Gut microbial metabolites and transit stratify novel irritable bowel syndrome clusters

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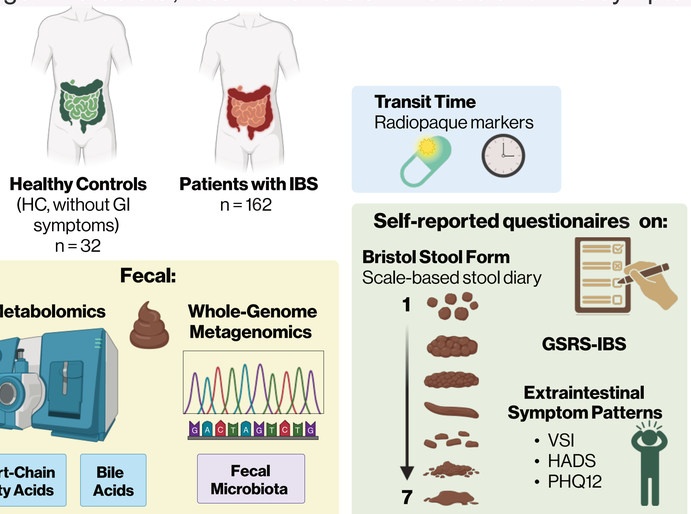
Introduction

Irritable bowel syndrome (IBS) is a common disorder rooted in a disruption of the gut-brain-axis, characterized by abdominal pain and altered bowel habits. Altered gut microbiota is reported in IBS[1], with microbially produced metabolites, including bile acids (**BA**) and short-chain fatty acids (**SCFA**), recognized to potentially be involved in the generation of IBS symptoms[2]. Our study aims to clarify the link between the gut microbiota, fecal BA and SCFA levels and IBS symptoms.



VSI Visceral Sensitivity Index
HADS Hospital Anxiety and Depression Scale
PHQ12 Patient Health Questionnaire-12
GSRS-IBS Gastrointestinal Symptom Rating Scale - Irritable Bowel Syndrome
BSF Bristol Stool Form Scale
BA Bile Acids
SCFA Short-Chain Fatty Acids

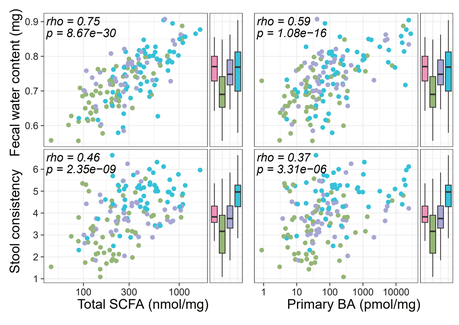


Figure 1. BAs and SCFAs are associated with stool consistency in IBS. Spearman correlations and scatter plots between BAs and SCFAs, and metrics of stool consistency in individuals with IBS.

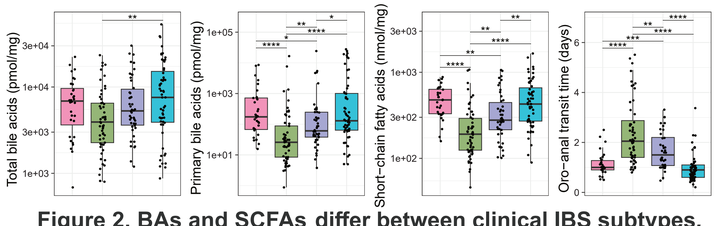


Figure 2. BAs and SCFAs differ between clinical IBS subtypes. Boxplots of BAs, SCFAs, and oro-anal transit time.

