v. 4, n. 75, 2024

International Journal of Health Science

THE INFLUENCE OF THE GUT MICROBIOTA AND ITS DYSBIOSIS ON MENTAL HEALTH: RELATIONSHIPS WITH STRESS AND ANXIETY DISORDERS AND DEPRESSION

Erika Veríssimo Villela
Professor of the Medicine course at Estácio de Sá University, Institute of Medical Education (IDOMED)
http://lattes.cnpq.br/9928826045142082

Isabelly de Freitas Cruz
Student of the Medicine course at Estácio de Sá University, Institute of Medical Education (IDOMED)
http://lattes.cnpq.br/0461772975667140

Manuela Sanchez Campos
Student of the Medicine course at Estácio de Sá University, Institute of Medical Education (IDOMED)
http://lattes.cnpq.br/2039976015524045

Helena Almeida Vardiero
Student of the Medicine course at Estácio de Sá University, Institute of Medical Education (IDOMED)
http://lattes.cnpq.br/5407392149078267

Abstract: The intestinal microbiota plays important roles in our bodies, including the production of vitamins (K and B), the maturation of the immune system and the prevention of pathogenic bacteria. In recent years, there has been an increase in studies on the important benefits that the enteric microbiota brings to the nervous system through the gut-brain axis. While the role of the intestinal microbiota in the body's homeostasis is highlighted, its alteration, known as dysbiosis, has been widely studied and related to important changes in the health-disease process, including the role it plays in mental disorders. Some studies relate dysbiosis to psychological distress, such as some mental illnesses such as depression and anxiety, and also to increased susceptibility to stress. Research on the relationship between the intestinal microbiota and mental health has intensified in recent years, but many studies still need to be conducted to better elucidate this important relationship. In view of the above, the present study aims to understand the relationship between the intestinal microbiota and its alteration (dysbiosis) with depression and anxiety, as well as to elucidate the factors that relate stress to alterations in the intestinal microbiota. In order to achieve the proposed objectives, an exploratory qualitative research was carried out through a narrative review of the literature, carried out by searching for publications from the last 10 years, in the PubMed and Scielo databases, in Portuguese and English, using the following descriptors: Intestinal Microbiota, Dysbiosis, Anxiety, Depression and Stress. The selection of studies took into consideration, the relevance and originality of the data obtained, which were analyzed, discussed and used to elucidate the influence of the intestinal microbiota and its dysbiosis on mental health, as well as the factors that promote the balance of this microbiota, leading to new proposals for future studies on the subject.
Keywords: Intestinal Microbiota; Intestinal Dysbiosis; Anxiety; Depression; Stress

INTRODUCTION

The gastrointestinal tract is colonized soon after birth by a set of commensal microorganisms that form the intestinal microbiota, which is formed by many microorganisms that establish a permanent colonization in the area and others that establish a temporary colonization. The intestinal microbiota is formed throughout the individual's life and is already of great importance for the health of the baby, continuing to influence that of the adult individual (BARBOSA et al., 2010).

The composition of the microbiota is formed according to the type of birth and is influenced by the type of diet, lifestyle, use of medications and the individual's own genetics, establishing, mainly in adulthood, a set of microorganisms formed mainly by bacteria, but also by archaea, protozoa, fungi and viruses (LYNCH & PEDERSEN, 2016).

Among the bacteria that make up the enteric microbiota, we can highlight the genera Bifidobacterium spp., Bacteroidetes spp. and Lactobacillus sp. as beneficial, but we also find the large family Enterobacteriaceae and other genera such as Clostridium sp., Fusobacterium spp., Ruminococcus sp, among others, adding up to a population of around 1000 distinct bacteria (LYNCH & PEDERSEN, 2016).

Acting commensally in the intestine, the enteric microbiota provides a series of benefits, such as protection against pathogens, production of vitamins, absorption of nutrients, in addition to an important role in modulating the immune system and metabolism (NEUHANNIG, 2019).

In recent years, much has been said about the mutual relationship between the

gastrointestinal tract, represented by the intestinal microbiota, and the central nervous system, which establish a bidirectional communication pathway, the gut-brain axis. This pathway is directly related to health and well-being and its imbalance can lead to different types of disorders, as well as mental disorders (TONINI, VAZ & MAZUR, 2020). The brain and intestine establish a complex and dynamic communication network, in which molecules derived from the intestinal microbiota, such as short-chain fatty acids, lipopolysaccharides, tryptophan and others, play an important role in signaling responses from the intestine to the brain, and can bring benefits or harm depending on the type of molecule produced (FARZI et al., 2018).

