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Original Research Article

ASSOCIATION OF ALTERNATION IN INTESTINAL MICROBIOTA WITH IMPAIRED PSYCHOLOGICAL FUNCTION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES IN REMISSION

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Abstract: *The prospective study was conducted in the Department of Gastroenterology, THQ Hospital, from April 2021 to April 2022 to evaluate the association between mucosa-associated psychological functioning and intestinal microbiota in IBD remission patients. The study was conducted on 200 patients with comparable numbers of UC and CD. At inclusion, clinical phenotyping of disease status, including disease activity, was done using modified Truelove and Witt's activity index (MTWAI) and CD activity index (CDAI). Biopsies were used for DNA extraction. The microbial profile of UC and CD patients was evaluated in correlation to depression. Like anxiety, the highest taxonomic changes were noted in the Firmicutes phylum. Many negative correlations were noted between the abundance of various taxa in Firmicutes phylum and depression. An analysis was conducted to determine the relationship between anxiety, the abundance of certain microbial taxa, and the quality of life (QoL) of individuals with Crohn's disease (CD) and ulcerative colitis (UC). The results showed that there was a significant correlation between anxiety and a relative increase of taxa in CD only. Additionally, the QoL of those with CD had a negative correlation with the increase in taxa. For UC, the relationship was partly accurate. However, higher QoL was associated with the abundance of the RF32 family and Sutterella, indicating that these taxa could be potential markers of favorable outcomes.*

Keywords: Inflammatory Bowel Diseases, Intestinal Microbiota, Gut-Brain Complex

Introduction

There is increasing acknowledgment of intestinal microbiota as a risk factor for the onset of inflammatory bowel disease (IBD). Bi-directional interaction between host and microbes can reduce or promote intestinal inflammation (Macpherson et al., 2018; Miyoshi and Chang, 2017). Research showed that Crohn's disease is characterized by a significantly increased level of Proteobacteria and a reduced level of Firmicutes, whereas these alterations are less significant in ulcerative colitis (UC) (Khan et al., 2019; Yilmaz et al., 2019). There is limited understanding of the mechanism by which these alterations cause disease. Interaction between intestinal microbiota and the central nervous system modulates cognitive function, mood, and behavior. Microbial components are important to this gut-brain axis and impact the intestinal immune system, hormonal signaling, brain, and submucosal autonomic nervous system (de Araujo Goes et al., 2022; Zhou et al., 2023).

There has been an association between IBD and depressive symptoms, including anxiety and stress. Studies show that patients with mood disturbances have distinctive alterations in gut microbiota (Gracie et al., 2018). Results of a randomized controlled trial suggested that brain regions responsible for processing sensation and emotions were more active in normal women who had probiotics compared to placebo (Tillisch et al., 2013). Another study showed an association between CD and perceived stress (Spagnuolo et al., 2022). It has also been observed that the quality of life is negatively associated with disease flares and activity, particularly in active CD (Knowles et al., 2018). This evidence suggests the significance of the gut complex. This study aims to evaluate the association between mucosa-associated microbiota and psychological factors in IBD remission patients.

Methodology

A prospective study was conducted in the Gastroenterology department of THQ Hospital from April 2021 to April 2022. Patients in IBD remission were selected for the study. All patients gave their informed consent. The ethical board of the hospital approved the study.

At inclusion, clinical phenotyping of the status of the disease, including disease activity, was done using modified Truelove and Witt's activity index (MTWAI), and CD activity index (CDAI) (CDAI cut-offs were established using disease-specific IBD Questionnaire (IBDQ) for QoL, Perceived Stress Questionnaire (PSQ), SF-36 and the HADS for Anxiety and Depression). 6 months follow up questionnaire including epidemiological data, disease course and depression, perceived stress, and anxiety scores, the overall status of health and QoL (36 items Short Form) was sent to the patients.

Biopsies were used for DNA extraction. Gene amplification and sequencing were done of V5/V6 variant regions of 16S rRNA genes. Bioinformatic analysis was performed using the QIIME 1.9.1. The Phyloseq pipeline

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was for calculating alpha and beta diversity. Multivariate analysis was used for taxonomic differentiation of tested groups. It detected an association between variables (age, gender, BMI, smoking, disease activity, resection surgery, medication, and anatomic location) and abundance of the microbial community. P value < 0.05 was considered statistically significant.

