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GUT MICROBIOTA AND DEPRESSION: MECHANISMS, EVIDENCE, AND IMPLICATIONS FOR TREATMENT AND SPORT: A CURRENT REVIEW

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ABSTRACT

Background: Major depressive disorder (MDD) affects over 264 million people globally. Growing evidence implicates the Microbiota-Gut-Brain axis in its pathogenesis, yet mechanisms and therapeutic implications remain incompletely understood.
Aim: To synthesise evidence on gut microbiota alterations in MDD, neurobiological mechanisms, microbiota-targeted interventions, and implications for sport populations.
Material and methods: A narrative review of 28 peer-reviewed publications (2019-2025) using PubMed. Search terms included gut microbiota, major depressive disorder, dysbiosis, probiotics, HPA axis, and short-chain fatty acids.
Results: Depletion of SCFA-producing genera – particularly Faecalibacterium, Coprococcus, and Prevotellaceae – alongside enrichment of pro-inflammatory taxa was identified across multiple systematic reviews. Three neurobiological pathways were delineated: serotonergic and GABAergic dysregulation, HPA axis dysfunction via the kynurenine pathway, and LPS-mediated neuroinflammation. Adjunctive probiotic supplementation demonstrated a modest antidepressant effect (SMD = 0.83). Moderate physical activity increases SCFA-producing taxa overlapping with those depleted in MDD.
Conclusions: Gut microbiota alterations are associated with MDD through identifiable pathways. Probiotics show adjunctive therapeutic potential. Sport populations represent a clinically relevant group for microbiota-targeted research.

KEYWORDS

Gut Microbiota, Major Depressive Disorder, Microbiota-Gut-Brain Axis, Probiotics, Dysbiosis, Short-Chain Fatty Acids, Physical Activity

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1. Introduction

Major depressive disorder (MDD) is one of the most disabling mental conditions worldwide. It is estimated that more than 264 million people suffer from MDD globally, and approximately 800,000 deaths by suicide each year are linked to depression (Nikolova et al., 2021). The COVID-19 pandemic substantially increased rates of both depression and anxiety: using a Global Burden of disease modeling approach, an additional 53.2 million cases of major depressive disorder were estimated globally in 2020, representing a 27.6 % increase compared with the pre-pandemic period, with estimates extrapolated to 204 countries and territories (Santomauro et al., 2021).

Over the past two decades, the gut microbiota has attracted growing scientific attention as a potential contributor to psychiatric disorders. The Microbiota-Gut-Brain Axis (MGBA) is a bidirectional communication network linking gut microbial communities to the central nervous system (CNS) through neural, immune, and endocrine pathways (Cryan et al., 2019). Systematic reviews and large cohort studies have documented recurrent but heterogenous differences in gut microbiota composition between MDD patients and healthy controls, driving interest in whether such differences are causally involved in depression (Simpson et al., 2021); (McGuinness et al., 2022); (Gao et al., 2023).

This narrative review summarizes published evidence on: (1) gut microbiota alterations associated with MDD; (2) the mechanisms through which the gut microbiota may influence depressive symptomatology; (3) therapeutic strategies targeting the gut microbiota in depression; and (4) the implications of these findings for sport and physical activity contexts.

Research Objective.

To provide a focused, evidence-based synthesis of the role of gut microbiota in MDD, based exclusively on findings reported in the referenced publications.

Research Problems.

(1) What gut microbiota alterations are consistently reported in MDD? (2) Through which biological pathways do these alterations influence mood? (3) What is the current clinical evidence for microbiota-targeted interventions in depression? (4) What are the implications of gut microbiota-depression research for sport and physical activity populations?

2. Materials and Methods

2.1. Study Design

This study is a narrative review aimed at providing a focused and evidence-based synthesis of current knowledge on the relationship between gut microbiota and major depressive disorder (MDD). The review is based on analysis and interpretation of previously published literature and does not involve primary data collection.

As no human participants or animal subjects were directly involved, ethical approval and informed consent were not required. All referenced studies were conducted in accordance with the ethical standards of their respective institutions.

2.2. Literature Search Strategy

A structured literature search was conducted using the PubMed databases to identify relevant publications on the gut microbiota and its role in depression.