In addition to recognizing the numerous benefits of the intestinal microbiota, it is also known that its imbalance, known as dysbiosis, is responsible for a series of pathological manifestations in the human body, mainly by triggering changes that favor a pro-inflammatory state, related to various types of diseases, especially mental ones, such as depression and anxiety (NEUHANNIG, 2019).

Depression is a disease that affects more than 300 million people globally (WHO, 2017). It is characterized by a sad, empty or irritable mood, clear variations in affect, related to somatic, cognitive and neurovegetative changes, which significantly compromise the individual's ability to carry out daily activities (SILVA, 2021). Anxiety is described as a common form of mood disorder, with nervous, endocrine and immunological pathophysiology. Both are diseases associated with the psychosocial stress that people experience on a daily basis, as well as with stress (GROCHOWSKA, 2018; MARESE, 2019).

Depression and anxiety are multifactorial diseases, without a completely established biological mechanism, which involve the hypothalamic-pituitary-adrenal axis, genetic and growth factors, monoamine deficiency, stress and other possible mechanisms, such as changes in the intestinal microbiota, which has been emerging as a potential modulator of human behavior (GROCHOWSKA, 2018).

The role of the intestinal microbiota and its dysbiosis in interfering in the health and disease process is already well established, but more specific studies on the relationship between the intestinal microbiota and its imbalance with mental disorders are lacking, disorders that increase substantially in the population every year. In view of the above, the present study aimed to understand the relationship between changes in the intestinal microbiota (dysbiosis) and depression and anxiety, in addition to elucidating the factors that relate stress to changes in the intestinal microbiota.

METHODOLOGY

This study is an exploratory qualitative research through a narrative review of the literature on the researched topic, based on the search for publications from the last ten years, in Portuguese and English, in the US National Library of Medicine National Institutes of Health (PubMed) and Scientific Electronic Library Online (Scielo) databases. The search was based on the intersection of the following descriptors: Intestinal Microbiota, Intestinal Dysbiosis, Mental Health, Stress, Anxiety and Depression, submitted to the Boolean combinations "AND".

After selecting the studies found according to their relevance to the topic and originality, and according to the inclusion and exclusion criteria established by the research group, the data were organized and analyzed for the interpretation and discussion of the results presented below.

RESULTS AND DISCUSSION

The microbiota-gut-brain axis has been widely studied in recent years, mainly in relation to the influence that the intestinal microbiota has on the health status of individuals. This axis represents a complex system of communication between the intestine and the brain, which involves a network of nerve connections and chemical substances, whose concept was described by Pista in 1980, based on discoveries about hormonal signaling of the gastrointestinal endocrine system in neurons and brain cells (CARABOTTI et al, 2015).

Silvestre (2015) highlights the influence of commensal microorganisms of the intestinal microbiota on the Enteric and Central Nervous Systems, showing the dynamic interaction between the "big" and "small" brain (gut). Several signaling pathways are important for this axis, including hormonal, metabolic and immunological, which establish communication between the enteric microbiota and its metabolites with the brain, allowing inferences about the influence that this microbial community can exert on human behavior (DYNAN & CRYAN, 2015).

The enteric nervous system, composed of millions of neurons, is capable of operating independently of the brain, but also maintains constant bidirectional communication with it. This interaction is essential for the regulation of mood, behavior, mental health and gastrointestinal functioning, demonstrating the relevance of the gut-brain axis for the general well-being of the organism (MAIUOLO et al., 2021; MARGOLIS et al., 2021).

Studies point to the contribution of the beneficial intestinal microbial population in the production of important neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA) and catecholamines, along with other neuroactive substances that influence the gut-brain axis and whose normal levels are important for preventing depression and anxiety (SILVESTRE, 2015).

On the other hand, the imbalance of the microbiota, known as dysbiosis, by interfering in the composition of beneficial microbial species and the products of their metabolism, leads to disharmony in the health-disease process in a broad sense, including mental health (AISSA et al, 2021).