Results

The study was conducted on 200 patients with comparable numbers of UC and CD. The association between alteration in species richness (alpha diversity) and psychological distress scores was tested using Shannon and Simpson indices. For decreased species richness with higher depression in UC and anxiety in CD patients, the Shannon index was decreased in those with higher perceived stress scores (PSQ >.45) than those with lower scores (PSQ < .15) (Figure I).

Microbial differences (beta diversity) in disease groups were tested according to overall psychological distress scores, and it was observed that several groups were significantly clustered according to the extent of depression and anxiety. For anxiety, both groups differed significantly with low or no anxiety, and this difference was maintained after cut-off values were used for anxiety. Analysis of depression had similar results. As beta dispersion was statistically significant, its contribution to clustering in depression and anxiety cannot be excluded (Figure II).

Relative abundances of disease subtypes were compared based on the severity of psychological distress. The microbial profile of UC and CD patients was also evaluated in correlation to depression. Like anxiety, the highest taxonomic changes were noted in Firmicutes. Depression in CD patients was negatively associated with the abundance of Ruminococcus, Roseburia, Lachnospiraceae, Clostridiales, and Eubacterium. Similarly, Streptococcus, Phascolarctobacterium, Blautia, Lachnospira, and Erysipelotrichaceae had a negative correlation in UC patients. Positive association with depression in CD was noted for Bifidobacterium and in UC for Desulfovibrio. Many negative correlations were noted between the abundance of various taxa in Firmicutes phylum and depression (Figure III). A similar analysis for anxiety showed a significant correlation with a relative increase of taxa in CD only. Only phylum Fusobacterium reduces significantly with an increase in anxiety. CD QoL had a negative correlation with the increase in taxa. For UC, it was partly accurate. There was a positive correlation between QoL and the relative abundance of Lactococcus, Sutterella, and RF32 family (Figure IV).

There was a negative association between perceived stress and relative abundance of Eubacterium, RF32 family, Parabacteroides, Lachnospira, Haemophilus, and Sutterella in UC. A similar association was seen with depression. Higher QoL was associated with the abundance of the RF32 family and Sutterella, indicating that these taxa are markers of favorable outcomes. Perceived stress and microbial profile were not significantly associated with CD. Figure 5