Search terms included combinations of following keywords: „gut microbiota", „gut microbiome", „depression", „major depressive disorder", „dysbiosis", „microbiota-gut-brain axis", „probiotics", „HPA axis", „fecal microbiota transplantation", „short-chain fatty acids", „tryptophan", and „kynurenine".

Boolean operators (AND, OR) were used to refine the search.

Publications were selected based on their relevance to the topic, with preference given to:

- peer-revieved original articles, systematic reviews, and meta-analyses,
- studies published between 2020 and 2025, with key earlier works from 2019 included where necessary,
- research focusing on gut microbiota and depression in human populations or validated animal models.

Non-peer-reviewed sources, conference abstracts, and studies lacking sufficient methodological detail were generally not considered. A total of 28 key publications were ultimately included in this review.

2.3. Data Collection and Synthesis

Relevant information was identified and synthesized from the selected publications, including study design, sample charakteristics, microbiome analysis methods, reported changes in microbial composition and diversity, proposed biological mechanisms, and outcomes of microbiota-targeted interventions.

The findings were synthesized qualitatively and are presented in a structured manner to highlight recurring patterns, areas of agreement, and sources of heterogeneity across studies. As this is a narrative review, no formal systematic data extraction protocol was applied.

2.4 Statistical Considerations

As this study is a narrative review, no primary statistical analyses were performed. Where relevant, statistical outcomes such as efect sizes, confidence intervals, and p-values are reported as presented in the original studies, particularly from cited systematic reviews and meta-analyses.

3. Research Results

3.1. Gut Microbiota Alterations in Major Depressive Disorder

3.1.1. Evidence from Systematic Reviews and Meta-Analyses

Several systematic reviews and meta-analyses have examined gut microbiota composition in MDD. The meta-analysis of gut microbiota in MDD identified that the genera Coprococcus, Faecalibacterium, and the family Prevotellaceae were among the most frequently reported taxa decreased in MDD patients compared to non-depressed controls in observational studies (Sanada et al., 2020). The same review found that probiotic interventions improved depressive symptoms compared to controls.

A systematic review of 17 studies totalling 738 MDD patients and 782 healthy controls found that four studies reported reduced alpha diversity in MDD patients, while gut microbiota compositions clustered separately by beta diversity in 12 of the included studies. At the taxon level, the review indentified increased

relative abundance of Eggerthella, Atopobium, and Bifidobacterium, and decreased abundance of Faecalibacterium in MDD patients compared to controls (Knudsen et al., 2021).

A systematic review of 26 studies on gut microbiota in anxiety and depression found that depression and anxiety were characterized by an enrichment of pro-inflammatory bacteria and a depletion of anti-inflammatory, SCFA-producing bacteria. The review noted substantial heterogeneity in methodology and findings across included studies (Simpson et al., 2021).

A systematic review of 44 studies including 2510 psychiatric cases and 2407 controls covering MDD, bipolar disorder, and schizophrenia found no strong evidence for a difference in alpha diversity between those with mental disorders and controls. However, studies were relatively consistent in reporting differences in beta diversity. Specific bacterial taxa were identified as commonly altered across mental disorders: lower levels of genera producting short-chain fatty acids (e.g., butyrate-producing genera), higher levels of lactic acid-producing bacteria, and higher levels of bacteria associated with glutamate and GABA metabolism (McGuinness et al., 2022).

A systematic review, meta-analysis, and meta-regression of studies comparing gut microbiota composition in depressive disorder versus healthy controls, searching 8 databases, identified a total of 44 studies representing 2091 patients and 2792 controls. The meta- analysis found no consistent difference in alpha diversity. However, beta diversity frequently differed between groups, though not consistently. The meta-regression analysis identified regional variation (east/west) and psychotropic medication use as factors influencing microbiota composition across studies, though these variables did not fully explain the observed heterogeneity (Gao et al., 2023).

A systematic review of 24 articles found that the findings on alpha and beta diversity in MDD and anxiety were inconssistent across studies. In gut microbiota composition, depression and anxiety were characterized by an enrichment of pro-inflammatory bacteria and a depletion of anti-inflammatory SCFA-producing bacteria (Cao et al., 2025).