Intestinal dysbiosis has been associated with the primary or secondary cause of several diseases, as it can lead to changes in intestinal permeability, allowing toxins and pro-inflammatory molecules, produced by bacteria, to enter the bloodstream and affect the central nervous system. The resulting inflammation can impair communication between the intestine and the brain, contributing to the development or worsening of neuropsychiatric conditions, such as depression (IEBBA et al., 2016; ASAHARA et al., 2016).

In addition, intestinal dysbiosis can interfere with the production of several neurotransmitters and substances that play a fundamental role in mood control, such as serotonin, which are found to be altered in depression and anxiety (GROCHOWSKA et al, 2018). Intestinal dysbiosis has also been related to stress, which, in turn, interferes with the composition of the intestinal microbiota, reducing species diversity and the number of beneficial species (DELEEMANS, 2020; KLEIMAN, 2017).

Peptides and their receptors, released in the intestine in a state of dysbiosis caused by stress, are expressed in the brain and play neurobiological roles in anxiety. Stress leads to an imbalance in the secretion of peptides in the intestine, with harmful interferences to the gut-brain axis. Thus, exploring the study of how the microbiota can influence the physiology of these peptides is extremely

important for the development of new strategies in the treatment of disorders such as anxiety (LACH et al, 2018).

A study analyzed by Kumar and collaborators was able to relate people who maintained a nutrient-poor eating pattern and low consumption of foods considered beneficial to the intestine, to the presence of an intestinal microbiota formed by *Bacteroides, Prevotella, Proteobacteria and Eggerthella*, bacteria that cause intestinal irritation and are related to increased anxiety symptoms (KUMAR et al, 2023).

According to a study evaluated by Xiong and collaborators (2023), people diagnosed with anxiety have an abundance of bacteria such as *Prevotella, Bacteroidetes* and *Faecalibacterium* and a reduction in bacteria such as *Lactobacillales, Sellimonas and Enterococcus*, data that show the importance of future studies related to different species of bacteria and how they contribute to anxiety.

Yang and collaborators (2023) pointed out the relationship between repetitive exposure to anesthesia in children and the subsequent development of anxiety behaviors. The use of general anesthesia has been considered safe in children, however, little is discussed about its long-term neurotoxic effects on a still developing brain and its impact on the microbiota and the gut-brain axis. Some studies have emphasized the importance of the intestinal microbiota early in life as one of the main modulators of a person's future health, such as the study that points to the relationship between prolonged and excessive exposure to anesthetics during surgeries and the modification of the composition of the intestinal microbiota, which subsequently favors the development of children with anxiety disorders (YANG et al, 2023).

According to Mackie et al. (1999), the composition of the microbiota is the result of several factors related to changes in the intestinal environment, lifestyle and eating habits, and is therefore unique to each individual. Desbonnet (2015) warns against the indiscriminate use of antibiotics, especially in children, due to their ability to modulate the composition of the microbiota, which can interfere with the mesocrotic-limbic circuit, causing disorders such as depression and anxiety.

Studies show that antidepressant medications are also capable of interacting with the intestinal microbiota, increasing and decreasing certain microbial taxa in a specific manner depending on the medication. Fluoxetine, for example, increases the population of *Lactobacillus, Alistipes, Parabacterioides*, among others, while decreasing *Firmicutes, Escherichia, Enterococcus*, and others (SUN et al., 2021).

Huang et al. (2018) concluded that individuals with depression have a significant decrease in the amount of Firmicutes, a bacteria that contributes to the fermentation of carbohydrates, generating short-chain fatty acids, which causes the weakening of the protective factors of the intestinal barrier and consequently increases the risk of inflammation.

Although the composition of the bacterial microbiota is stable throughout life, it is known to be susceptible to environmental changes and can respond to internal and external factors, such as stress, sleep quality, physical and psychological stressors, and nutrition. Thus, stressors can alter intestinal balance, leading to low diversity and uneven distribution of species (COOKE et al, 2022).

Furthermore, stress is a significant risk factor for depression, as it impairs communication between the intestinal microbiota and the brain, altering the composition and proportion of the intestinal microbiota, significantly reducing the levels of *Firmicutes* and bacteria from the *Lactobacillaceae* family, which are

important for the health of the gut-brain axis (JIANG et al., 2015).