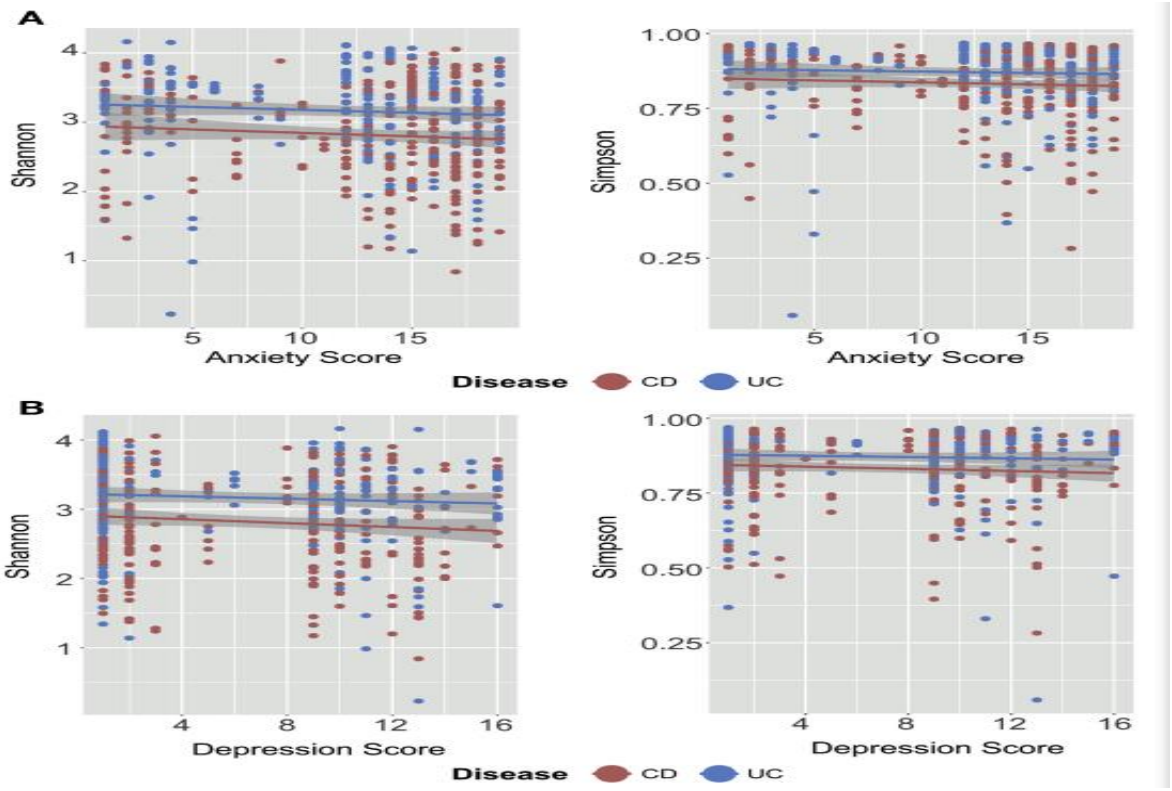

Figure I Association between psychological outcome and species richness

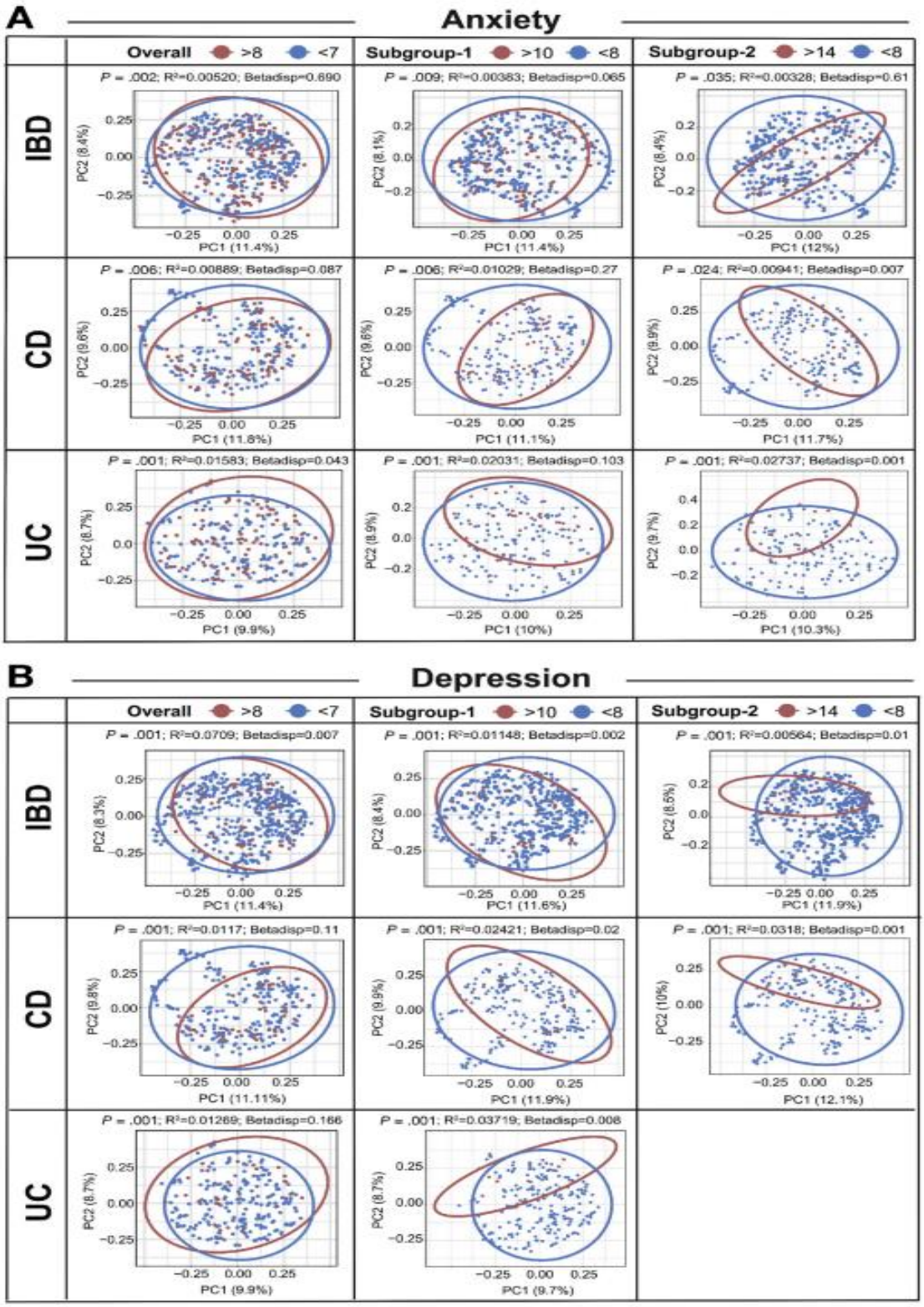