A microbiome-wide association study conducted in 1054 participants from the Rotterdam Study cohort, validated in 1539 subjects from the Amsterdam HELIUS cohort, identified 13 microbial taxa associated with depressive symptoms, including genera Eggerthella, Subdoligranulum, Coprococcus, Sellimonas, Lachnoclostridium, and Hungatella, and family Ruminococcaceae. These bacteria are associated with metabolic pathways related to glutamate, butyrate, serotonin, and GABA (Radjabzadeh et al., 2022).

3.1.2. Evidence from Clinical Studies

A study analyzing gut microbiota and intestinal integrity markers in 16 MDD inpatients treated with escitalopram found a positive correlation between depression severity (HDRS-24 score) and abundance of Paraprevotella ($r = 0.80$, $q = 0.012$), and strong negative correlations with Clostridiales ($r = -0.70$, $q = 0.016$), Clostridia ($r = -0.70$, $q = 0.016$), and the RF32 order ($r = -0.70$, $p = 0.016$). Intestinal integrity and inflammation markers were associated with treatment response and symptom severity (Liśkiewicz et al., 2021).

A study investigating gut microbiota in 106 antidepressant-naive depressive patients and 151 healthy controls using 16S rRNA sequencing found notably lower alpha diveristy and distinct beta diversity in depressed patients. Eleven taxa with differentia abundance were identified, including decreased Dialister and Lactococcus, and elevated Hungatella, Sellimonas, and Lachnoclostridium. Functional pathway analysis identified 36 altered pathways, including purine degradation, lipopolysaccharide biosynthesis, and amino acid metabolism (Lin et al., 2025).

A multi-omics study combining pre-clinical models with three human cohorts found that microbial functions and metabolites converging on glutamate/GABA metabolism, particularly proline, were linked to depression. Bacterial pathways involving arginine, proline, and histidine metabolism were negatively associated with depression severity. High proline consumption was identified as the dietary factor with the strongest impact on depression, and the depression phenotype was transferable from humans to mice through microbiota transplantation (Mayneris-Perxachs et al., 2022).

3.2. Mechanisms Linking Gut Microbiota to Depression

3.2.1. Neural Pathway: Vagus Nerve and Neurotransmitters

The gut-brain axis enables bidirectional communication between the gastrointestinal tract and the central nervous system, involving neural pathways such as thevagus nerve and the enteric nervous system, as well as immune and metabolic mechanisms. The gut microbiota has been shown to influence tryptophan metabolism and peripheral serotonin (5-HT) production, with the majority of serotonin synthesized in the gastrointestinal tract. However, peripheral serotonin does not cross the blood-brain barier, and its effects on the central nervous system are therefore considered to be indirect (Liu et al., 2023).

Bacteria commonly altered in MDD are specifically associated with glutamate and GABA metabolism, butyrate production, and lactic acid production, reresenting plausible neurochemical pathways between microbial composition and mood regulation (McGuinness et al., 2022). Similarly, the 13 microbial taxa associated with depressive symptoms identified in a microbiome-wide association study are involved in the synthesis of glutamate, butyrate, serotonin, and GABA (Radjabzadeh et al., 2022).

Microbial metabolites – particularly short-chain fatty acids – regulate serotonin synthesis in enterochromaffin cells. Altered tryptophan availability due to dysbiosis further reduces central serotonin synthesis, a mechanism elaborated in section 3.2.2. This mechanism links gut microbial composition to serotonergic dysfunction in MDD (Liu et al., 2023).

3.2.2. Neuroendocrine Pathway: HPA Axis and Tryptophan-Kynurenine Pathway

Gut microbial metabolites, including SCFAs and bile acids, may modulate hypothalamic-pituitary-adrenal (HPA) axis activity, influencing cortisol release. Chronic HPA dysregulation is a well-established feature of MDD. Animal studies demonstrate that germ-free mice show exaggerated corticosterone responses to acute stress that are normalised by microbial colonization, supporting a role for gut microbiota in HPA axis calibration (Liu et al., 2023).

Dysbiosis shifts tryptophan metabolism away from serotonin biosynthesis toward the kynurenine pathway. This shift is driven partly by inflammation-induced upregulation of indoleamine 2,3-dioxygenase (IDO), resulting in accumulation of neurotoxic metabolites including quinolinic acid and depletion of neuroprotective kynurenic acid. Additionally, gut microbiota-targeted interventions have been associated with increases in brain-derived neurotrophic factor (BDNF) levels in MDD patients, a neurotrophin critical for hippocampal neurogenesis and implicated in antidepressant response. These mechanisms represent direct neurochemical links between gut disbiosis, peripheral inflammation, and central nervous system dysfunction in MDD (Liu et al., 2023).

