported in IBS (27, 28). However, whether these increases reflect a compensatory ecological response, changes in health behaviour during recovery, or pre-existing inter-individual variation cannot be determined in the absence of pre-infection samples.

Similar dysbiosis prevalence, different bacterial composition

A notable finding was the consistent separation between SARS-CoV-2 patients and IBS across all time points (adjusted p=0.011, 0.004 and 0.004), despite comparable Dysbiosis Index prevalence. At baseline, approximately one-quarter of participants in both cohorts were classified as dysbiotic, but the overall microbial beta diversity differed significantly. Thus, similar dysbiosis prevalence reflected a comparable proportion of individuals falling outside the normative reference range rather than convergence toward a shared microbiota profile. Dysbiosis status was also dynamic, with transitions between normobiosis and dysbiosis over time and no participant remaining dysbiotic throughout follow-up. This pattern suggests instability, consistent with previous reports of long-lasting microbiota instability after mild SARS-CoV-2 infection (21).

The distinction was evident at the taxonomic level. Five taxa separated SARS-CoV-2 patients from both healthy controls and IBS at every time point, with *Eubacterium rectale*, *Bacteroides stercoris*, *Ruminococcus gnavus* and Proteobacteria depleted and *Shigella* spp. & *Escherichia* spp. elevated. Three of the five findings replicated the post-COVID follow-up literature. *Eubacterium rectale* depletion is among the most reproducible post-COVID findings, persisting after viral clearance (8) and correlating inversely with post-acute symptoms at six months (9). *Escherichia/Shigella* enrichment has been reported in mild non-hospitalised infection (29) and *Bacteroides stercoris* depletion has been reported after 6 months in a study of non-hospitalised young individuals (30). The remaining findings diverged from the dominant pattern reported in the literature. *Ruminococcus gnavus* is consistently reported as enriched, including in predominantly mild cohorts followed for six

Følsomhet Intern (gul)

months or longer (8, 9, 31). However, its ecological role does appear to vary with severity, being positively correlated with co-resident microbes in severe disease and negatively correlated in non-severe disease (32). Proteobacteria enrichment is likewise widely reported (25) and linked to severe disease (33). However, findings after mild community-managed infection are less consistent, and the Proteobacteria *Escherichia coli* and *Klebsiella pneumoniae* were recently reported to be more abundant in never-infected controls than three months after mild infection (20). Three further taxa separated SARS-CoV-2 patients from IBS at all three time points, but not from healthy controls. These included depleted *Bacteroides fragilis* and *Streptococcus salivarius ssp. thermophilus & S. sanguinis*, and elevated Clostridia. Given the substantial heterogeneity of microbiota findings in IBS (27), interpretation should be cautious. Thus, our IBS cohort did not separate from healthy controls. This finding is not surprising given that the difference between IBS and healthy controls is small even in large pooled analyses, and several individual cohorts find none (34). However, the observation that several taxa consistently distinguished SARS-CoV-2 from IBS despite comparable dysbiosis prevalence, supports the conclusion that post-COVID dysbiosis does not converge toward an IBS-like microbiota profile.

Symptoms and microbiota appeared largely uncoupled

The gastrointestinal symptom burden was modest and declined over time, with only a minority of patients remaining within the IBS range at six months. In contrast, fatigue and cognitive symptoms persisted. Mental fatigue remained elevated at levels comparable to IBS throughout follow-up, and approximately half of patients reported cognitive symptoms at six months. This pattern is consistent with reports from post-COVID cohorts and previous Norwegian studies of non-hospitalised infection, in which fatigue and cognitive symptoms are among the most common and enduring sequelae (1, 4-6). However, despite these persistent symptoms, neither overall dysbiosis nor individual bacterial taxa were associated with symptom severity. This is consistent with findings from both community-based, hospital-based, and outpatient cohorts showing little or no association between gut microbiota composition and symptom duration, recovery, diarrhoea, or persistent symptoms following SARS-CoV-2 infection (21, 25, 35). It contrasts with studies linking microbiota alterations to PCC symptom burden and specific symptom clusters, including one large cohort reporting that the gut microbiome explained 12.7% of variation in post-acute COVID symptoms and accurately predicted symptoms such as fatigue and difficulty concentrating (9, 10, 30, 31). The absence of significant associations should be interpreted cautiously given the modest

Følsomhet Intern (gul)

sample size and restricted taxonomic panel, and the strict correction for multiple testing applied here. Taken together, our observations suggest that persistent symptoms may be driven by mechanisms not captured by taxonomic composition alone, such as immune dysregulation, epithelial dysfunction, altered host metabolism, or other disturbances within the gut-brain axis (1, 24).

