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Impact of gut microbiota on the central nervous system relevance in neurodegenerative and psychiatric diseases

Znaczenie nienasyconych kwasów tłuszczowych w leczeniu depresji - międzynarodowe wytyczne kliniczne i rekomendacje towarzystw psychiatrycznych

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Abstract

Introduction: The gut microbiota plays an important role in regulating the function of the gut-brain axis. Incorrect dietary habits promote the development of metabolic syndrome, which negatively affects the biodiversity of the microbiome. The aim of the study was to determine the influence of the gut microbiota on the function of the gut-brain axis and the development of mental and neurodegenerative diseases.

Material and methods: A review of available literature was performed by searching the official databases PubMed and Google Scholar using the following keywords: metabolic syndrome, gut microbiome, metabolic microbiome, mental illness, neurodegenerative diseases with reference to original papers, meta-analyses and reviews in Polish, Ukrainian and English published in scientific journals and articles.

Results: Studies evaluating the role of gut microbiota in the pathogenesis of psychiatric and neurodegenerative diseases show promising results, suggesting that gut microbiota influences brain function by modulating the gut-brain axis, the immune system, and neurotransmitter production. Despite the growing evidence implicating microbiota in the development of diseases such as depression, schizophrenia, Alzheimer's disease, and Parkinson's disease, study results often remain inconsistent, which may be due to methodological differences, heterogeneity of study populations, and sample size limitations.

Conclusions: Further research on the influence of gut microbiota on the development of psychiatric and neurodegenerative diseases may contribute to a better understanding of the pathophysiology of these disorders and the discovery of new strategies for their treatment and prevention. Further research in this direction is needed to better understand the influence of gut microbiota on psychiatric and neurodegenerative disorders.

Keywords: metabolic syndrome, mental illness, neurodegenerative diseases, gut microbiome, metabolic microbiome

Abbreviations: International Diabetes Federation (IDF), short-chain fatty acids (SCFA), peptide YY (PYY), glucagon-like peptide-1 agonist (GLP-1), adenosine triphosphate (ATP), blood-brain barrier (BBB), central nervous system (CNS), Alzheimer's disease (AD), pathogen-associated molecular patterns (PAMPs), Toll-like receptors (TLRs), autism spectrum disorder (ASD), social anxiety disorder (SAD), bipolar disorder (BD), Young's Mania Rating Scale (YMRS), World Health Organization (WHO), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD)

Introduction

The complex community of bacteria, fungi, and viruses, called the gut microbiome, plays an important role in regulating the functions of the digestive system, nervous system, metabolism and mental state [1-3]. Communication between the microbiota and the brain takes place via the gut-brain axis. It is co-created by the vagus nerve and mediators - tryptophan and microbiome metabolites, primarily short-chain fatty acids [4-7]. Dysfunction of this pathway is associated with the pathogenesis of diseases, such as depression, Parkinson's disease, Alzheimer's disease, autism, schizophrenia and ADHD [8-13].

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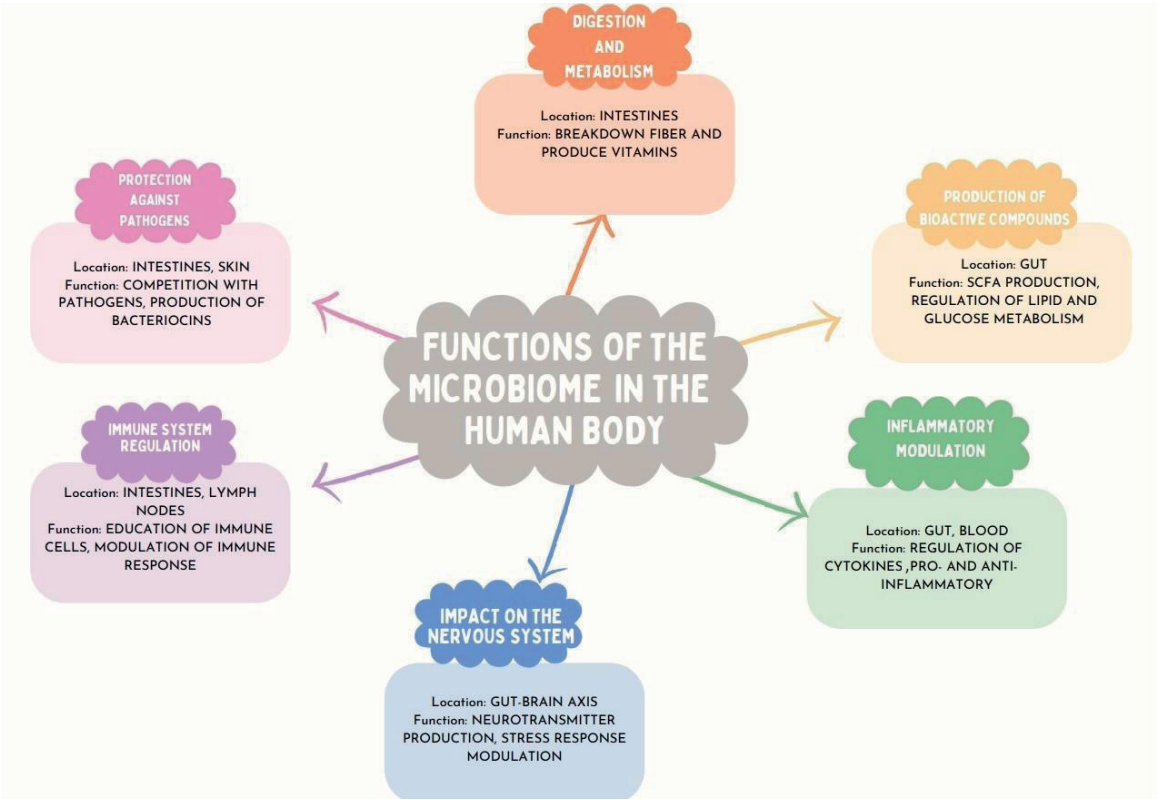