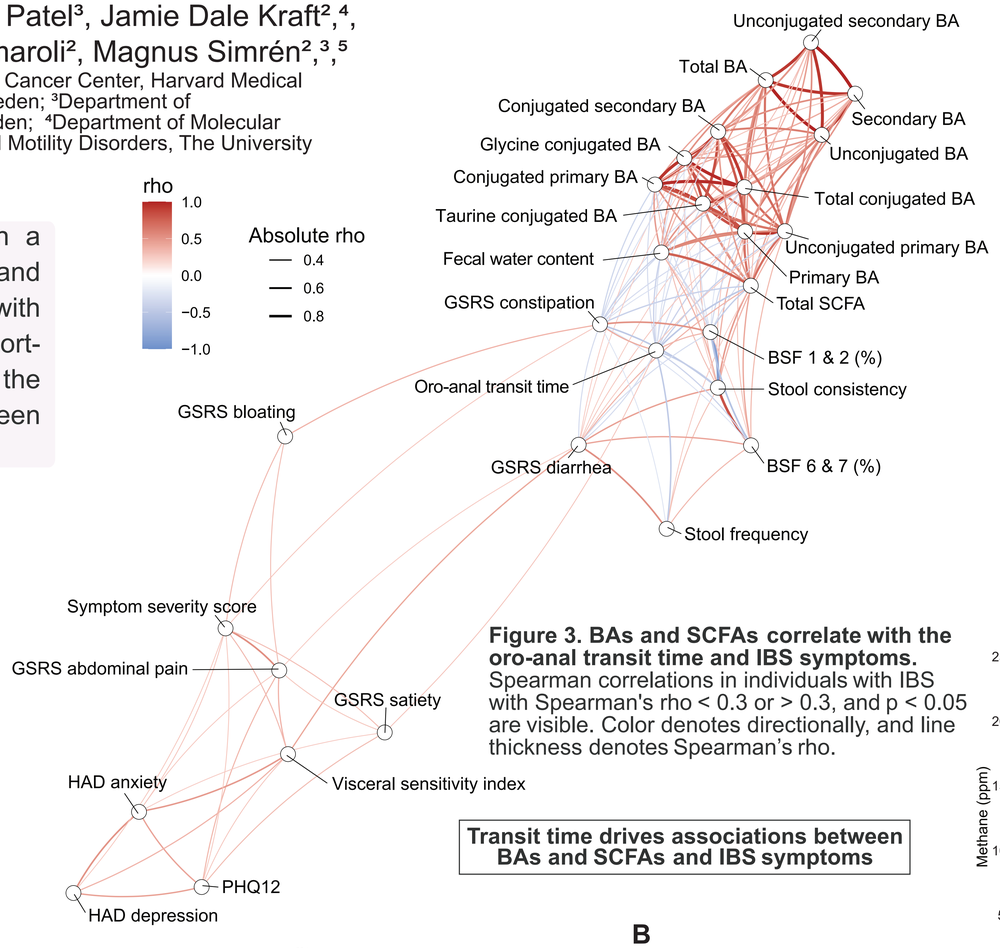


Figure 3. BAs and SCFAs correlate with the oro-anal transit time and IBS symptoms. Spearman correlations in individuals with IBS with Spearman's rho < 0.3 or > 0.3, and p < 0.05 are visible. Color denotes directionally, and line thickness denotes Spearman's rho.

Transit time drives associations between BAs and SCFAs and IBS symptoms

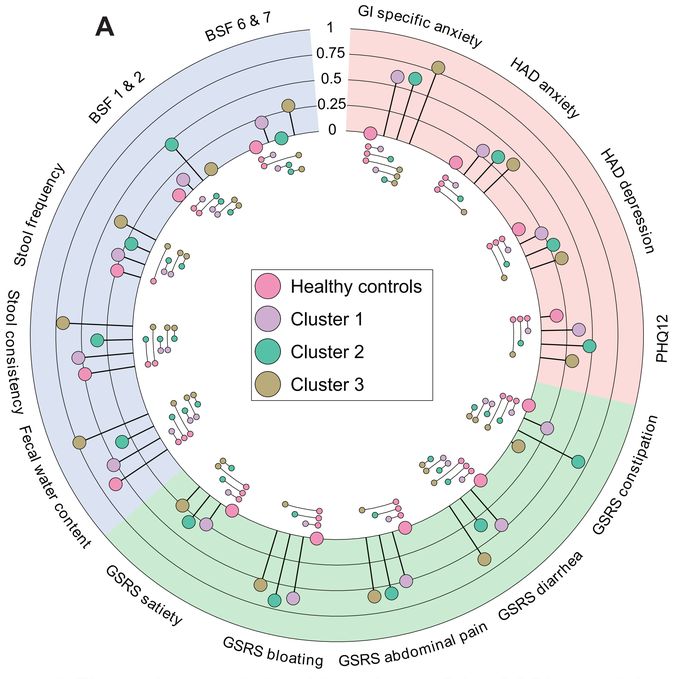
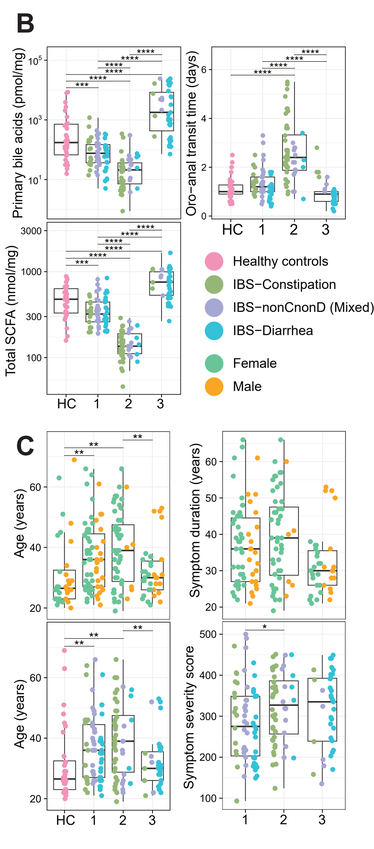


Figure 4. Three clusters defined by primary BAs, SCFAs, and the oro-anal transit time differentiate symptom patterns of IBS. (A) Symptom patterns in HC and clusters. Lollipops represent the median of scaled values. Connected dots in center represent p < 0.05. (B) Levels of features in clusters. (C) Age, sex, IBS subtype, symptom duration and symptom severity in clusters.