Data from some studies evaluated by Järbrink-Sehgal & Andreasson (2020) show that changes in the intestinal microbiota are highly correlated with stress. When a person is constantly exposed to stressful situations, the body releases stress hormones, such as cortisol, which can affect the bacterial community in the intestine. There is also a change in intestinal permeability, allowing toxins and harmful bacteria to pass into the bloodstream, causing inflammation and damaging the balance of the microbiota.

According to a study analyzed by Madison et al. (2019) in stressed participants, increased cortisol together with mast cells helps to weaken the intestinal barriers, allowing bacteria to leak through these barriers remodeled by stress, thus favoring increased inflammation.

As observed in several studies, imbalances in the intestinal microbiota can cause a decrease in hormone levels and lead to mood or behavioral instability that is related to stress, anxiety and depression, which increase every year in a large part of the population (SARAIVA; CARVALHO; LANDIM, 2020).

A study carried out by Da Silva et al. (2021) found that people with anxiety disorders and depression have an altered microbial composition, possibly due to stress, caused by such disorders, causing changes in colon mobility. In contrast, it was observed that prebiotic supplementation reduced the ability to respond to stress, anxiety and depressive-like behavior, increasing the expression of brain-derived neurotrophic factor (BDNF) with improved cognition.

To date, the main treatment for anxiety disorders and depression is based on pharmacotherapy and is associated with numerous side effects. However, studies have shown that the use of probiotics and changes in diet and lifestyle play an important role in modulating the microbiota and reducing anxiety symptoms (GUARNER, 2014 & KUMAR, 2023).

Probiotics, live microorganisms capable of conferring health benefits to the host when administered in adequate amounts, positively influence the intestinal microbiota in several ways, such as competition for nutrients or adhesion sites in the intestinal wall and the production of growth substrates that benefit other bacteria present in the intestinal environment, among other mechanisms (GUARNER et al 2014).

Recent clinical studies have shown that some probiotic strains can help alleviate symptoms of stress, anxiety, and depression, particularly those from the genera *Bifidobacterium* and *Lactobacillus* (MA et al, 2021).

A randomized controlled trial analyzed by Järbrink-Sehgal & Andreasson (2020) evaluating the effect of multispecies probiotics on anxiety in university students, found improvements in panic anxiety, neurophysiological anxiety, worry, and better regulation of negative mood in the group that used the probiotic compared to the placebo group.

Studies analyzed by Xiong (2023) pointed to the relationship between probiotics, particularly Lactobacillus, and the fight against anxiety, by increasing the release of GABA in the hippocampus and alleviating symptoms of anxiety and depression. Additionally, a study conducted in New Zealand with 423 women showed that the use of *Pediococcus acidilactici* as a probiotic alleviated symptom of anxiety by inhibiting the hyperproliferation of Escherichia coli and stimulating the proliferation of *Bifidobacterium*. In short, probiotics such as Lactobacillus, Bifidobacterium, and Pediococcus acidilactici have shown significant prevention and treatment of anxiety (XIONG, 2023).

The Western lifestyle, based on the deliberate consumption of inflammatory foods, such as ultra-processed flours and sugars, prevents the diversification of the intestinal microbiota, contributing directionally to a diseased intestinal microbiota. The correct functioning of the gut-brain axis is based on dietary support of nutrients such as vitamins, minerals, and amino acids. As a result, there is a relationship between Western dietary patterns, based on low consumption of fruits and vegetables and high consumption of refined, processed foods, red meat, dairy products, and high fat content, with symptoms of anxiety (KUMAR et al, 2023).

The provision of foods rich in fiber and fermented foods (such as Kombucha and Kimchi) to intestinal bacteria is a way to increase the diversity of the intestinal microbiota, increasing the number of "healthy" bacteria with reversal of intestinal dysbiosis (XIONG et al, 2023).

Studies with mice have shown that there was a reduction in hormones linked to stress and symptoms of anxiety and depression with the modulation of the microbiota through diet and have shown that changes in the intestinal microbiota can facilitate or hinder the absorption of tryptophan, an amino acid necessary for the production of serotonin, a neurotransmitter linked to well-being and with a prominent role in cases of depression and anxiety (O`MAHONY, 2015).