Function of the microbiome in human body

Gut Microbiome

The human body consists of approximately 10^{13} - 10^{14} bacteria [14]. The dominant microorganisms in the gastrointestinal tract are *Firmicutes* and *Bacteroidetes*, which are the most abundant and variable species [15]. *Bacteroidetes* and *Firmicutes* degrade complex polysaccharides into monosaccharides and short-chain fatty acids (SCFAs): acetate, propionate, and butyrate [16-18]. These substances activate G protein-coupled receptors (GPR41 and GPR43) on intestinal epithelial cells, leading to the secretion of peptide YY (PYY), which inhibits gastrointestinal motility and delays intestinal transit. SCFAs also demonstrate the ability to activate the GPR120 receptor, which promotes the release of GLP-1 and the maintenance of immune homeostasis, and thus reduces inflammation [19,20]. Bacteria obtain energy through the fermentation of amino acids. The by-products of these processes, such as cresol, skatole, indole, hydrogen sulphide, mercaptan, and benzoic acid, are highly harmful to the host epithelial cells, as they promote the development of leaky gut syndrome, leading to numerous dysfunctions and the development of diseases [21,22].

Gut microbiota composition and body weight

Metabolic syndrome is defined as a pathological condition characterized by elevated blood pressure, dyslipidemia (elevated triglyceride levels and decreased high-density lipoprotein cholesterol levels), elevated fasting glucose levels, and central obesity [23,24].

Diet and exercise play a key role in shaping the composition of the intestinal microbiota [25,26]. Studies on the composition of the intestinal microbiota in animals have shown that in obese individuals the number of *Bacteroidetes bacteria* was reduced by about 50%, while the number of *Firmicutes bacteria* increased proportionally compared to individuals with normal body weight [27]. A similar analysis was carried out in humans. The control group consisted of lean individuals on a normocalorie diet. The research group consisted of 12 obese individuals. They were randomly assigned to two groups – the first received a diet with reduced fat content, while the second – a diet with reduced carbohydrate supply. The composition of bacteria in stool samples was monitored for 12 months. Before the study began, the research group had a lower number of *Bacteroidetes bacteria* and a higher number of *Firmicutes* compared to the control group. It was observed that the weight loss was accompanied by an increase in the ratio of *Bacteroidetes* to *Firmicutes*, proportionally to the amount of weight lost, regardless of the type of diet. Initially, *Bacteroidetes bacteria* constituted about 3%, but after weight loss their number increased to 15% of the entire gut microbiome. The changes in the gut microbiome were reversed after cessation of exercise. Therefore, regular physical activity helps maintain a favorable composition of the microbiota [28,29].

In turn, Scheiman et al. observed an increase in the relative number of bacteria of the genus *Veillonella* in participants after running a marathon [30]. A possible explanation for this phenomenon may be the ability of *Veillonella* to use L-lactate produced by Lactobacillus as an energy source. Lactate fermentation by Veillonella alcalescens proceeds as follows: lactate → acetate + H2 + CO2 + propionate + ATP [31]. In an experiment on mice using labeled lactate, it was shown that lactate produced during exercise penetrates the intestinal lumen, where it is metabolized by *Veillonella bacteria* to propionate. As a result, ATP production increases and lactate concentration decreases, which is responsible for muscle microdamage and delayed muscle pain, commonly called "soreness" [32,33]. The interaction between *Lactobacillus* and *Veillonella* explains the anti-inflammatory effect of the microbiome on the host's health and supports the improvement of physical performance.

Gut microbiota composition and neuropsychiatric disorders

The stage of adolescence is characterized by high sensitivity to pathological factors, which makes it a critical period in the development of mental disorders, such as schizophrenia, mood disorders or addictions [34]. Exposure to stress, stimulants, poor diet combined with the instability and immaturity of the gut microbiota lead to the susceptibility of the brain to the emergence of disorders at this stage of life [35]. The quality of the gut microbiota and its stability decrease with age. Aging and harmful external factors negatively affect the gut microbiota and thus the maintenance of health. Ensuring an appropriate intestinal bacterial flora seems to be an important factor in the prevention of mental illnesses and cognitive disorders associated with aging [36].

Genes involved in the formation of synapses between neurons in the brain and in the gastrointestinal tract are similar, so any mutation can lead to abnormalities in both the brain and the gastrointestinal tract [83]. Theoharides et al. described transcriptome changes in individuals with autism, bipolar disorder, major depressive disorder, schizophrenia, and multiple sclerosis, such as decreased expression of genes involved in mitochondrial function and ATP production and increased expression of genes involved in inflammatory and immune processes, as well as genes responsible for oligodendrocyte activity [84].

Alzheimer's disease

The microbiota produces compounds that increase the permeability of the intestinal barrier, allowing contact between the intestinal microbiota and submucosal lymphoid tissue. This, in turn, triggers a systemic inflammatory response that weakens the blood-brain barrier (BBB) and promotes inflammation in the central nervous system (CNS) [37]. Chronic inflammation in the CNS causes prolonged activation of glial cells, which generate cytokines and neurotoxins, leading to neural degeneration [38]. The microbiota can regulate these processes [39]. Amyloids, present in both microorganisms and the human brain, despite differences in the process of their formation, have similar physicochemical properties and pathogen-associated molecular patterns (PAMPs) structures. They are recognized by the same Toll-like receptors (TLR2 and TLR1), which induces an immune response, including the production of proinflammatory cytokines IL-17 and IL-22. Damage to the blood-brain barrier (BBB) disrupts the exchange of chemical compounds between the brain and the circulatory system, disrupting the protective function of the CNS. It promotes the aggregation of β-amyloid (Aβ) and chronic neuroinflammation [40]. Animal studies have shown that age-related cognitive impairment correlates with changes in the gut flora – there is an increase in the number of *Proteobacteria* and a decrease in the number of probiotic species [41]. In turn, high levels of proinflammatory cytokines have been associated with impaired microbiome metabolism, especially the production of neuroactive molecules such as short-chain fatty acids (SCFA) [42].