3.2.3. Immune Pathway: Neuroinflammation and Intestinal Barrier

Gut dysbiosis – particularly depletion of SCFA-producing bacteria – reduces butyrate production and impairs intestinal barier integrity, increasing intestinal permeability and facilitating translocation of bacterial lipopolysaccharide (LPS) into systemic circulation (Liu et al., 2023). Circulating LPS activates toll-like receptor 4 (TLR4) signalling, triggering release of pro-inflammatory cytokines including IL-6, IL-1β, and TNF-α, which have been implicated in the pathogenesis of depression (Liu et al., 2023); (Zhu et al., 2025).

These circulating cytokines activate microglia – the CNS-resident immune cells – in hippocampal regions including the dentate gyrus, disrupting hippocampal neurogenesis and contributing to the structural changes observed in MDD. Additionally, the Th17/Treg immune cell balance, modulated in part by microbial metabolites, is disrupted in MDD, sustaining neuroinflammatory signalling (Zhu et al., 2025).

Clinical evidence for this pathway was provided in a study of hospitalized MDD inpatients, which found correlations between gut microbiota composition, intestinal integrity biomarkers – specifically plasma intestinal fatty acid-binding protein (IFABP) and fecal calprotectin – and depression severity. Clinical outcomes correlated negatively with plasma IFABP levels at baseline and positively with changes in fecal calprotectin during hospitalization (Liśkiewicz et al., 2021).

3.2.4. Short-Chain Fatty Acids as Key Mediators

Depletion of butyrate-producing genera has been identified as a consistent finding in MDD across multiple systematic reviews (Simpson et al., 2021); (McGuinness et al., 2022). SCFAs- primarily acetate, propionate, and butyrate – produced by anaerobic fermentation of dietary fibre, are proposed to exert neuroprotective and immunomodulatory effects. Butyrate maintains intestinal barier integrity, reduces LPS translocation, and acts as a histone deacetylase (HDAC) inhibitor, promoting BDNF expression (Liu et al., 2023).

4. Discussion

4.1. Probiotic and Psychobiotic Interventions

An updated review and meta-analysis of randomized controlled trials on probiotics for clinical depression, conducted following Cochrane guidelines and searching PubMed and Web of Science, identified seven studies meeting selection criteria, capturing 404 people with depression. Probiotics were effective in reducing depressive symptoms when administered as adjuncts to antidepressants (SMD = 0.83, 95% CI 0.49–1.17), but did not offer significant benefits when used as stand-alone treatment (SMD = −0.02, 95% CI −0.34–0.30). Potential mechanisms of action were proposed to include increases in BDNF and decreases in C-reactive protein, although the authors noted that limited evidence was available at the time of publication (Nikolova et al., 2021).

A meta-analysis of 13 RCTs with 786 participants evaluating prebiotic, probiotic, and synbiotic interventions for clinical depression found an overall small effect-size reduction in depression severity (SMD = −0.34; 95% CI: −0.45, −0.22) in favour of treatment compared to placebo. Subgroup analysis revealed that only probiotics – both single and multiple strain – were associated with reductions in depression severity, and meta-regression identified a larger reduction in studies with a lower proportion of female participants (coefficient = 1.925, p = 0.026) (Zhang et al., 2023). A subsequent systematic review and meta-analysis of 23 RCTs involving 1401 clinically diagnosed patients found that probiotics were associated with reductions in depression symptoms (SMD = −0.96; 95% CI −1.31, −0.61), while prebiotics did not reach statistical significance (Asad et al., 2025).

A systematic review and meta-analysis of RCTs of probiotics in treating depressive symptoms, searching multiple databases through March 2022 and including 776 patients in total, found that BDI scores in the probiotic group were statistically lower than in the control group (MD = −1.98, 95% CI −3.14 to −0.82). Probiotic administration was also associated with reduced IL-6 levels (SMD = −0.55, 95% CI −0.88 to −0.23) (Lin et al., 2023).