Figure II Association between differences in microbial composition and psychological symptoms

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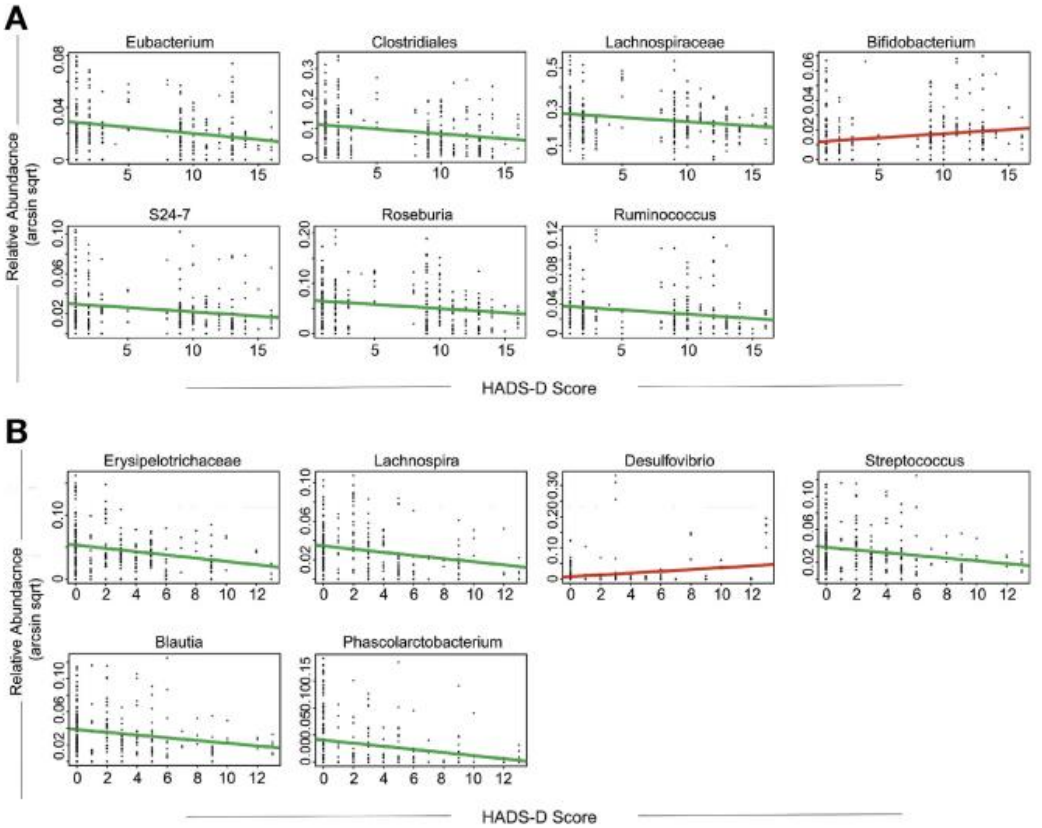