Studies show that changing your diet to include vegetables, fruits, cereals, fish, nuts, legumes, seeds, and herbs such as curcumin can prevent the development of anxiety. In addition, dietary control based on a Mediterranean diet can reduce intestinal inflammation by dramatically reducing the amount of Bacteroides and *Campylobacter jejuni*, bacteria that induce symptoms of anxiety and depression, while also increasing the number of Lactobacillus and *Bifidobacterium*, species that have been shown to reduce anxiety (KUMAR et al, 2023).

CONCLUSIONS

The results presented in this study highlight the growing importance of the relationship between the intestinal microbiota and mental health, demonstrating how intestinal dysbiosis, by intensifying the state of neuroinflammation, may be closely linked to the development and severity of psychiatric conditions such as anxiety and depression, and is also influenced by stress.

The evidence presented indicates that intestinal health plays a fundamental role in the proper functioning of the brain and central nervous system, through the gut-microbiota-brain axis. Given this, it is important to explore the complex relationship between the intestinal microbiota and depression, anxiety and stress, with the aim of opening new paths for the development of effective and holistic therapies for the treatment of these conditions.

Intensifying research and studies on the mechanisms by which the dysbiotic microbiota can interfere in mental suffering, and how its modulation can be a potential therapeutic target by contributing to a healthy intestinal microbiota, is of utmost importance, and can bring important contributions to significantly improving the quality of life of affected patients.

REFERENCES

AISSA, R. S. N et al. **Saúde Mental e suas interfaces: rompendo paradigmas**. Editora Poisson, 1ª. Edição, 2021.

Asahara, t. et al. Possible association of Bifidobacterium and Lactobacillus in the gut microbiota of patients with major depressive disorder. Journal of affective disorders, v. 202, p. 254-257, 2016.

BARBOSA, F. et al. Microbiota indígena do trato gastrintestinal. **Revista de Biologia e Ciência da Terra**, Aracaju, v. 10, n. 1, p. 78-93, jan./jun. 2010.

CARABOTTI, M. et al. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. **Annals of Gastroenterology**, v. 28, p. 203-209, 2015.

COOKE, M. B.; CATCHLOVE, S.; TOOLEY, K. L. Examining the Influence of the Human Gut Microbiota on Cognition and Stress: A Systematic Review of the Literature. **Nutrients**, v. 14, n. 21, p. 4623, 2022.

DA SILVA, B. M. F. *et al*. Associação da microbiota intestinal com o transtorno da ansiedade e depressão. **Pesquisa, Sociedade e Desenvolvimento**, v. 10, n. 4, 2021.

DELEEMANS, J. M. et al. The chemo-gut study: investigating the long-term effects of chemotherapy on gut microbiota, metabolic, immune, psychological and cognitive parameters in young adult Cancer survivors; study protocol. **BMC Cancer**, v. 19, n. 1, p. 1243, 2019.

DESBONNET, L. et al. Gut microbiota depletion from early adolescence in mice: Implications for brain and behaviour. Brain, Behavior, and immunity, v. 48, p. 165-173, 2015.

DINAN, T.G., CRYAN, J.F. The impact of gut microbiota on brain and behaviour: implications for psychiatry. **Curr Opin Clin Nutr Metab Care**. v. 6, p. 552-8, 2015.

FARZI, A., FRÖHLIC, E. E. & HOLZER, P. Gut Microbiota and the Neuroendocrine System. **Neurotherapeutics,** v. 15, p. 5–22, 2018.

GUARNER, F. et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. **Nature Reviews – Gastroenterology and hepatology**, v. 11, p. 506-514, 2014.

GROCHOWSKA, M., WOJNAR, M., & RADKOWSKI, M. The gut microbiota in neuropsychiatric disorders. **Revista Acta Neurobiol**, v. 78, p. 69-81, 2018.

HEBERLING, C.; DHURJATI, P. Novel Systems Modeling Methodology in Comparative Microbial Metabolomics: Identifying Key Enzymes and Metabolites Implicated in Autism Spectrum Disorders. **International Journal of Molecular Sciences**, v. 16, n. 12, p. 8949–8967, 2015.

HUANG, Y. et al. Possible association of Firmicutes in the gut microbiota of patients with major depressive disorder. **Neuropsychiatric Disease and Treatment**, v. 18, p. 3329-3337, 2018.