Autism

It was observed that individuals with autism (ASD) present a significantly increased number of *Clostridium* and the pathogenesis of this condition begins in infancy [43,44]. Due to endogenous translocation, over 200 strains of live intestinal bacterial cultures enter breast milk and during breastfeeding the child takes on the microbiome found on the mother's nipple [45]. A correlation has been presented between a shorter breastfeeding period and late expansion of the diet in children with ASD and poorer food tolerance compared to children without ASD. Studies have shown that breastfeeding children with autism spectrum disorders for more than 12 months may be beneficial in reducing symptoms characteristic of ASD [46]. In recent years the role of environmental factors, such as the mother's diet during pregnancy, on the child's neurological development has been demonstrated [47]. An adequate amount of folic acid is necessary for the proper development of the neural tube. Mothers of children with ASD have a lower total folic acid intake in the first three months of pregnancy than mothers of neurotypical children [48]. Prenatal vitamin, folate, and omega-3 fatty acid deficiencies correlate with an increased risk of ASD in the child [49]. Taking these vitamins and acids near the time of conception is associated with a 40% reduction in the risk of having a child with ASD. The use of antibiotics during pregnancy negatively affects the composition

of the fetal microbiome, which may exacerbate ASD symptoms in the future. It has been shown that the use of probiotics in the prenatal period can have a beneficial effect on the child's development and potentially reduces the development of symptoms of neurodevelopmental disorders, such as autism [50].

Further evidence supporting the role of microbiota in the pathogenesis of autism was obtained by observing the improvement in behavior and communication skills after the use of antibiotics and probiotics [51].

Patients with autism spectrum disorders are more likely to suffer from metabolic syndrome [52]. Possible etiological factors include: genetic variants (e.g. 16p11.2 deletion, 11p14.1 microdeletion) [53], prenatal infections, drugs, toxins, maternal obesity, and diabetes, prematurity, and intrauterine growth retardation [54]. Neuroatypical individuals are characterized by dietary selectivity, physical limitations, sedentary lifestyle, and sleep disorders, which also contribute to the pathogenesis of metabolic syndrome [55].

Depression

Patients with depression are at significant risk of metabolic syndrome [56]. In this group of patients, unfavorable health behaviors are common, such as alcohol consumption, smoking, poor diet, and sedentary lifestyle [57]. An important factor is antidepressants, which promote the development of abdominal obesity, increase blood pressure, and triglyceride levels [58, 59]. In depression, there is increased activity of the hypothalamic-pituitary-adrenal axis, which leads to increased secretion of corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol, and consequently, the accumulation of visceral fat [60]. In this group of patients, a balanced diet rich in fruits, vegetables, and fish not only reduces the risk of metabolic syndrome, but also reduces the severity of depression symptoms [61].

The quantitative and qualitative composition of the gut microbiota correlates with the presence of mood changes and anxiety disorders. The flora of patients with depression is characterized by a lower number of *Bacteroidetes bacteria*, with an increased number of *Alistipes bacteria* [62-63]. In the study by Rao et al., supplementation *with L. casei Shirota* alleviated the occurrence of anxiety disorders in patients with chronic fatigue syndrome [64]. In a study assessing the gut microbiome in social anxiety disorder (SAD), the control group showed higher amounts of *Parasutterella bacteria* compared to the SAD group [65]. Five generations of gut bacteria were associated with anxiety and exacerbated it. It was found that people suffering from anxiety disorder have lower levels of *Coprococcus* [66, 67]. *Enterorhabdus* showed a decreasing trend in a mouse model of anxiety and depression caused by social failure [68].

Schizophrenia

People with schizophrenia are more likely to develop metabolic syndrome, having a 4.4-fold increased risk of central obesity, a 2.7-fold increased risk of hypertriglyceridemia, a 2.4-fold increased risk of low HDL, a 1.4-fold increased risk of hypertension, and a 1.99-fold increased risk of diabetes compared to the general population [69]. The estimated prevalence of metabolic syndrome in individuals with schizophrenia is 37–67%, representing a 2- to 3-fold increased risk compared to the general population [70]. Psychopathology that interferes with insight into physical health is significant in this group of patients, as well as lower social support, low income, and limited access to general medical care [71]. Furthermore, patients with schizophrenia are more likely to smoke tobacco to alleviate psychotic symptoms [72].

Numerous studies of the microbiome of patients with schizophrenia have reported increases in *Bifidobacterium*, *Lactobacillus*, and *Megasphaera species*. Based on this, researchers sought a unique pattern of microbiome composition that could serve as a biomarker of schizophrenia. One study developed a panel consisting of *Aerococcaceae*, *Bifidobacteriaceae*, *Brucellaceae*, *Pasteurellaceae*, and *Rikenellaceae* that distinguished patients with schizophrenia from healthy individuals [73,74]. Differences in brain structure, metabolic pathways, and symptom severity may be associated with changes in microbiota composition [75]. There is inconsistency in the bacterial taxa identified as markers in these studies. This may be due to small sample sizes and insufficient overlap between the studied populations [76]. The lack of specificity limits the potential diagnostic utility of the data, and indeed their reliability.

Bipolar affective disorder

The microbiome of patients with bipolar disorder (BD) is characterized by lower diversity compared to healthy individuals. Studies on the microbiome composition in the BD population have shown a significant decrease in butyrate-synthesizing bacteria of the *Ruminococcaceae family*, *Faecalibacterium genus*, and *Faecalibacterium prausnitzii species* [77].