A systematic review and meta-analysis of probiotics, prebiotics, and synbiotics in patients with depression found that the majority of included studies reported reductions in depression and anxiety outcomes following intervention. Probiotic bacteria including Lactobacillus and Bifidobacterium were associated with reductions in depressive symptoms, with anti-inflammatory mechanisms proposed as a contributing pathway (Moshfeghinia et al., 2025).

A meta-analysis of RCTs evaluating the effect of prebiotics and probiotics on depression, anxiety, and cognitive function found improvements in depression and anxiety outcomes following probiotic intervention. Certain Lactobacillus strains – including L. casei, L. rhamnosus, and multistrain products containing L. plantarum – were identified as potentially influencing psychiatric disorders and stress-related behaviours. However, numerous studies failed to detect alterations in microbiota composition, potentially due to participants' unchanged dietary and lifestyle habits during short-term probiotic intake (Zandifar et al., 2025).

The first RCT to assess both depressive symptom reduction and simultaneous gut microbial and neuroimaging changes in MDD patients was a multispecies probiotic add-on trial conducted over 31 days. In 47 participants completing the intervention, HAM-D scores decreased over time, with interactions between time and group indicating a stronger decrease in the probiotic relative to the placebo group. Quantitative microbiome profiling confirmed changes in microbial composition in the probiotic compared to the placebo group (Schaub et al., 2022).

4.2. Fecal Microbiota Transplantation

A pilot randomized controlled trial assessed the feasibility, acceptability, and safety of FMT in MDD patients, representing the first RCT of FMT as a treatment for MDD. The study demonstrated that FMT was feasible and acceptable in this population (Green et al., 2023). The rationale for this approach is supported by preclinical evidence demonstrating that transplanting microbiota from depressed human donors into germ-free animals induces depressive-like behaviours, while FMT from healthy donors into animal models of depression has been shown to reverse depressive behaviours, providing important experimental suport for a potential causal role of gut microbiota in depression (Liu et al., 2023). Full efficacy conclusions from human FMT trials in MDD await larger, adequately powered studies, and the clinical use of FMT for MDD remains experimental.

4.3. Dietary Interventions

Evidence from preclinical and clinical studies indicates that diet exerts a modulatory influence on brain-gut-microbiome interactions, with important implications for brain health. Two RCTs confirmed beneficial effects of Mediterranean-style dietary interventions on depression. The PREDIMED randomized trial, involving 7447 participants, had reduction of cardiovascular mortality as its primary endpoint but also documented effects on depressive symptoms. Diet-induced microbiome changes have been implicated as a contributing mechanism through which dietary patterns influence mental health outcomes (Horn et al., 2022).

A systematic review of the biological mechanisms linking diet and depression identified numerous pathways through which diet may plausibly influence mental health. These included gut microbiota modulation, inflammatory pathways, oxidative stress, epigenetics, mitochondrial dysfunction, and tryptophan-kynurenine metabolism. The review noted that dietary patterns consistent with the Mediterranean diet are associated with reduced depression risk in epidemiological studies, and that dietary intervention RCTs in depressed populations demonstrate improvements in depressive symptoms (Marx et al., 2021).

4.4. Methodological Limitations

Substantial methodological heterogeneity represents a key limitation across reviewed studies. Sources of variability identified include geographic region and psychotropic medication use, which were found to contribute to differences in microbiota findings between studies, though these factors did not fully explain the observed heterogeneity (Gao et al., 2023). Variations in study design – including differences in DNA purification methods, sequencing platforms, and data analysis models – have also been highlighted as contributors to inconsistent findings across studies (Knudsen et al., 2021). Notably, meta-analytic approaches have proven important in clarifying the evidence base, with pooled analyses finding no strong evidence for alpha diversity differences in MDD, in contrast to conclusions drawn in some earlier narrative reviews (McGuinness et al., 2022).

Alpha and beta diversity findings were also noted to be inconsistent across studies, further underscoring the need for methodological consistency in future research (Simpson et al., 2021).

A scoping review concluded that while microbiota is altered in MDD, the mechanism of this relationship remains unknown. The authors hypothesised that the taxonomic changes observed are associated – rather than definitively causally linked – with bacterial pro-inflammatory activity, reduced SCFA production, impaired intestinal barier integrity, impaired neurotransmitter production, and impaired tryptophan and glutamate metabolic pathways (Łoniewski et al., 2021).

