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ARTICULO DE INVESTIGACIÓN

INFLUENCIA DEL MICROBIOMA INTESTINAL EN LOS TRASTORNOS NEUROPSIQUIÁTRICOS: UNA REVISIÓN SISTEMÁTICA

INFLUENCE OF THE INTESTINAL MICROBIOME ON NEUROPSYCHIATRIC DISORDERS: A SYSTEMATIC REVIEW

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Resumen Este estudio investiga la intrincada interacción entre el microbioma intestinal, la dieta y el entorno en relación con los trastornos neuropsiquiátricos, con un enfoque particular en la depresión y la ansiedad. Adoptando una metodología cualitativa, se llevó a cabo una investigación basada principalmente en una revisión sistemática, ofreciendo una panorámica detallada de la conexión entre estos componentes. Los hallazgos enfatizan la influencia directa del microbioma en la fisiopatología de estos trastornos, destacando su función crucial en la salud mental y subrayando la complejidad de este sistema interactivo. Se pone de manifiesto cómo la composición del microbioma se ve directamente afectada por la dieta, desempeñando un papel significativo en el bienestar mental de los individuos. Estos resultados no solo resaltan la urgencia de investigaciones más integradas y completas para abordar las brechas actuales en el conocimiento, sino que también señalan la necesidad apremiante de desarrollar enfoques terapéuticos y preventivos más específicos y eficaces para abordar los trastornos neuropsiquiátricos desde un punto de vista holístico y multidisciplinario.

PALABRAS CLAVE: Microbioma intestinal, trastornos neuropsiquiátricos, dieta, eje microbiota-intestino-cerebro, salud mental

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ABSTRACT

This study investigates the intricate interplay between the gut microbiome, diet, and environment in relation to neuropsychiatric disorders, with a particular focus on depression and anxiety. Adopting a qualitative methodology, an investigation was carried out based mainly on a systematic review, offering a detailed overview of the connection between these components. The findings emphasize the direct influence of the microbiome on the pathophysiology of these disorders, highlighting its crucial role in mental health and underlining the complexity of this interactive system. It is revealed how the composition of the microbiome is directly affected by diet, playing a significant role in the mental well-being of individuals. These results not only highlight the urgency of more integrated and comprehensive research to address current gaps in knowledge, but also point to the pressing need to develop more specific and effective therapeutic and preventive approaches to address neuropsychiatric disorders from a holistic point of view and multidisciplinary.

KEYWORDS intestinal microbiome, neuropsychiatric disorders, diet, gut-brain axis, mental health.

INTRODUCTION

The gut microbiome (GM), which comprises a variety of microorganisms in the gastrointestinal tract, has emerged as a critical component in the bidirectional communication between the gut and the brain, known as the gut-brain axis [GBI] (Stilling et al., 2016; Vermehren & Suarez, 2022). The GM plays a bidirectional role in the connection between the brain and the gastrointestinal tract, using the vagus nerve as a communication pathway to transmit signals in both directions (Felix da Silva et al., 2021).

This bidirectional communication process involves at least five signaling pathways that transmit responses from the gut to the brain via substances originating in the gut microbiota (Felix da Silva et al., 2021). Therefore, understanding the neurobiological processes involved in the ICE is crucial for targeting conditions such as addiction and depression (Benneyworth et al., 2019).

Several studies have linked GM to mental health conditions, such as depression, through its interaction with the gut-brain axis (de Castro et al., 2022). However, it is important to note that human research in this area is limited, although existing studies have highlighted a strong relationship between the microbiota, the gut-brain

axis, and mental pathologies (Marese et al., 2019).

Understanding the influence of GM on mental health has generated growing interest in recent years, specifically in aspects related to neuropsychiatric disorders such as depression and anxiety. The microbiome has been found to affect the composition of gut microbiota, thus contributing to these disorders (Logroño et al., 2021). Recent studies, such as that of Zhang et al. (2021), have revealed that the composition and activity of the microbiome can influence brain neurochemistry, including the production of neurotransmitters and the modulation of inflammatory pathways.