Shahrbabaki et al. conducted a randomized trial in which patients with bipolar type I disorder were selected. They were divided into placebo and probiotic groups for 8 weeks. Patients in both groups received antipsychotic treatment. The research group received a probiotic capsule containing *Bifidobacterium bifidum*, *Bifidobacterium lactis*, and *Bifidobacterium langum*, as well as *Lactobacillus acidophilus*. Both groups showed a decrease in the incidence of mania and depression

throughout the study period, and the research group additionally showed a significant reduction in the severity of symptoms (assessed using the Young Mania and Hamilton Scale – YMRS). Although the probiotic group showed greater improvement in the questionnaire scores compared to the placebo group, there was no significant difference in the overall scores of mania and depression between the two groups [78].

Hospitalized patients were divided into a research and control group, shortly after hospitalization, they received probiotics: *Lactobacillus rhamnosus* and *Bifidobacterium animalis subsp.* for 24 weeks. During the follow-up, there were 8 re-hospitalizations among patients who received probiotics compared to the placebo group, while a total of 17 participants in the placebo group required at least one re-hospitalization [79]. The length of stay was significantly shorter in the study group (2.8 days) compared to the control group (8.3 days) [80].

Another study analyzed the role of probiotics in improving cognitive functions in people with euthymic bipolar disorder. Significant improvements in concentration and psychomotor processing speed were found after 1 and 3 months of treatment. In a related study, bipolar patients were treated with probiotics containing *Lactobacillus* and *Bifidobacterium strains*, there was no placebo group. The severity of manic symptoms was compared using the YMRS scale between treatment groups at different times of the study. Symptoms improved over the 3-month study period. Manic symptoms significantly decreased over time and in patients who received probiotic supplementation, a significantly reduced score on the Leiden Index of Depression Sensitivity-Revised was observed [81-82].

Parkinson's disease

Parkinson's disease is one of the most common neurodegenerative diseases. In PD, there is aggregation of abnormally folded alpha-synuclein (α-syn) proteins, forming intracellular inclusions in Lewy bodies and neurons located in the central, autonomic, and enteric nervous systems. Changes in the composition of the gut microbiota can lead to changes in intestinal permeability and intestinal barrier function, affecting gastrointestinal epithelial cells and the immune and enteric nervous systems [83]. Gut bacteria activate the immune system due to a defective gut barrier, causing a systemic inflammatory response that weakens the blood-brain barrier and promotes neuroinflammation and ultimately neurodamage and degeneration [84]. Gut inflammation induced by bacterial pathobionts may also contribute to the initiation of α-syn missplicing, and further α-syn pathology occurs in the brain via the vagus nerve [85]. A study conducted in PD-bearing mice confirmed that the gut microbiota contributes to motor dysfunction and neuroinflammation, suggesting that changes in the human gut microbiome are a risk factor for PD. Studies show that in PD, changes in SCFA-producing bacteria and an increase in putative pathobionts can act together, potentially compromising the integrity of the gut barrier and/or the blood-brain barrier, stimulating systemic and neuroinflammation. SCFA-producing bacteria can decrease or increase. Considering that *Bifidobacterium*, *Lactobacillus*, and *Akkermansia* are beneficial to human health, increased levels of *Bifidobacterium* and *Lactobacillus* may be associated with PD drugs, especially COMT inhibitors, while high levels of *Akkermansia* may be associated with aging [86].

ADHD - attention deficit hyperactivity disorder

The pathogenesis of ADHD is thought to be multifactorial, with heritability estimated at about 70–90% [87]. These genetic associations suggest some dependence on underlying metabolic reactions involving gene products. Each bacterium has a unique genetic material that produces a distinct set of metabolites that interact with each other and with host metabolites [88], creating a complex web of host-microbiome interactions. This constitutes a bidirectional communication network, providing the gut microbiota and metabolites with the ability to influence brain development and function. The fact that individuals with ADHD suffer from gastrointestinal (GI) dysfunction, including childhood digestive problems and low-grade inflammation, as well as constipation [89], suggests a potential role for the gut microbiome in this disorder. For example, plasma levels of the cytokine TNF-α were found to be significantly lower in children with ADHD compared with healthy controls, and these levels were also negatively correlated with gut microbiome diversity in the same samples. Plasma levels of short-chain fatty acids (SCFA) were also found to be lower in patients with ADHD (both children and adults) [90]. This is particularly interesting because SCFAs are produced during bacterial fermentation and are hypothesized to improve neuroimmunoendocrine functionality and play a mediator role in communication between the microbiota, gut, and brain [91].

Conclusions

Studies on the gut microbiota show that there is a complex and dynamic interaction between the microbiota and the central nervous system (CNS). Changes in the composition of the microbiota can affect neurological functions, suggesting that the microbiota may play a role in the pathogenesis of neurodegenerative and psychiatric diseases. The results of studies indicate multiple mechanisms by which the microbiota affects

the CNS, such as metabolite production, modulation of inflammation, and interaction with the gut-brain axis. These mechanisms may contribute to the development of the diseases mentioned in the work. Dietary interventions, such as the use of pre- and probiotics, may have therapeutic potential in the treatment of psychiatric and neurodegenerative diseases. Introduction of dietary changes can improve the balance of the microbiota, which may have a beneficial effect on mental and neurological health. There is an urgent need for further research to better understand the role of the gut microbiota in the pathogenesis of CNS diseases. Future studies should focus on identifying specific strains of microorganisms and their metabolites that may be useful in diagnostics and therapy. Understanding the impact of microbiota on the CNS opens new therapeutic perspectives. Potential therapies based on microbiota modulation may revolutionize the approach to treating neurodegenerative and psychiatric diseases, reducing the need for pharmacotherapy.

Conflict of interest

The author has declared no conflict of interest.