For therapeutic interventions, current evidence is limited by high heterogeneity between trials and the absence of consensus on optimal probiotic strains, dosages, and treatment durations (Asad et al., 2025). Furthermore, evidence for stand-alone probiotic use in depression is not statistically significant, with the more robust effect observed only as adjunctive treatment alongside antidepressants (Nikolova et al., 2021).

4.5. Implications for Sport and Physical Activity

The findings of this review carry relevance for sport and exercise contexts. Depression is not uncommon among athletes: a systematic review and meta-analysis of 22 studies comprising 5555 current elite athletes found that the prevalence of anxiety and depression symptoms reached 34%, and a further meta-analysis of 37 studies including 24732 former elite athletes found that the prevalence of depression was over twice that of the general population (prevalence ratio 2.58, 95% CI 2.04–3.12) (Gouttebarge et al., 2019); (Runacres & Marshall, 2024). These figures suggest that sport populations represent a clinically relevant group in whom gut microbiota-targeted approaches to depression may warrant dedicated investigation.

Physical activity has been identified as a modulator of gut microbiota composition. A systematic review of physical activity-induced alterations of gut microbiota in humans found that moderate-intensity exercise increased the relative abundance of SCFA-producing bacteria, including Faecalibacterium, Roseburia, and Akkermansia muciniphila, and positively influenced beta diversity (Dziewiecka et al., 2022). These exercise-associated microbiota changes overlap with the taxa consistently depleted in MDD as documented throughout this review – particularly Faecalibacterium and butyrate-producing genera – suggesting a plausible biological mechanism through which regular physical activity may confer protection against depression via microbiota modulation. However, the same review noted that prolonged high-intensity exercise may exert adverse effects on gut microbiota, potentially leading to dysbiosis, which underscores the importance of exercise intensity and volume in this context (Dziewiecka et al., 2022).

Probiotic interventions, already established in the sport context for gastrointestinal and immune health, may represent an additional avenue for supporting mental health in athletes. The antidepressant effects of probiotics documented in this review – particularly as adjunctive treatment – suggest potential dual-purpose applications in sport populations where both gut integrity and psychological wellbeing are relevant performance determinants. Future research should investigate whether microbiota-targeted interventions, including probiotics and dietary strategies, produce measurable mental health benefits specifically in athletic populations, and whether exercise-induced microbiota modulation interacts with the neurobiological pathways linking gut dysbiosis to depression outlined in this review.

5. Conclusions

The reviewed evidence indicates that gut microbiota composition differs between MDD patients and healthy controls, with recurrent findings across multiple systematic reviews and meta-analyses, despite substantial heterogeneity, showing depletion of SCFA-producing and anti-inflammatory genera – particularly Faecalibacterium, Coprococcus, and Prevotellaceae – alongside enrichment of pro-inflammatory taxa (Simpson et al., 2021); (McGuinness et al., 2022); (Gao et al., 2023). These alterations are hypothesised to be associated with MDD through three main pathways: dysregulation of neurotransmitter synthesis (serotonin, GABA, glutamate) via the vagus nerve and enteroendocrine signalling; HPA axis dysfunction and kynurenine pathway imbalance; and intestinal barier disruption leading to LPS-mediated neuroinflammation. However, the causal directionality of these associations remains incompletely established, and methodological heterogeneity limits cross-study comparisons (Łoniewski et al., 2021); (McGuinness et al., 2022).

For therapeutic interventions, the current evidence suggests a modest benefit of probiotic administration as an adjunct to antidepressant treatment (SMD = 0.83; (Nikolova et al., 2021), while stand-alone probiotic treatment and dietary interventions show smaller and less consistent effects. FMT in MDD remains in early-stage clinical investigation, with the first published RCT demonstrating feasibility and safety but not powered for efficacy (Green et al., 2023). Future research should prioritise large-scale, standardised, longitudinal studies, including pre-specified mechanistic biomarker endpoints, to enable clinical translation of microbiota-targeted therapies in depression. The elevated prevalence of depression in elite and former athletes, combined with evidence that moderate physical activity modulates gut microbiota composition in ways that mirror taxa depleted in MDD, further highlights sport populations as a clinically relevant group fr dedicated microbiota-targeted research.

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