Clinical implications

Disorders of gut-brain interaction (DGBI) have become more prevalent since the pandemic (36) and persistent gastrointestinal symptoms affect around 10% of COVID-19 survivors (37). Gut dysfunction after SARS-CoV-2 infection may present much like IBS. However, our data suggest that this clinical resemblance is not mirrored at the level of microbiota composition. Thus, our results support the notion that post-COVID gastrointestinal symptoms may represent a form of post-infectious DGBI that resembles IBS clinically while remaining biologically distinct. Consequently, microbiome-targeted therapies developed for IBS should not be assumed to address the processes underlying post-COVID gut dysfunction (11).

Strengths and limitations

This study has several strengths. It is prospective, following non-hospitalised patients from acute infection through six months, a design repeatedly identified as missing from a literature dominated by cross-sectional studies, and/or hospitalised patients (38). It sets the SARS-CoV-2 cohort against both healthy controls and an IBS reference group, and it applies a validated, standardised assay identically across all three cohorts (19). Several limitations should be considered. The cohort was small, and the symptom-microbiota analyses could detect correlations of rho 0.53 or stronger at six months. Pre-infection samples were not available, so it cannot be determined whether the compositional alterations were caused by the infection or predated it. The reference groups were sampled once, which precludes group-by-time modelling. Dietary data were not collected. GA-map measures a fixed panel of predefined probes, so diversity indices are bounded and less sensitive to community-wide diversity loss than sequencing (19). The cohort was infected with the Alpha variant before vaccination, thus, the findings may not apply to later variants or vaccinated populations.

Conclusions

Mild-to-moderate non-hospitalised SARS-CoV-2 infection was associated with a persistent alteration in gut microbiota composition that remained detectable for six months and differed

Følsomhet Intern (gul)

from both healthy controls and a moderate-to-severe IBS reference cohort. Although clinically significant dysbiosis occurred at a prevalence comparable to IBS, the underlying bacterial abundance remained distinct. Dysbiosis status changed over time within individuals, and no participant remained dysbiotic throughout follow-up. Fatigue and cognitive symptoms persisted after gastrointestinal symptoms had largely resolved and were not associated with the Dysbiosis Index or individual bacterial taxa. Together, these findings suggest that post-COVID gut dysbiosis represents a distinct microbial state rather than an IBS-like microbiota phenotype.

Competing interests

Genetic Analysis AS, the manufacturer of the GA-map® Dysbiosis Test used in this study, provided in-kind support by performing the faecal sample analyses at no cost and supplying the sample-collection materials, and funded a part-time (50%) research position for six months. Genetic Analysis AS performed the GA-map laboratory analysis but had no role in study design, statistical analysis, data interpretation, or the decision to publish. The authors declare no other competing interests.

Author contributions

BB: Conceptualization, Funding Acquisition, Project Administration, Methodology, Formal analysis, Writing – original draft. EMRH: Project Administration, Investigation, Data curation, Writing – review & editing. IB: Data curation, Investigation, Writing – review & editing, AJL: Supervision, Writing – review & editing. RJC: Resources, Supervision, Funding acquisition, Writing – review & editing. NL: Resources, Supervision, Funding acquisition, Writing – review & editing.

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Følsomhet Intern (gul)

Availability of data and materials

Data are available from the corresponding author upon reasonable request.