References:

1. Vplyv mikrobioty na stan orhanizmu ludyny. Bobyak YU. Mandziy L. Yastrebova O., Medicine actual problems in education and introduction of new technologies, 204-207.
2. Iliev, Iliyan D., and Ken Cadwell. "Effects of intestinal fungi and viruses on immune responses and inflammatory bowel diseases." Gastroenterology 160.4 (2021): 1050-1066.
3. Krawczyk, Krzysztof. "Archeony halofilne jako stymulatory komórek układu odpornościowego człowieka." (2023).
4. Cryan JF, O'Riordan KJ, Cowan CS, et al. The microbiotagut-brain axis. Physiol Rev. 2019;99:1877–2013.
5. Cryan JF, O'Mahony SM. The microbiome-gut-brain axis: from bowel to behavior. Neurogastroenterol Motil. 2011;23(3):187–192.
6. Heitzman, Janusz. Stres w etiologii przestępstw agresywnych. Kraków: Wydawnictwo Uniwersytetu Jagiellońskiego, 2002.
7. Kaur, Harrisham, Chandrani Bose, and Sharmila S. Mande. "Tryptophan metabolism by gut microbiome and gut-brain-axis: an in silico analysis." Frontiers in neuroscience 13 (2019): 493713.
8. Guo, Cen, et al. "Gut-brain axis: Focus on gut metabolites short-chain fatty acids." World journal of clinical cases 10.6 (2022): 1754.
9. Peirce, Jason M., and Karina Alviña. "The role of inflammation and the gut microbiome in depression and anxiety." Journal of neuroscience research 97.10 (2019): 1223-1241.
10. Zacharias, Helena U., et al. "Microbiome and metabolome insights into the role of the gastrointestinal–brain axis in Parkinson's and Alzheimer's disease: Unveiling potential therapeutic targets." Metabolites 12.12 (2022): 1222.
11. Pulikkan, Joby, Agnisrota Mazumder, and Tony Grace. "Role of the gut microbiome in autism spectrum disorders." Reviews on biomarker studies in psychiatric and neurodegenerative disorders (2019): 253-269.
12. Checa-Ros, Ana, et al. "Current evidence on the role of the gut microbiome in ADHD pathophysiology and therapeutic implications." Nutrients 13.1 (2021): 249.
13. Kelly, John R., et al. "The role of the gut microbiome in the development of schizophrenia." Schizophrenia Research 234 (2021): 4-23.
14. Tessmer, Kimberly. Leczenie odżywianiem. Zdrowe jelita. Wydawnictwo Kobiece, 2022.
15. Dobrowolski P., Prejbisz A., Kuryłowicz A. i wsp Metabolic syndrome — a new definition and management guidelines; Arterial Hypertension 2022;26(3):99-121;
16. Cavali, M. D. L. R., Escrivão, M. A. M. S., Brasileiro, R. S., & Taddei, J. A. D. A. C. (2010). Metabolic syndrome: comparison of diagnosis criteria. Jornal de Pediatria, 86, 325-330.
17. Freeman AM, Acevedo LA, Pennings N. Insulin Resistance. 2023 Aug 17. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29939616.]
18. Castro-Barquero S, Ruiz-León AM, Sierra-Pérez M, Estruch R, Casas R. Dietary Strategies for Metabolic Syndrome: A Comprehensive Review. Nutrients. 2020 Sep 29;12(10):2983. doi: 10.3390/nu12102983. PMID: 33003472; PMCID: PMC7600579
19. Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., et al. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464, 59–65. doi: 10.1038/nature08821
20. Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D. R., et al. (2011). Enterotypes of the human gut microbiome. Nature 473, 174–180. doi: 10.1038/nature09944
21. Dahl, Wendy J., Daniela Rivero Mendoza, and Jason M. Lambert. "Diet, nutrients and the microbiome." Progress in molecular biology and translational science 171 (2020): 237-263.
22. Laiola M, De Filippis F, Vitaglione P, Ercolini D. A Mediterranean Diet Intervention Reduces the Levels of Salivary Periodontopathogenic Bacteria in Overweight and Obese Subjects. Appl Environ Microbiol. 2020 Jun 2;86(12):e00777-20. doi: 10.1128/AEM.00777-20. PMID: 32276980; PMCID: PMC7267188.
23. Korpela K, Salonen A, Vepsäläinen O, Suomalainen M, Kolmeder C, Varjosalo M, Miettinen S, Kukkonen K, Savilahti E, Kuitunen M, de Vos WM. Probiotic supplementation restores normal microbiota composition and function in antibiotic-treated and in caesarean-born infants. Microbiome. 2018 Oct 16;6(1):182. doi: 10.1186/s40168-018-0567-4. PMID: 30326954; PMCID: PMC6192119.
24. Portune, Kevin J., et al. "Gut microbiota role in dietary protein metabolism and health-related outcomes: The two sides of the coin." Trends in Food Science & Technology 57 (2016): 213-232.
25. Morowitz M.J., Carlisle E.M., Alverdy J.C.: Contributions of intestinal bacteria to nutrition and metabolism in the critically ill. Surgical Clinics of North America, 2011, 91: 771–785.
26. J. Oziom, S. Budrewicz Rola mikrobioty jelitowej w patogenezie i przebiegu wybranych schorzeń układu nerwowego; Polski Przegląd Neurologiczny 2019; 15 (1), 1–11.
27. Cullen JMA, Shahzad S, Dhillon J. A systematic review on the effects of exercise on gut microbial diversity, taxonomic composition, and microbial metabolites: identifying research gaps and future directions. Front Physiol. 2023 Dec 19;14:1292673. doi: 10.3389/fphys.2023.1292673. PMID: 38187136; PMCID: PMC10770260.
28. Strasser B. Physical activity in obesity and metabolic syndrome. Ann N Y Acad Sci. 2013 Apr;1281(1):141-59. doi: 10.1111/j.1749-6632.2012.06785.x. Epub 2012 Nov 21. PMID: 23167451; PMCID: PMC3715111.
29. Ley R.E., Bäckhed F., Turnbaugh P. i in. Obesity alters gut microbial ecology. Proc. Natl. Acad. Sci., 2005; 102: 11070-11075