Figure III Correlation between microbial taxa and depression

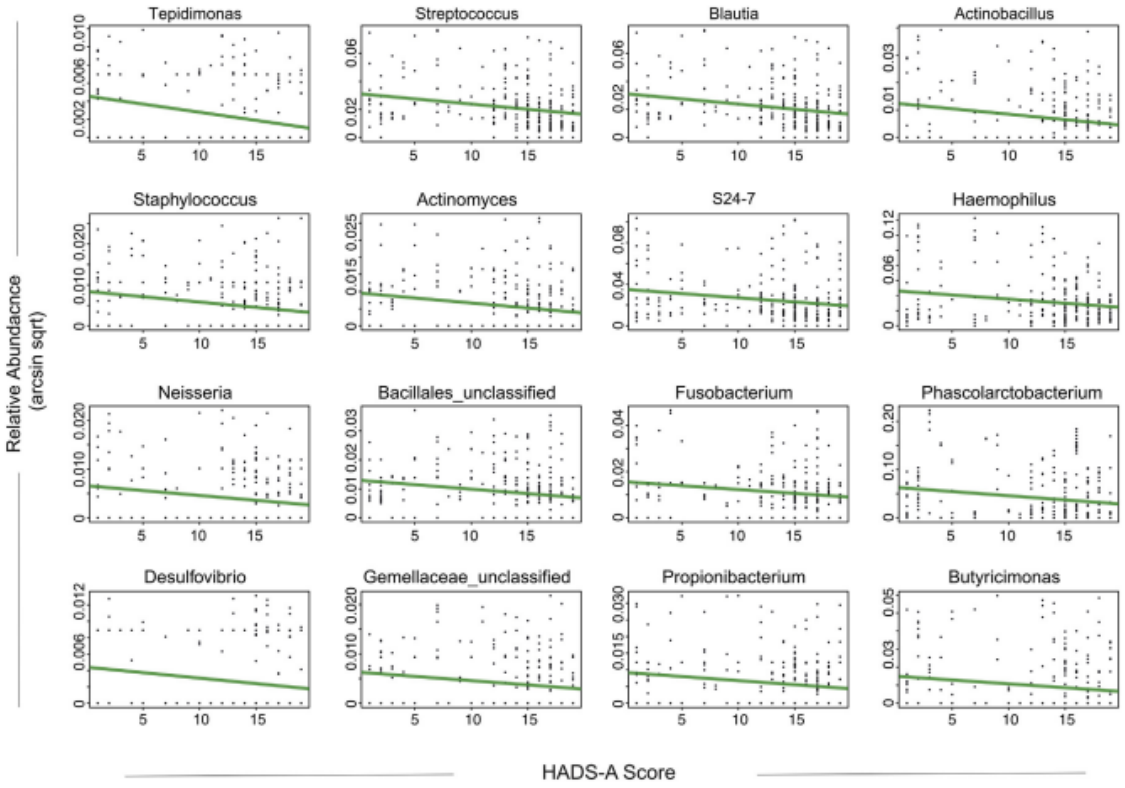

Figure IV Correlation between microbial taxa and anxiety

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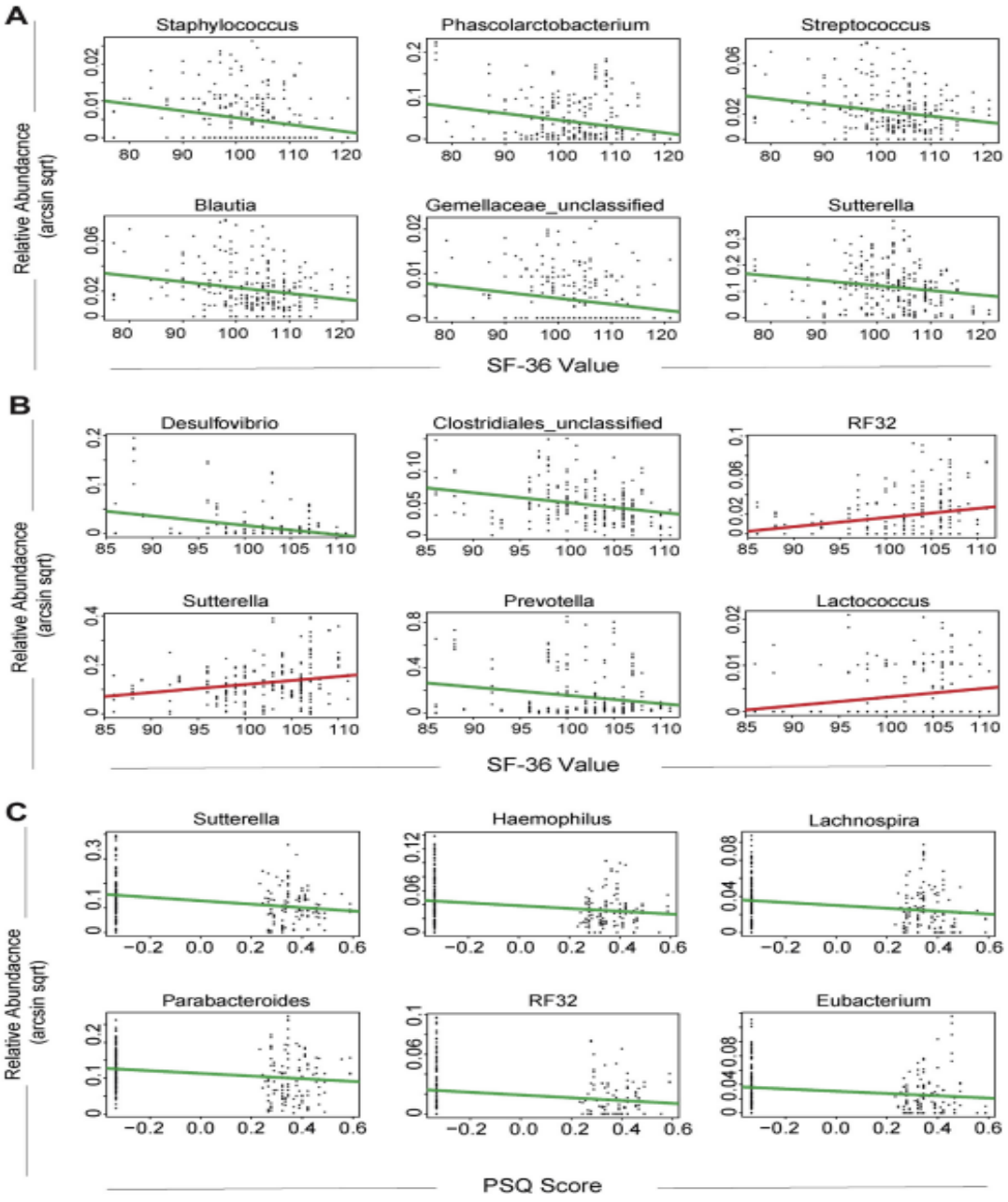

Figure 5

Discussion

We evaluated associations between psychological outcomes and alterations in intestinal microbiota in IBD patients. Much evidence is available suggesting intestinal microbiota as a factor in the pathogenesis of IBD. However, there is less clarity about the brain axis. In the current study, we found that patients with and without psychological outcomes have differences in gut mucosa(Mei et al., 2023). These differences were observed in IBD patients with remission. A previous study showed that alterations in bowel movements, even in patients without inflammatory bowel diseases were also related to significant microbiota changes, including the segmental difference in noninflamed and inflamed tissues(Dong et al., 2019). An increase in disease activity considerably impacts psychological well and overall quality of life. Inverse interaction with anxiety, stress, and depression may increase disease flare. Our study was based on patient and physician-derived data acquired in a standardized way, which is the strength of our study. However, our study has limited verification that patients in clinical remission were also in endoscopic remission, similar to a previous study(Narula et al., 2019).

Association between psychological and intestinal microbial changes may be reciprocal as alterations in mood have subsequent effects on gastrointestinal motility and lifestyle, including factors like smoking, diet, and stool frequency

(Antinozzi et al., 2022; Ferraris et al., 2020). Moreover, we cannot rule out the possibility that microbiota-based prediction of psychological outcomes may reflect some of the impacts of modifying agents like medical therapy or interference with undiagnosed disease activity. This may be specific for corticosteroids as patients often take these on a short term. It is reported that corticosteroids have no major impact on microbiota(Yilmaz et al., 2019). In addition, the composition of microbiota was not related to the response to corticosteroids. Questionnaires cannot effectively evaluate the psychiatric symptoms as a standard psychiatric interview. However, the questionnaire in our study was designed by individuals experienced in psychology and psychiatry. We obtained psychological end results through validated scores, but some are still uncertain. We did not include patients from different cultures, but the assessment done through PSQ does not apply to the transcultural population.

We planned to keep the time interval short in the study. However, HADS evaluates the depression and anxiety scores for 1 week only. The time difference between the questionnaire and endoscopy was 30 days for 55 patients and 180 days for 94 patients.