IEBBA, V, et al. Eubiosis and dysbiosis: the two sides of the microbiota. New Microbiology, v. 39, n. 1, p. 1-12, 2016.

JÄRBRINK-SEHGAL, E.; ANDREASSON, A. The gut microbiota and mental health in adults. **Current opinion in neurobiology**, v. 62, p. 102-114, 2020

JIANG, I. Altered fecal microbiota composition in patients with major depressive disorder. **Brain, Behavior, and Immunity**, v. 48, p. 186-194. 2015.

KLEIMAN, S. C. et al. The Gut-Brain Axis in Healthy Females: Lack of Significant Association between Microbial Composition and Diversity with Psychiatric Measures. **PLOS ONE**, v. 12, n. 1, 2017.

KUMAR, A et al. **Gut Microbiota in Anxiety and Depression: Unveiling the Relationships and Management Options.** Pharmaceuticals. 2023.

LACH.G. et al. **Anxiety, Depression, and the Microbiome: A Role for Gut Peptides**. Neurotherapeutics. 2018.

LYNCH, S. V. & PEDERSEN, O. The human intestinal microbiome in health and disease. **N. Engl. J. Med**, v.375, p.2369–2379, 2016.

MA, T. et al. Probiotic consumption relieved human stress and anxiety symptoms possibly via modulating the neuroactive potential of the gut microbiota. **Neurobiology of Stress**, v. 14, p. 100294, 2021.

MACKIE, R. et al. Developmental microbial ecology of the neonatal gastrointestinal tract. The American Journal of Clinical Nutrition, v. 69, n. 5, p. 1035-1045, 1999.

MADISON, A.; KIECOLT-GLASER, J.K. Stress, depression, diet, and the gut microbiota: human–bacteria interactions at the core of psychoneuroimmunology and nutrition. **Current opinion in behavioral sciences**, v. 28, p. 105-110, 2019.

MAIUOLO, J. et al. The Contribution of Gut Microbiota-Brain Axis in the Development of Brain Disorders. Frontiers in neuroscience, v. 15, 2021.

MARGOLIS, K. G. et al. The Microbiota-Gut-Brain Axis: From Motility to Mood. Gastroenterology, v. 160, n. 5, p. 1486-1501, 2022.

MARESE, A. C. M. et al. Principais mecanismos que correlacionam a microbiota intestinal com a patogênese da depressão. **FAG Journal of health,** v. 1, n. 3 p 232-239, 2019.

NEUHANNIG, C. et al. Disbiose Intestinal: Correlação com doenças crônicas da atualidade e intervenção nutricional. **Research, Society and Development**, v. 8, n. 6, 2019.

O`MAHONY, S. M. et al. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. **Behav Brain Res**. v.277, p. 32-48, 2015.

SARAIVA, F. R. de S.; CARVALHO, L. M. F. de; LANDIM, L. A. dos S. R. Depressão e disbiose. **Nutrição Brasil**, v. 18, n. 3, p. 175–181, 2020.

SILVA, B. M. S et al. Associação da microbiota intestinal com o transtorno da ansiedade e depressão. **Research, Society and Development,** v. 10, n. 4, 2021.

SUN, L.; ZHANG, H., CAO, Y., WANG C. *et al*. Fluoxetine ameliorates dysbiosis in a depression model induced by chronicun predicted mild stress in mice. **International journal of medical sciences**, v.16, n. 9, p. 1260-1270, 2019.

TONINI, I. G. O., VAZ, D. S. S, MAZUR, C. E. Eixo intestino-cérebro: relação entre a microbiota intestinal e desordens mentais. **Research, Society and Development**, v. 9, n. 7, 2020.

WORLD HEALTH ORGANIZATION (WHO). **Depression**. Factsheet Updated in February 2017. Disponível em <http://www.who.int/mediacentre/factsheets/fs369/en/> Acesso em: 20 abr 2022.

XIONG, R.G et al. **The Role of Gut Microbiota in Anxiety, Depression, and Other Mental Disorders as Well as the Protective Effects of Dietary Components.** Nutrients. 2023.

YANG, X et al. **Impact of Repeated Infantile Exposure to Surgery and Anesthesia on Gut Microbiota and Anxiety Behaviors at Age 6–9.** Journal of personalized medicine. 2023.