Despite advances, gaps in the literature persist, particularly in the integration of dietary and environmental factors in the relationship between ICE and its impact on neuropsychiatric disorders (Crandall et al., 2015). Contemporary research, such as that by Andreo-Martínez et al. (2017), has highlighted the essential role of GM in the regulation of brain functions and its involvement in disorders such as depression and anxiety. Furthermore, it has been associated with the risk of cancers and cardiovascular diseases, and has been highlighted in the treatment of various disorders. However, despite the rapid advancement of science, more research is needed to demonstrate how diet and environment influence microbial diversity (Requena & Velasco, 2021).

Several clinical studies, such as those by Eltokhi et al. (2020), have also shown that alterations in the microbiota can be associated with a wide range of neuropsychiatric disorders, including autism spectrum disorder, attention-deficit/hyperactivity disorder, schizophrenia, and bipolar disorder. Likewise, Martin et al. (2023) in their study demonstrated that GM, affected by diet, has an impact on mental health, covering a wide spectrum including personality, mood, anxiety, and depression.

Regarding diet, recent studies such as those by DeCapo et al. (2019) and Liang et al. (2021) have established a strong connection between maternal nutrition during pregnancy and the risk of offspring developing neuropsychiatric disorders, including depression, anxiety, and attention-deficit/hyperactivity disorder. There are clear links between diet and neuropsychiatric disorders, making it important to understand the role of the microbiome in this causality.

Similarly, the influence of the Mediterranean diet on mood, anxiety, and depression has been explored, indicating a potential bidirectional pathway between the brain and GM,

presenting an opportunity for dietary involvement in mental health management (Loke et al., 2023). Furthermore, the Developmental Origins of Health and Disease (DOHaD) hypothesis suggests that maternal diet during intrauterine and early postnatal stages impacts individual lifespan and may contribute to the development of neuropsychiatric disorders (Smaga, 2022).

Therefore, the importance of work in the specific disciplinary field is justified by the lack of a comprehensive synthesis of the available evidence in this area and the urgent need for integrated prospective research.

Thus, a more complete understanding of the underlying mechanisms of the relationship between GM and mental health can guide therapeutic and preventive interventions, offering valuable insights for improving the quality of life of people affected by neuropsychiatric disorders.

Although several studies currently address the relationship between the microbiome and different pathologies (Requena & Velasco, 2021), it is important to clarify that the lack of a comprehensive synthesis constitutes a limitation in the understanding of the underlying mechanisms, which hinders the identification of interventions. This systematic review addresses these gaps and aims to explore the interaction between the gut microbiome, diet, and environment in neuropsychiatric disorders, with a particular emphasis on depression and anxiety.

METHODOLOGY

A qualitative study was carried out, where a methodology based on the guidelines proposed by Codina (2020) for conducting systematic reviews was applied. Likewise, some of the guidelines of the PRISMA Declaration (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) were considered as a methodological guide (Page et al., 2020), specifically regarding the formulation of research questions, eligibility criteria, document search procedure, as well as the analysis and synthesis of results, allowing multiple sources as main resources (Roman-Acosta and Velandia, 2023).

Research Questions:

1. What is the impact of the gut microbiome on the pathophysiology of depression and anxiety?
2. How does diet influence the composition and diversity of the gut microbiome in the context of neuropsychiatric disorders?
3. What is the role of the environment in modulating the interaction between the gut microbiome and neuropsychiatric disorders?

4. What are the potential interventions targeting the gut microbiome that could have an impact on the prevention or treatment of depression and anxiety?
5. What are the thematic gaps in current knowledge about the interaction between the gut microbiome, diet, and environment in the context of neuropsychiatric disorders that require further research?

The methodological approach was divided into several phases to ensure the comprehensiveness and validity of the review. First, a systematic literature search was conducted in relevant databases, including PubMed, Scopus, and Web of Science. To ensure a rigorous and replicable methodology for our systematic review, we defined a structured search strategy aimed at maximizing the retrieval of relevant studies in recognized scientific databases. The search was conducted in PubMed, Scopus, and Web of Science, selected for their broad coverage in the health sciences field.
In the initial phase, a search equation was developed using key terms related to the main themes of our study: the gut microbiome, diet, environmental factors, and neuropsychiatric disorders. The specific terms used in the English search were: ("gut microbiome" OR "intestinal microbiota") AND ("diet" OR "environmental factors") AND ("neuropsychiatric disorders" OR "depression" OR "anxiety"). This combination was designed to encompass the intersection of these fields of study and ensure the inclusion of a full range of relevant research.