Conclusion

The composition of intestinal microbiota was associated with inflammatory bowel disease and remission, quality of life, and psychological well-being.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department Concerned.
Consent for publication
Approved
Funding
Not applicable

Conflict of interest

The authors declared absence of conflict of interest.

References

Antinozzi, M., Giffi, M., Sini, N., Gallè, F., Valeriani, F., De Vito, C., Liguori, G., Romano Spica, V., and Cattaruzza, M. S. (2022). Cigarette smoking and human gut microbiota in healthy adults: a systematic review. *Biomedicines* **10**, 510.

de Araujo Goes, V., Tajudeen, Y. A., and El-Sherbini, M. S. (2022). The Correlations among Dietary Lifestyle, Microecology, and Mind-Altering Toxoplasmosis on the Health of People, Place, and the Planet. *Challenges* **13**, 63.

Dong, L.-N., Wang, M., Guo, J., and Wang, J.-P. (2019). Role of intestinal microbiota and metabolites in inflammatory bowel disease. *Chinese medical journal* **132**, 1610-1614.

Ferraris, C., Elli, M., and Tagliabue, A. (2020). Gut microbiota for health: how can diet maintain a healthy gut microbiota? , Vol. 12, pp. 3596. MDPI.

Gracie, D. J., Guthrie, E. A., Hamlin, P. J., and Ford, A. C. (2018). Bi-directionality of brain–gut interactions in patients with inflammatory bowel disease. *Gastroenterology* **154**, 1635-1646. e3.

Khan, I., Ullah, N., Zha, L., Bai, Y., Khan, A., Zhao, T., Che, T., and Zhang, C. (2019). Alteration of gut microbiota in inflammatory bowel disease (IBD): cause or consequence? IBD treatment targeting the gut microbiome. *Pathogens* **8**, 126.

Knowles, S. R., Graff, L. A., Wilding, H., Hewitt, C., Keefer, L., and Mikocka-Walus, A. (2018). Quality of life in inflammatory bowel disease: a systematic review and meta-analyses—part I. *Inflammatory bowel diseases* **24**, 742-751.

Macpherson, A. J., Yilmaz, B., Limenitakis, J. P., and Ganal-Vonarburg, S. C. (2018). IgA function in relation to the intestinal microbiota. *Annual review of immunology* **36**, 359-381.

Mei, H., Li, J., Liu, S., Jeyaraj, A., Zhuang, J., Wang, Y., Chen, X., Yuan, Q., and Li, X. (2023). The Role of Green Tea on the Regulation of Gut Microbes and Prevention of High-Fat Diet-Induced Metabolic Syndrome in Mice. *Foods* **12**, 2953.

Miyoshi, J., and Chang, E. B. (2017). The gut microbiota and inflammatory bowel diseases. *Translational Research* **179**, 38-48.

Narula, N., Alshahrani, A.-A., Yuan, Y., Reinisch, W., and Colombel, J.-F. (2019). Patient-reported outcomes and endoscopic appearance of ulcerative colitis: a systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology* **17**, 411-418. e3.

Spagnuolo, R., Basile, A., Corea, A., Iaquinta, F. S., Milić, N., Doldo, P., Luzza, F., and Abenavoli, L. (2022). Measuring Mood and Anxiety Disorders by Patient Reported Outcomes in Inflammatory Bowel Disease: A Literature Review Update. *Reviews on Recent Clinical Trials* **17**, 156-170.

Tillisch, K., Labus, J., Kilpatrick, L., Jiang, Z., Stains, J., Ebrat, B., Guyonnet, D., Legrain–Raspaud, S., Trotin, B., and Naliboff, B. (2013). Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology* **144**, 1394-1401. e4.

Yilmaz, B., Juillerat, P., Øyås, O., Ramon, C., Bravo, F. D., Franc, Y., Fournier, N., Michetti, P., Mueller, C., and Geuking, M. (2019). Microbial network disturbances in relapsing refractory Crohn's disease. *Nature medicine* **25**, 323-336.

Zhou, Y., Chen, Y., He, H., Peng, M., Zeng, M., and Sun, H. (2023). The role of the indoles in microbiota-gut-brain axis and potential therapeutic targets: A focus on human neurological and neuropsychiatric diseases. *Neuropharmacology*, 109690.

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