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Abbreviations

BH — Benjamini-Hochberg
CFQ-11 — Chalder Fatigue Questionnaire
COVID-19 — coronavirus disease 2019
FDR — false discovery rate
HC — healthy controls
IBS — irritable bowel syndrome
IBS-SSS — Irritable Bowel Syndrome Symptom Severity Scale
IQR — interquartile range
OR — odds ratio
PCC – Post COVID Condition
PCR / RT-PCR — polymerase chain reaction / reverse transcription PCR
PERMANOVA — permutational multivariate analysis of variance
REK — Regional Committee for Medical and Health Research Ethics (Norway)
RNA — ribonucleic acid
SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2
SD — standard deviation
VAS — visual analogue scale

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Følsomhet Intern (gul)

Figures

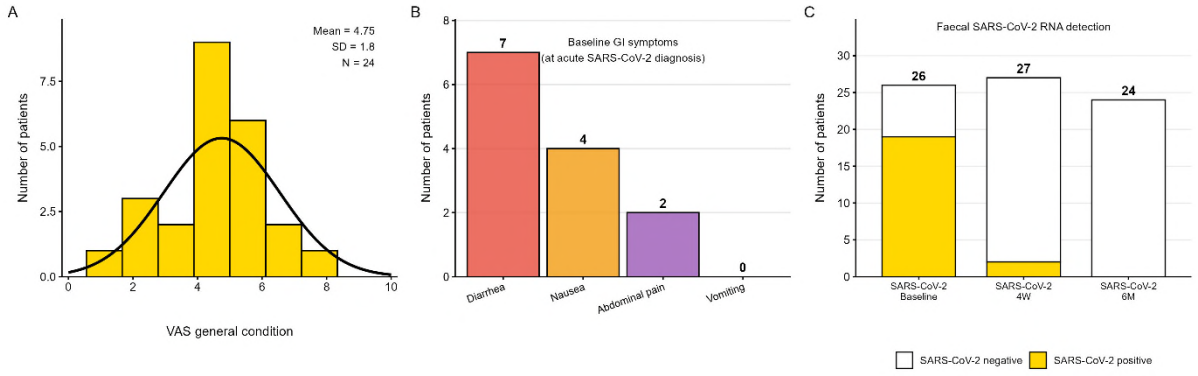


Figure 1. Clinical outcomes and faecal viral shedding in SARS-CoV-2 patients. A) General health status at acute infection. Visual analogue scale (VAS) scores for general condition at acute SARS-CoV-2 diagnosis (n=24). The histogram shows the distribution of patient-reported health status on a scale from 1 to 10, where 1 is noticed nothing and 10 is became seriously ill or hospitalised. The black curve is a fitted normal distribution. Mean 4.8 ± 1.8, observed range 1 to 8. **B)** Gastrointestinal symptoms at acute infection. Number of patients reporting each symptom at acute diagnosis. Diarrhoea was most common (7/23, 30.4%), followed by nausea (4/23, 17.4%) and abdominal pain (2/20, 10.0%), with no patient reporting vomiting (0/24). At least one gastrointestinal symptom was reported by 9 of 24 patients (37.5%). Denominators vary by item because completion was incomplete, and only 18 patients answered all four items, so the composite is a lower bound. **C)** Faecal SARS-CoV-2 RNA detection over time. Stacked bars show patients with positive (yellow) or negative (white) faecal RT-PCR results at acute infection (n=26), four weeks (n=27) and six months (n=24). Numbers above the bars give the total tested at each time point. Faecal viral RNA was detected in 19/26 patients (73.1%) at acute infection, declining to 2/27 (7.4%) at four weeks, with complete clearance by six months (0/24). VAS: visual analogue scale, GI: gastrointestinal. RT-PCR: reverse transcription polymerase chain reaction. SD: standard deviation.

Følsomhet Intern (gul)