For the Spanish search, we adjusted the terms to: ("gut microbiome" OR "gut microbiota") AND ("diet" OR "environmental factors") AND ("neuropsychiatric disorders" OR "depression" OR "anxiety"). This was done to capture studies that may have been published in languages other than English, considering the relevance of research from Spanish-speaking contexts and the potential inclusion of regional studies that provide unique perspectives on the topic.

Date filters were established, limiting the search to publications from the last five years to ensure the data was current and relevant. Additional filters were applied to exclude non-academic documents, such as editorials and commentaries, thus focusing the review on empirical studies, systematic reviews, and meta-analyses. The use of Boolean operators facilitated an efficient and targeted search, allowing for appropriate combinations of search terms to cover studies with different approaches within the broad spectrum of the topic.

To ensure the quality and relevance of the studies included in our systematic review, detailed inclusion and exclusion criteria were established before data collection began.

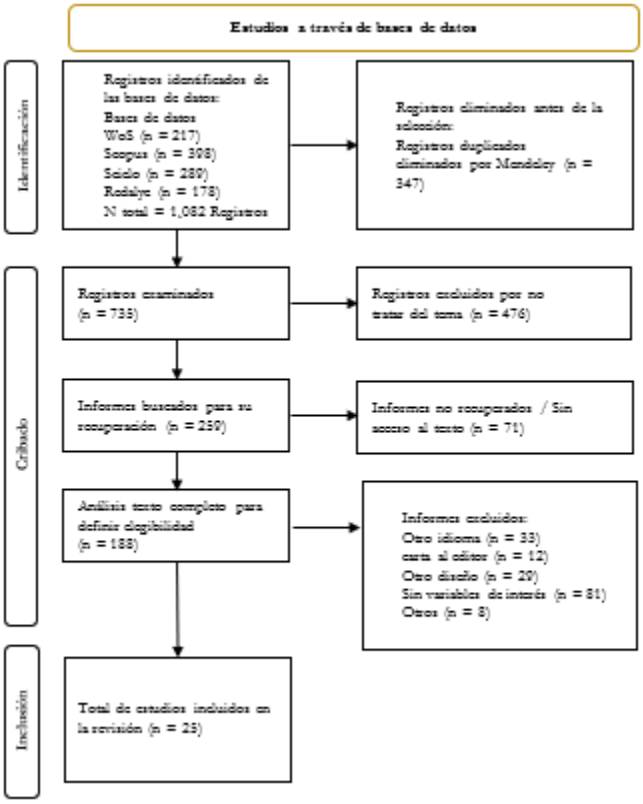
Inclusion Criteria

1. Type of studies: Primary studies (randomized controlled trials, cohort studies, case-control studies) and secondary studies (systematic reviews and meta-analyses) that provided empirical data on the relationship between the gut microbiome and neuropsychiatric disorders, including depression and anxiety, were selected.
2. Study Topics: Articles should focus specifically on the impact of the gut microbiome on neuropsychiatric disorders, covering aspects such as diet and environmental factors.
3. Languages: Articles written in English and Spanish were included to capture a broader range of research.
4. Publication period: Only studies published within the last five years were considered to ensure the relevance and timeliness of the information collected.

Exclusion Criteria

1. Publication types: Editorials, commentaries, letters to the editor, conference proceedings, conference abstracts, and books were excluded, as these do not typically offer the methodological robustness or depth of data required for a systematic review.
2. Non-relevant studies: Articles that did not directly address the relationship between the gut microbiome and neuropsychiatric disorders, or that dealt with other types of microbiomes (such as oral or cutaneous), were discarded.
3. Study quality: Studies with inadequate methodologies, insufficiently small sample sizes, or ambiguous results that did not allow clear conclusions were discarded.