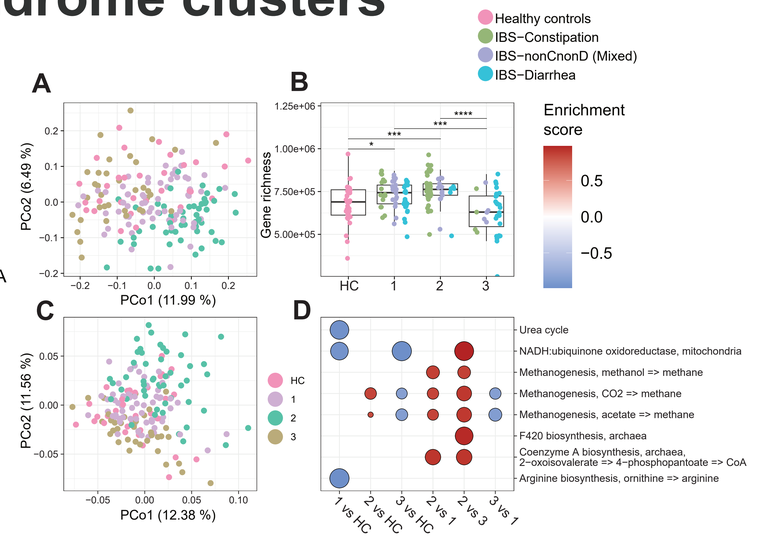


Figure 5. Gut microbial community composition and functional potential differs between IBS clusters. (A) Principal coordinates analysis (PCoA) of community composition. (B) Metagenomic gene richness. (C) PCoA of KEGG orthology groups. (D) KEGG module enrichment analysis.

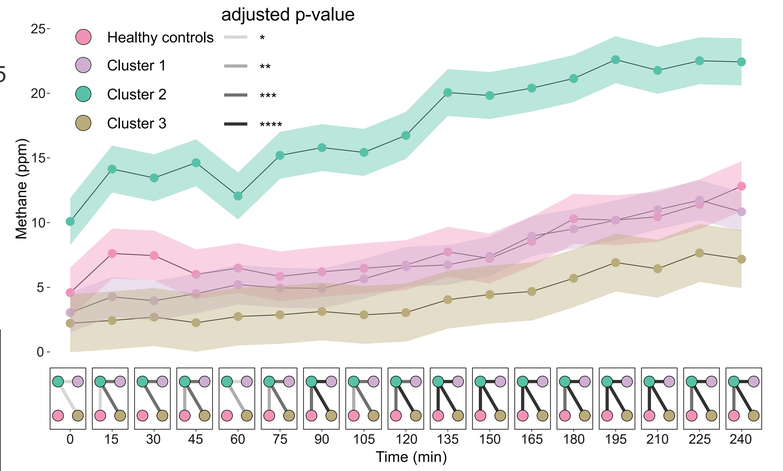


Figure 6. Exhaled methane concentrations after lactulose nutrient challenge differ between IBS clusters. Top panel: curves represent estimated marginal means and shaded areas represent the standard error. Bottom panel: connected dots indicate significant Benjamini-Hochberg adjusted p-values. Shading between dots represents the significance level.

Conclusions

- Bile- and short chain fatty acids are associated with stool consistency in IBS.
- Transit time is a driver of associations between bile acids and short-chain fatty acids, and symptoms.
- Clustering with transit and bile- and short-chain fatty acid levels defined three clusters with distinct symptom patterns.
- Gut microbial community composition and functional potential differs between clusters, and compared to healthy controls.
- Functional potential for methanogenesis is increased in cluster 2 and decreased in cluster 3.
- Exhaled methane concentrations align with microbial methanogenesis functional potential.

1: Pittayanon R et. al. Gut Microbiota in Patients With Irritable Bowel Syndrome-A Systematic Review. Gastroenterology. 2019 Jul;157(1):97-108. 2: Jiang W et. al. The Role of Short Chain Fatty Acids in Irritable Bowel Syndrome. J Neurogastroenterol Motil. 2022 Oct 30;28(4):540-548.

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