30. Schwiertz A. Microbiota and SCFA in lean and overweight healthy subjects. Obesity 2010; 18: 190–195
31. Ley RE, Turnbaugh PJ, Klein S. i in. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444(7122):1022-1023
32. Scheiman J, Luber JM, Chavkin TA, et al. Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism. Nat Med. 2019;25:1104–1109.
33. Kostic AD. Reply to "Is physical performance (in mice) increased by Veillonella atypica or decreased by Lactobacillus bulgaricus?" J Sport Health Sci. 2020;9:201–202.
34. Ng SKC, Hamilton IR. Lactate metabolism by Veillonella parvula. J Bacteriol. 1971;105:999–1005.
35. Bielik V, Hric I, Hammami R. Is Veillonella a unique marker of physical exercise? Commentary on: "Is physical performance (in mice) increased by Veillonella atypica or decreased by Lactobacillus bulgaricus?". J Sport Health Sci. 2024 Sep;13(5):682-684. doi: 10.1016/j.jshs.2023.12.003. Epub 2023 Dec 20. PMID: 38135273; PMCID: PMC11282330.
36. Borre YE, O'Keeffe GW, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota and neurodevelopmental windows: Implications for brain disorders. Trends Mol. Med. 2014; 20(9): 509–518.
37. Biagi F, Nylund F, Candela M, Ostan R, Bucci L, Pini E i wsp. Through ageing and beyond: Gut microbiota and inflammatory status in seniors and centenarians. PLoS ONE 2010; 5(5): e10667.
38. O'Toole PW, Claesson MJ. Gut microbiota: Changes throughout the lifespan from infancy to elderly. Int. Dairy J. 2010; 20(4): 281–291.
39. Gulas E, Wysiadecki G, Strzelecki D, Gawlik-Kotelnicka O, Polguj M. Can microbiology affect psychiatry? A link between gut microbiota and psychiatric disorders. Psychiatria Polska. 2018;52(6):1023-1039. doi:10.12740/PP/OnlineFirst/81103.
40. Quigley EMM. Microbiota-Brain-Gut Axis and Neurodegenerative Diseases. Curr Neurol Neurosci Rep. 2017 Oct 17;17(12):94. doi: 10.1007/s11910-017-0802-6. PMID: 29039142.
41. Zhao Y, Lukiw WJ. Microbiome-generated amyloid and potential impact on amyloidogenesis in Alzheimer's disease (AD). J Nat Sci. 2015 Jul;1(7):e138. PMID: 26097896; PMCID: PMC4469284.
42. Sochocka M, Donskow-Łysoniewska K, Diniz BS, Kurpas D, Brzozowska E, Leszek J. The Gut Microbiome Alterations and Inflammation-Driven Pathogenesis of Alzheimer's Disease-a Critical Review. Mol Neurobiol. 2019 Mar;56(3):1841-1851. doi: 10.1007/s12035-018-1188-4. Epub 2018 Jun 23. PMID: 29936690; PMCID: PMC6394610.
43. Zhu F, Li C, Chu F, Tian X, Zhu J. Target Dysbiosis of Gut Microbes as a Future Therapeutic Manipulation in Alzheimer's Disease. Front Aging Neurosci. 2020 Oct 6;12:544235. doi: 10.3389/fnagi.2020.544235. PMID: 33132894; PMCID: PMC7572848.
44. Claesson MJ, Cusack S, O'Sullivan O, Greene-Diniz R, de Weerd H, Flannery E, Marchesi JR, Falush D, Dinan T, Fitzgerald G, Stanton C, van Sinderen D, O'Connor M, Harnedy N, O'Connor K, Henry C, O'Mahony D, Fitzgerald AP, Shanahan F, Twomey C, Hill C, Ross RP, O'Toole PW. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proc Natl Acad Sci U S A. 2011 Mar 15;108 Suppl 1(Suppl 1):4586-91. doi: 10.1073/pnas.1000097107. Epub 2010 Jun 22. PMID: 20571116; PMCID: PMC3063589.
45. Piekarczyk, N., Ruciński, J., Kurowska, E., & i Człowieka, K. F. Z. (2021). The impact of the microbiome on the development of the operating system and its functioning. Research and Development of Young Scientists in Poland, 75.
46. Finegold SM, Molitoris D, Song Y, Liu C, Vaisanen ML, Bolte E i wsp. Gastrointestinal microflora studies in late-onset autism. Clin. Infect. Dis. 2002; 35(Suppl. 1): S6–S16.
47. Parracho HM, Bingham MO, Gibson GR, McCartney AL. Differences between the gut microflora of children with autistic spectrum disorder. J. Med. Microbiol. 2005; 54(pt10): 987–991.
48. Kotlińska, Huras The sources and function of microbiota in breast milk. A review of literature, Zdrowie Publiczne i Zarządzanie, 2017, s. 178 – 180
49. Aldegheri, Luana, et al. "Impact of Human Milk Oligosaccharides and Probiotics on Gut Microbiome and Mood in Autism: A Case Report." Microorganisms 12.8 (2024): 1625.
50. Sullivan E.L., Nousen L., Chamlou K. (2014), Maternal high fat diet consumption during the perinatal period programs offspring behavior, Physiol Behav, 123 (17): 236–42.
51. Madore C., Leyrolle Q., Lacabanne C., Benmamar-Badel A., Joffre C., Nadjar A. (2016), Neuroinflammation in autism: plausible role of maternal inflammation, dietary omega 3, and microbiota, Neural Plast, 359, 7: 209.
52. Schmidt R.J., Hansen R.L., Hartiala J., Allayee H., Schmidt L.C., Tancredi D.J. (2011), Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism, Epidemiology, 22 (4): 476–85
53. Collado M.C., Cernada M., Bauerl C., Vento M., Perez-Martinez G. (2012), Microbial ecology and host-microbiota interactions during early life stages, Gut Microbes, 3 (4): 352–65.
54. Song Y, Liu C, Finegold SM. Real-time PCR quantitation of clostridia in feces of autistic children. Appl. Environ. Microbiol. 2004; 70(11): 6459–6465
55. Kahathuduwa CN, West BD, Blume J, Dharavath N, Moustaid-Moussa N, Mastergeorge A. The risk of overweight and obesity in children with autism spectrum disorders: a systematic review and meta-analysis. Obes Rev. 2019;20(12):1667-1679. doi:10.1111/obr.12933
56. Shinawi M, Sahoo T, Maranda B, et al. 11p14.1 microdeletions associated with ADHD, autism, developmental delay, and obesity. Am J Med Genet A. 2011;155A(6):1272-1280. doi:10.1002/ajmg.a.33878
57. Dhanasekara CS, Ancona D, Cortes L, et al. Association Between Autism Spectrum Disorders and Cardiometabolic Diseases: A Systematic Review and Meta-analysis. JAMA Pediatr. 2023;177(3):248–257. doi:10.1001/jamapediatrics.2022.5629
58. Hack M, Taylor HG, Schluchter M, Andreias L, Drotar D, Klein N. Behavioral outcomes of extremely low birth weight children at age 8 years. J Dev Behav Pediatr. 2009;30(2):122-130. doi:10.1097/DBP.0b013e31819e6a16
59. Vancampfort D, Correll CU, Wampers M, Sienaert P, Mitchell A, De Herdt A, et al. Metabolic syndrome and metabolic abnormalities in patients with major depressive disorder: a meta-analysis of prevalences and moderating variables. Psychological medicine. 2014;44(10):2017–28.
60. Gheshlagh RG, Parizad N, Sayehmiri K. The relationship between depression and metabolic syndrome: systematic review and meta-analysis study. Iranian Red Crescent Medical Journal. 2016;18(6):1–6.
61. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160(14):2101–7.
62. van Reedt Dortland AK, Giltay EJ, Van Veen T, Zitman FG, Penninx BW. Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. Acta Psychiatr Scand. 2010;122(1):30–9.
63. Dunbar JA, Reddy P, Davis-Lameloise N, Philpot B, Laatikainen T, Kilkkinen A, et al. Depression: an important comorbidity with metabolic syndrome in a general population. Diabetes Care. 2008;31(12):2368–73.