Figure 1 PRISMA flowchart



Nota. Elaboración propia basado en Page et al. (2021)

The methodological quality of the selected studies was assessed based on their level of relevance (High, Medium, or Low) in relation to the topic of study in question. Thus, 25 articles were classified as High, eight as Medium, and five as Low. Considerations included sample size, which was 38 out of a total of 54 documents identified during the course of the research, as well as the validity of the measurements and methodological rigor in the interpretation of the results. The evidence synthesis was conducted using a narrative approach, highlighting the

Key findings and emerging trends were discussed. Particular attention was paid to the interrelationships between MI, diet, and environment, as well as their impact on neuropsychiatric disorders, with a particular focus on depression and anxiety. Critical analysis of the literature identified thematic gaps and provided recommendations for future research.

RESULTS

The results of the surveys carried out according to the theories that support the influence of the intestinal microbiome on neuropsychiatric

disorders: a systematic review are presented below.

Table 1

Main findings regarding the influence of the Gut Microbiome on Neuropsychiatric Disorders

Research Questions	Authors and Results
What is the impact of the gut microbiome on the pathophysiology of depression and anxiety?	Millones-Morales & Gonzales-Guevara (2021) found a significant association between the Covid-19 health crisis and increased anxiety and depression. Mariños-Llajaruna & Chafloque-Chafloque (2019) found elevated anxiety in patients with irritable bowel syndrome. Monroy-Hidalgo et al. (2019) highlighted the influence of fibromyalgia, with alterations in the microbiome, on quality of life. Studies such as that of López de la Llave (2021) showed a relationship between resilience and emotional and sociodemographic variables. Pérez (2022) indicated an increase in anxiety symptoms during the pandemic, related to a greater psychological impact. Logroño et al. (2021) and Di Micco et al. (2019) emphasized the influence of nutritional habits on the microbiome and its connection with mental health. Tapia Rodríguez et al. (2021) established alterations in the GM triggering metabolic and physiological changes, including chronic inflammation. These studies highlight the importance of understanding the complex

	relationship between the microbiome and neuropsychiatric disorders. The results show a significant association between stressful situations, such as the COVID-19 health crisis, and increased anxiety and depression. Furthermore, they point to a possible relationship between specific conditions, such as irritable bowel syndrome and fibromyalgia, and changes in the microbiome, suggesting an influence on mental health. These findings highlight the importance of understanding the complexity of the relationship between the microbiome and neuropsychiatric disorders.
How does diet influence the composition and diversity of the gut microbiome in the context of neuropsychiatric disorders?	Sieler et al. (2023) indicated that diet modulates brain inflammatory pathways and affects microbiome sensitivity. Maher et al. (2020) showed a direct relationship between specific nutrients and GM composition. Sajdel-Sulkowska (2021) evidenced a shared "microbial signature" in neuropsychiatric disorders, characterized by lower diversity and reduced anti-inflammatory bacteria. Chung et al. (2020) highlighted the impact of exercise on the microbial community. Leeming et al. (2019) identified key factors in the microbiome response to dietary interventions. These studies reveal the influence of diet on GM composition and diversity in neuropsychiatric contexts.

	It is evident that diet plays an essential role in modulating the microbiome, with specific nutrients impacting its composition and diversity. Furthermore, the influence of physical exercise on the microbial community is highlighted, demonstrating the complexity of the relationship between diet, lifestyle, and mental health.
What is the role of the environment in modulating the interaction between the gut microbiome and neuropsychiatric disorders?	Ribeiro et al. (2022) explored dietary interventions targeting the microbiome-gut-brain axis as strategies for mental health problems. González and Salgado-Morales (2021) linked occupational exposure in specific environments with microbiome composition and mental health. Kong et al. (2022) suggested an influence of the gut environment on mental health, with an emphasis on obsessive-compulsive disorder. Puntillo (2023) and Villalobos-Orozco (2023) supported the connection between the microbiome, metabolic functions, and immune responses, showing implications for mental health. These studies highlight the influence of the environment on the microbiome-neuropsychiatric disorders interaction. Studies suggest that the environment, both work and other contexts, can influence the composition of the microbiome, potentially having implications for mental health.