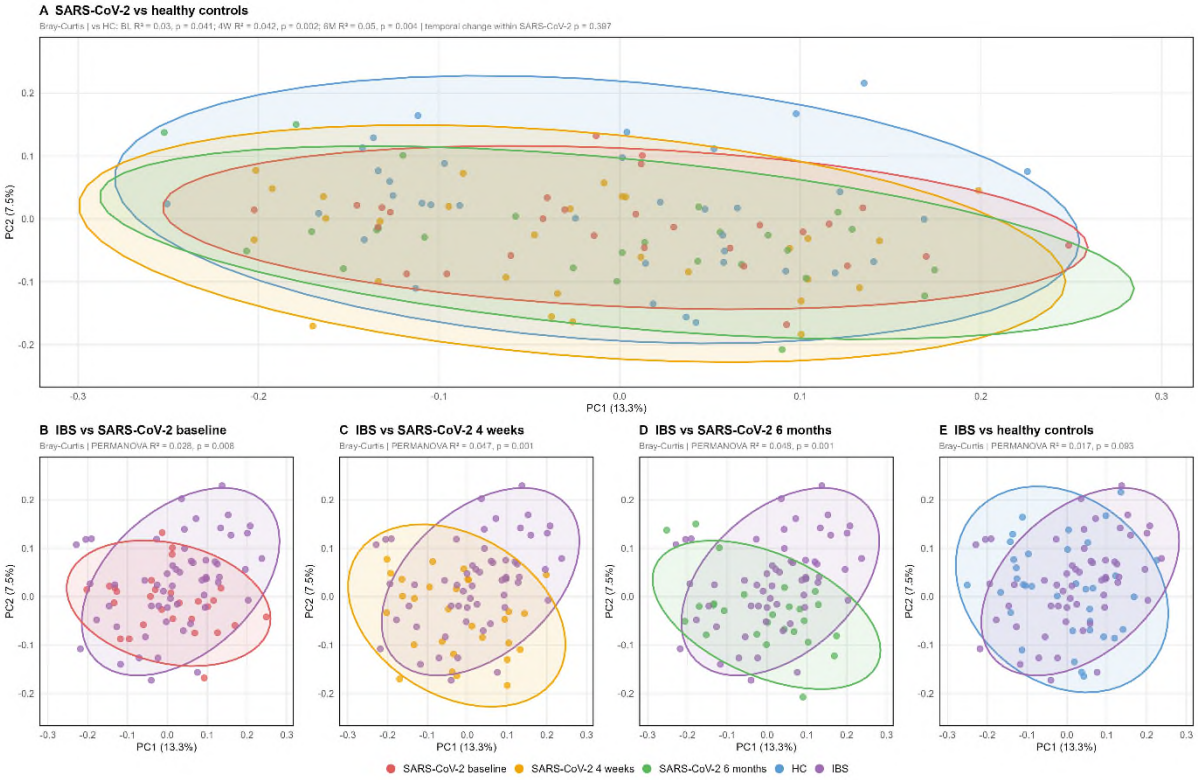


Figure 2. Gut microbiota beta diversity in SARS-CoV-2 patients, healthy controls and IBS patients. Beta diversity assessed by PCoA of Bray-Curtis dissimilarities across the 46 bacterial markers included in the cross-cohort panel. **A)** SARS-CoV-2 patients at acute infection, four weeks and six months compared with healthy controls. **B–D)** SARS-CoV-2 patients at each time point compared with IBS. **E)** IBS compared with healthy controls. Each point is one sample, and ellipses enclose 95 percent of the fitted multivariate t distribution for each group. Between-group differences were tested by PERMANOVA on Bray-Curtis dissimilarities with 999 permutations under a fixed random seed, with results shown above each panel and full statistics in **Table 1**. Axis percentages are the proportion of variation represented by each coordinate, calculated from the eigenvalues. HC: healthy controls. PCoA: principal coordinate analysis. PERMANOVA, permutational multivariate analysis of variance, IBS: irritable bowel syndrome.

Følsomhet Intern (gul)