64. Le Port A, Gueguen A, Kesse-Guyot E, Melchior M, Lemogne C, Nabi H, et al. Association between dietary patterns and depressive symptoms over time: a 10-year follow-up study of the GAZEL cohort. PloS one. 2012;7:12.
65. Critchfield JW, Hemert van S, Ash M, Mulder L, Ashwood P. The potential role of probiotics in the management of childhood autism spectrum disorders. Gastroenterol. Res. Pract. 2011; 2011: 161358. 92.
66. Dash S, Clarke G, Berk M, Jacka FN. The gut microbiome and diet in psychiatry: Focus on depression. Curr. Opin. Psych. 2015; 28(1): 1–6.
67. Rao AV, Bested AC, Beaulne TM, Katzman MA, Iorio C, Berardi JM i wsp. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. Gut Pathog. 2009; 1(1): 6.
68. Butler MI, Bastiaanssen TFS, Long-Smith C, Morkl S, Berding K, Ritz NL, Strain C, Patangia D, Patel S, Stanton C, O'Mahony SM, Cryan JF, Clarke G, Dinan TG. The gut microbiome in social anxiety disorder: evidence of altered composition and function. Transl Psychiatry. 2023 Mar 20;13(1):95. doi: 10.1038/s41398-023-02325-5. PMID: 36941248; PMCID: PMC10027687.
69. Mysonhimer AR, Cannavale CN, Bailey MA, et al. Prebiotic consumption alters Microbiota but not biological markers of stress and inflammation or mental health symptoms in healthy adults: a randomized, controlled, crossover trial[J]. J Nutr. 2023;153:1283–96.
70. Chen YH, Bai J, Wu D, et al. Association between fecal microbiota and generalized anxiety disorder: severity and early treatment response[J]. J Affect Disord. 2019;259:56–66.
71. Zou R, Tian P, Xu M, et al. Psychobiotics as a novel strategy for alleviating anxiety and depression[J]. J Funct Foods. 2021;86:104718.
72. Vancampfort, D.; Wampers, M.; Mitchell, A.J.; Correll, C.U.; De Herdt, A.; Probst, M.; De Hert, M. A meta-analysis of cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia versus general population controls. World Psychiatry 2013, 12, 240–250.
73. De Hert, M.; Schreurs, V.; Vancampfort, D.; Van Winkel, R. Metabolic syndrome in people with schizophrenia: A review. World Psychiatry 2009, 8, 15–22.
74. Sun, M.J.; Jang, M.H. Risk Factors of Metabolic Syndrome in Community-Dwelling People with Schizophrenia. Int. J. Environ. Res. Public Health 2020, 17, 6700.
75. Ward, H.B.; Beermann, A.; Nawaz, U.; Halko, M.A.; Janes, A.C.; Moran, L.V.; Brady, R.O., Jr. Evidence for Schizophrenia-Specific Pathophysiology of Nicotine Dependence. Front. Psychiatry 2022, 13, 804055.
76. Shen Y, Xu J, Li Z, Huang Y, Yuan Y, Wang J, et al. Analysis of gut microbiota diversity and auxiliary diagnosis as a biomarker in patients with schizophrenia: a cross-sectional study. Schizophr Res. (2018) 197:470–7. doi: 10.1016/j.schres.2018.01.002
77. Zheng P, Zeng B, Liu M, Chen J, Pan J, Han Y, et al. The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviors in mice. Sci Adv. (2019) 5:eaau8317. doi: 10.1126/sciadv.aau8317
78. N. Murray, S. Khalaf, T. F S Bastiaanssen, D. Kaulmann, E. Lonergan, J. F Cryan, G. Clarke, A. S Khashan, K. O'Connor, Compositional and Functional Alterations in Intestinal Microbiota in Patients with Psychosis or Schizophrenia: A Systematic Review and Meta-analysis, Schizophrenia Bulletin, Volume 49, Issue 5, September 2023, Pages 1239–1255, https://doi.org/10.1093/schbul/sbad049
79. Cheung SG, Goldenthal AR, Uhlemann AC, Mann JJ, Miller JM, Sublette ME. Systematic review of gut microbiota and major depression. Front Psychiatry. (2019) 10:34. doi: 10.3389/fpsyt.2019.00034
80. M. Elizabeth Sublette, Stephanie Cheung, Evan Lieberman, Shaohua Hu, J. John Mann, Anne-Catrin Uhlemann, Jeffrey M. Miller. Bipolar disorder and the gut microbiome: A systematic review. Bipolar Disorders.(2022). doi:10.1111/bdi.13049
81. Eslami Shahrbabaki, M., Sabouri, S., Sabahi, A., Barfeh, D., Divsalar, P., Esmailzadeh, M., & Ahmadi, A. (2020). The efficacy of probiotics for treatment of bipolar disorder-type 1: A randomized, double-blind, placebo controlled trial. Iranian Journal of Psychiatry, Jan, 15(1), 10–16.