	Exposure to specific environments appears to be linked to changes in the microbiome and its ability to regulate immune responses, which may be linked to neuropsychiatric disorders.
What are the potential interventions targeting the gut microbiome that could have an impact on the prevention or treatment of depression and anxiety?	Rosa et al. (2022) examined the role of the microbiome and microRNAs in depression and anxiety. Browne et al. (2019) highlighted the potential of probiotics in pregnant women with depression and anxiety. Talbott et al. (2019) considered coordinated supplementation as a strategy for microbiome and mood balance. Kim et al. (2021) explored the effect of buspirone on anxiety, depression, and microbiome modulation in mice. Psychological approaches such as mindfulness (López-Zamora & Morales, 2019) and educational programs (Larios-Jiménez et al., 2023) have also been linked to benefits in reducing symptoms of anxiety and depression. These studies show potential interventions that could impact the prevention and treatment of neuropsychiatric disorders. Studies in this area are investigating multiple strategies for intervening in neuropsychiatric disorders, opening up a wide range of possibilities. From the use of probiotics to pharmacological and psychological approaches such as mindfulness, these interventions suggest diverse avenues for addressing these

	conditions, taking into account the influence the gut microbiome can have on mental health. These studies highlight the importance of adopting comprehensive approaches to treating neuropsychiatric disorders, recognizing that a single strategy may not be sufficient to address the complexity of these disorders. Combining interventions that consider both biological and psychological aspects can be critical to providing more effective and personalized treatments to people suffering from these conditions.
What are the gaps in current knowledge about the interaction between the gut microbiome, diet, and environment in the context of neuropsychiatric disorders that require further research?	Requena and Velasco (2021) highlighted the need for detailed studies to understand the specific mechanisms of how the microbiome affects brain physiology. González-Ortiz (2022) pointed out the lack of knowledge about the benefits and risks of a vegan diet on GM and mental health. Soriano-Ferrer & Echegaray-Bengoa (2020) highlighted the importance of understanding how the work environment can interact with GM and contribute to neuropsychiatric disorders. Cacho (2022) emphasized the need to investigate the implications of GM on digestive system health and its relationship with mental health. These studies identified gaps in knowledge about the interaction of the microbiome, diet,

and environment in neuropsychiatric contexts that require further investigation.

The findings raise the urgent need for further research that explores in more detail and specifically how the microbiome impacts brain physiology and, consequently, how it contributes to the development and manifestation of neuropsychiatric disorders. This emerging area of study requires continued attention to unravel the precise mechanisms through which the microbiome influences brain function, thereby affecting mental health.

Furthermore, these results underscore the critical importance of understanding how diet and environment can directly influence the microbiome and, consequently, mental health. The intricate relationship between dietary habits, nutritional quality, and environmental factors with microbiome composition and function underscores the need for interdisciplinary research that addresses this complex web of interactions.

The gaps identified in our current understanding represent an urgent call for further research to fully understand this complex and dynamic interaction between the microbiome, diet, environment, and mental health. This continued investigation is essential for identifying potential intervention or treatment options, as

	well as for developing more effective preventive strategies for addressing neuropsychiatric disorders from a holistic and integrated perspective.

Source: Prepared by the authors.

Discussion

The discussion of the results obtained in this article is situated in the context of previous scientific research addressing the complex interaction between GM, diet, and environment in the development of neuropsychiatric disorders, with a specific focus on depression and anxiety. Comparing the results of this study with the existing literature reveals similarities and divergences that shed important light on the current understanding of this field of research.

In relation to the findings of Millones-Morales and Gonzales-Guevara (2021), who explored the relationship between the COVID-19 health emergency and mental health, the present study confirms that there is a significant association between the health crisis and increased anxiety and depression. This supports the idea that environmental events, such as the pandemic, can have a direct impact on mental health through the modulation of GM.

On the other hand, Mariños-Llajaruna and Chafloque-Chafloque's (2019) research on the high prevalence of anxiety in patients with irritable bowel syndrome offers additional support to what is shown in this study, that alterations in the microbiome may contribute to neuropsychiatric disorders. This correlation between intestinal dysbiosis and mental health highlights the importance of considering the state of the microbiome in the context of gastrointestinal and neuropsychiatric disorders.