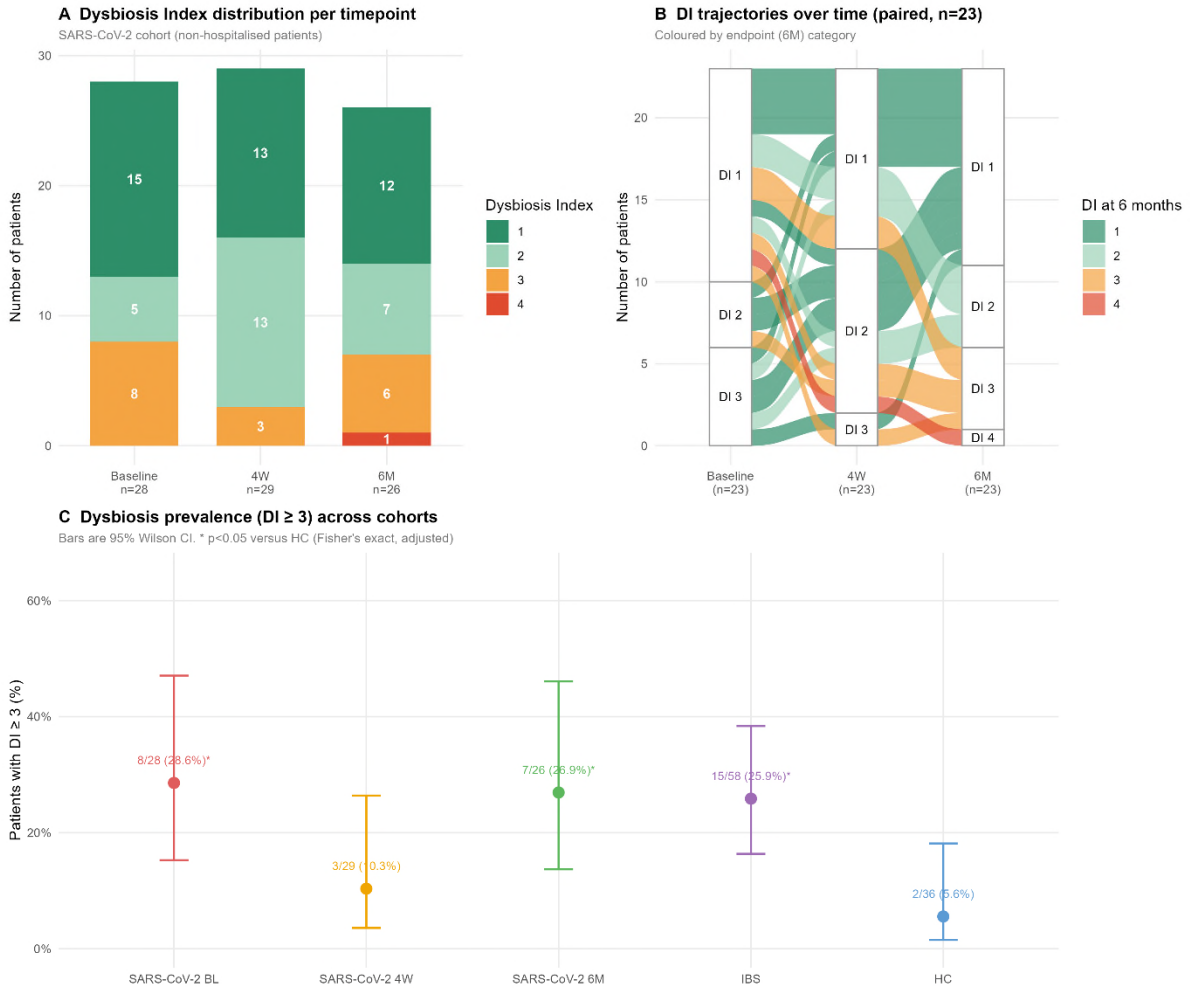


Figure 3. Gut microbiota dysbiosis in SARS-CoV-2 infection compared with IBS and healthy controls. A) Distribution of the GA-map® Dysbiosis Index (DI) at baseline (n=28), four weeks (n=29), and six months (n=26) after SARS-CoV-2 diagnosis. The DI ranges from 1 to 5, where 1 to 2 indicates normobiosis and 3 to 5 clinically significant dysbiosis. Only categories 1 to 4 were observed in this cohort. Numbers within bars are patient counts per DI category. **B)** Individual DI trajectories in the paired subset (n=23) with samples at all three time points. Flow colour reflects the DI category at six months. Three patients lacked a baseline sample and are not shown, one of whom was dysbiotic at six months, which is why panel B shows six dysbiotic patients at six months and panel A shows seven. **C)** Prevalence of dysbiosis (DI ≥ 3) across cohorts. Points are prevalence estimates and bars are 95% Wilson confidence intervals. Dysbiosis was more prevalent in SARS-CoV-2 patients than in healthy controls at baseline (adj. p=0.042) and at six months (adj. p=0.042), but not at four weeks (adj. p=0.649). IBS patients also had a higher prevalence than healthy controls (p=0.014). No SARS-CoV-2 time point differed from IBS. Fisher's exact test with Benjamini-Hochberg adjustment within pre-specified families. Asterisks mark p<0.05 versus healthy controls after adjustment. HC, healthy controls (BrainGut cohort, n=36). IBS, BrainGut cohort (n=58).

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