82. Obi-Azuike C, Ebiai R, Gibson T, Hernandez A, Khan A, Anugwom G, Urhi A, Prasad S, Souabni SA, Oladunjoye F. A systematic review on gut-brain axis aberrations in bipolar disorder and methods of balancing the gut microbiota. Brain Behav. 2023 Jun;13(6):e3037. doi: 10.1002/brb3.3037. Epub 2023 May 1. PMID: 37127945; PMCID: PMC10275531.
83. Dickerson, F., Adamos, M., Katsafanas, E., Khushalani, S., Origoni, A., Savage, C., Schweinfurth, L., Stallings, C., Sweeney, K., Goga, J., & Yolken, R. H. (2018). Adjunctive probiotic microorganisms to prevent rehospitalization in patients with acute mania: A randomized controlled trial. Bipolar Disorders, 20(7), 614–621. https://doi.org/10.1111/bdi.12652
84. Reininghaus, E. Z., Wetzlmair, L.-C., Fellendorf, F. T., Platzer, M., Queissner, R., Birner, A., Pilz, R., Hamm, C., Maget, A., Koidl, C., Riedrich, K., Klampfer, K., Ferk, K., & Dalkner, N. (2020). The impact of probiotic supplements on cognitive parameters in euthymic individuals with bipolar disorder: A pilot study. Neuropsychobiology, 79(1-2), 63–70. https://doi.org/10.1159/000492537
85. Obi-Azuike C, Ebiai R, Gibson T, Hernandez A, Khan A, Anugwom G, Urhi A, Prasad S, Souabni SA, Oladunjoye F. A systematic review on gut-brain axis aberrations in bipolar disorder and methods of balancing the gut microbiota. Brain Behav. 2023 Jun;13(6):e3037. doi: 10.1002/brb3.3037. Epub 2023 May 1. PMID: 37127945; PMCID: PMC10275531.
86. Hadhazy A. Think Twice: How The Gut's "Second Brain" Influences Mood and WellBeing. Scientific American; 2010.
87. Theoharides TC, Zhang B, Conti P. Decreased mitochondrial function and increased brain inflammation in bipolar disorders and other neuropsychiatric diseases. J. Clin. Psychopharmacol. 2011; 31(6): 685–687
88. 83Vizcarra JA, Wilson-Perez HE, Espay AJ. The power in numbers: gut microbiota in Parkinson's disease. Mov Disord. 2015;30(3):296-298.
89. Quigley E. Microbiota-brain-gut axis and neurodegenerative diseases. Curr Neurol Neurosci Rep. 2017;17(12):94.
90. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol. 2015;21(37):10609-10620.
91. Li Z, Liang H, Hu Y, Lu L, Zheng C, Fan Y, Wu B, Zou T, Luo X, Zhang X, Zeng Y, Liu Z, Zhou Z, Yue Z, Ren Y, Li Z, Su Q, Xu P. Gut bacterial profiles in Parkinson's disease: A systematic review. CNS Neurosci Ther. 2023 Jan;29(1):140-157. doi: 10.1111/cns.13990. Epub 2022 Oct 25. PMID: 36284437; PMCID: PMC9804059.
92. Larsson H, Chang Z, D'Onofrio BM, Lichtenstein P. The heritability of clinically diagnosed attention deficit hyperactivity disorder across the lifespan. Psychol Med. 2014. Jul;44(10):2223–9. doi: 10.1017/S0033291713002493
93. Manor O, Levy R, Borenstein E. Mapping the inner workings of the microbiome: Genomic- and metagenomic-based study of metabolism and metabolic interactions in the human microbiome. Cell Metabolism. 2014. Nov;20(5):742–52. doi: 10.1016/j.cmet.2014.07.021

94. Duel BP, Steinberg-Epstein R, Hill M, Lerner M. A survey of voiding dysfunction in children with Attention Deficit-Hyperactivity Disorder. Journal of Urology. 2003. Oct;170(4 Part 2):1521–4. doi: 10.1097/01.ju.0000091219.46560.7b
95. Yang LL, Stiernborg M, Skott E, Gillberg T, Landberg R, Giacobini M, et al. Lower plasma concentrations of short-chain fatty acids (SCFAs) in patients with ADHD. Journal of Psychiatric Research. 2022. Dec;156:36–43. doi: 10.1016/j.jpsychires.2022.09.042
96. Cickovski T, Mathee K, Aguirre G, Tatke G, Hermida A, Narasimhan G, Stollstorff M. Attention Deficit Hyperactivity Disorder (ADHD) and the gut microbiome: An ecological perspective. PLoS One. 2023 Aug 18;18(8):e0273890. doi: 10.1371/journal.pone.0273890. PMID: 37594987; PMCID: PMC10437823.

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