In line with recent studies by Rosa et al. (2022) and Browne et al. (2019), which explored the role of the microbiome and microRNAs in depression and anxiety, the present study highlights the relevance of MI-targeted interventions in the treatment of neuropsychiatric disorders. Therefore, the connection between microbiome modulation and mood improvement underscores the potential of these interventions as therapeutic and preventative approaches.

Furthermore, the discussion is aligned with the review conducted by Leeming et al. (2019), who examined the response of GM to short- and long-term dietary interventions. In this sense, the present review emphasizes the significant influence of diet on the composition and diversity of GM in the context of neuropsychiatric disorders, supporting the idea that nutrition plays a crucial role in mental health.

Regarding the impact of the environment, studies such as that of Kong et al. (2022) on the potential of probiotics in obsessive-compulsive disorder support what is presented in the present study on the influence of the intestinal environment on mental health. Furthermore, exposure to anthropogenic environments, such as farms, as evidenced in the work of González & Salgado-Morales (2021), also underlines the bidirectionality between the environment and GM, which in turn affects mental health.

However, although this review contributes to our understanding of the interaction between GM, diet, and environment in neuropsychiatric disorders, it recognizes its limitations, such as the lack of a comprehensive synthesis of some specific aspects. This comparative analysis with previous scientific research helps contextualize the results and highlight the importance of addressing the gaps identified in the literature for future research.

Despite the progress made in this systematic review, it is important to acknowledge the study's inherent limitations. First, most of the reviewed research is based on observational studies and correlational data, implying limitations in establishing definitive causal relationships. The multifactorial nature of neuropsychiatric disorders and the complexity of the microbiome-gut-brain interaction suggest that multiple variables could contribute to the observed outcomes.

Furthermore, most of the reviewed studies focus on depression and anxiety, which may not fully encompass the complexity of neuropsychiatric disorders. Other disorders, such as autism spectrum disorder, attention-deficit/hyperactivity disorder, schizophrenia, and bipolar disorder, are also relevant in this context and could benefit from more focused research.

To advance our understanding of the relationship between GM and neuropsychiatric disorders, several directions for future research are proposed.

First, more focused studies are suggested to assess the precise effects of interventions such as probiotics and prebiotics on the

microbiome and their impact on mental health. It is also essential to explore how environmental factors, such as exposure to nature or pollution, can modulate the microbiome-gut-brain relationship.

Thus, the inclusion of longitudinal and experimental research designs is also highlighted as a necessity to establish causal relationships and evaluate the effectiveness of interventions over time. Furthermore, the focus should be expanded beyond depression and anxiety to include other neuropsychiatric disorders, providing a more complete and holistic understanding of the microbiome-mental health interaction. Consideration of lifestyle factors, such as exercise, sleep quality, and stress, also merits greater attention in future research.

Finally, the importance of conducting targeted studies in diverse populations, considering ethnic, geographic, and genetic differences, is emphasized to ensure the global applicability of the findings and the effectiveness of the proposed interventions. Together, these recommendations can pave the way for more robust and applicable research, thus advancing the field of mental health and its impact on mental health.

Conclusions

Detailed research on the interaction between the gut microbiome, diet, and environment in relation to neuropsychiatric disorders has revealed significant findings that highlight the fundamental role of the microbiome in the pathophysiology of depression and anxiety. The identified results emphasize how alterations in the microbiome are intrinsically linked to changes in the composition of the gut flora, which directly contribute to the development of neuropsychiatric disorders.

Furthermore, the close connection between diet, gut microbiota, and mental health is highlighted, demonstrating how eating habits and nutritional quality can modulate mental health status through their influence on the gut microbiome. The modulating role of the environment in this complex relationship is also emphasized, highlighting how environmental factors can influence the composition and functioning of the microbiome, and in turn, mental health.

This review offers a more complete understanding of the combined influence of the gut microbiome, diet, and environment on the development of neuropsychiatric disorders, particularly depression and anxiety. It also highlights the need to address existing gaps in the literature, proposing specific recommendations

for future research that focuses on these key areas and integrates different disciplines for a more holistic understanding of these disorders and their potential treatments or interventions.

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