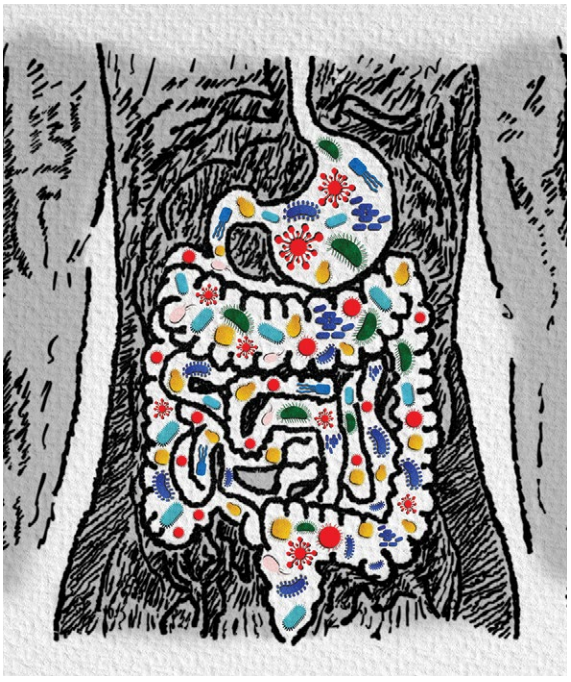
Current PSYCHIATRY

Gut microbiota and symptoms of psychosis: Is there a link?

Gut microbiome changes in schizophrenia may be symptom-specific

The human microbiota refers to the collection of bacteria, archaea, eukarya, and viruses that reside within the human body. The term gut microbiome indicates the composition of these microbes and genetic codes in the intestine.[1] Harkening back to the ancient Greek physician Galen, who treated gastrointestinal (GI) symptoms to relieve mental disturbances such as psychosis, the gut has been a therapeutic target in schizophrenia long before antipsychotics and the DSM.[2] In recent years, research into the gut microbiome has drastically increased, with genetic sequencing affording a more precise look into the specific bacteria that call the human intestines their home. This has led to the recognition that the gut microbiome may be severely disrupted in schizophrenia, a condition known as dysbiosis. Preliminary research suggests that gut bacteria are more helpful than many human genes in distinguishing individuals with schizophrenia from their healthy counterparts.[3,4] In this article, we discuss the potential role of the gut microbiome in schizophrenia, including new research correlating clinical symptoms of psychosis with dysbiosis. We also provide recommendations for promoting a healthy gut microbiome.



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The enteric brain across life

The composition of our bodies is far more microbiota than human. Strikingly, microbiota cells in the gut outnumber human cells, and the distal gut alone hosts bacteria with

Disclosures
The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0328

Gut microbiome and psychosis

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An increase in gut permeability is likely one of several reasons low-grade inflammation is common in schizophrenia

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100 times the genetic content of the entire genome.[5] The intricate meshwork of nerves in the gut is often called the enteric brain because the gut consists of 100 million neurons and synthesizes many neuroactive chemicals implicated in mood disorders and psychosis, including serotonin, dopamine, gamma-aminobutyric acid (GABA), and acetylcholine.[6] The variety of neuroimmunologic, hormonal, and metabolic paths by which the gut microbiome and the brain interact are collectively known as the gut-microbiota-brain axis.[7]

How do we acquire our gut microbiome, and how does it come to influence our brain and behavior? On the first day of life, as babies pass through the birth canal, they are bathed in their mother's vaginal microbiota. In the following weeks, the microbiome expands and colonizes the gut as bacteria are introduced from environmental sources such as skin-to-skin contact and breastmilk.[8] The microbiome continues to evolve throughout early life. As children expand their diets and navigate new aspects of the physical world, additional bacteria join the unseen ecosystem growing inside.[9] The development of the microbiome coincides with the development of the brain. From preclinical studies, we know the gut microbiome mediates important aspects of neurodevelopment such as the formation of the blood-brain barrier (BBB), synaptic pruning, glial activation, and myelination.[10] Interestingly, many of the risk factors for schizophrenia are associated with gut dysbiosis, including obstetric complications, infections treated with antibiotics, and urbanization.[11-15]

Throughout human life, the gut and brain remain in close communication. The gut microbiota continue to produce monoamines, along with other metabolites that are able to cross the BBB.[6] The HPA axis, stimulation of the immune system, and the vagus nerve all provide highways of communication between the gut and the brain.[7] The relationship between the enteric brain and cephalic brain continues through life, even up to a person's final hour. One autopsy study that is often cited (but soberingly, cannot be found online) allegedly revealed that 92% of schizophrenia patients had developed colitis by the time of death.[16,17]

First-episode psychosis and antipsychotic treatment

For patients with schizophrenia, first-episode psychosis (FEP) represents a cocktail of mounting genetic and environmental factors. Typically, by the time a patient receives psychiatric care, they present with characteristic psychotic symptoms—hallucinations, delusions, bizarre behavior, and unusual thought process—along with a unique gut microbiome profile.

This disrupted microbiome coincides with a marked state of inflammation in the intestines. Inflammation triggers increased endothelial barrier permeability, similar to the way immune signals increase capillary permeability to allow immune cells into the periphery of the blood. Specific gut bacteria play specific roles in maintaining the gut barrier.[18,19] Disruptions in the bacteria that maintain the gut barrier, combined with inflammation, contribute to a leaky gut. A leaky gut barrier allows bacterial and immune products to more easily enter the bloodstream and then the brain, which is a potential source of neuroinflammation in schizophrenia.[20] This increase in gut permeability (leaky gut syndrome) is likely one of several reasons low-grade inflammation is common in schizophrenia—numerous studies show higher serum levels of proinflammatory cytokines along with antibacterial immunoglobulins in patients with FEP.[21,22]

Fortunately, antipsychotics, especially the second-generation agents, help restore a healthy gut microbiome and have substantial anti-inflammatory properties.[23,24] These medications interact heavily with the gut microbiome: they have been found to have antibiotic properties, even in doses lower than would normally reach the gut microbiome.[25] In humans, a randomized controlled trial of probiotic supplementation for schizophrenia patients taking antipsychotics showed a reduction in GI symptoms but no significant improvement in psychotic symptoms.[26]

Dysbiosis in schizophrenia: cause or effect?

There is no consensus on what constitutes a healthy gut microbiome because the gut microbiome is highly variable, even among

Table

Studies linking clinical features of schizophrenia to gut microbiome changes

Study	Design	Features found to correlate with microbiome changes
Schwarz et al[34] (2018)	Case-control with prospective cohort component at 12 months: FEP (n = 28), HC (n = 16)	Psychotic symptoms, negative symptoms, positive symptoms, GAF score, chance of remission
Nguyen et al[35] (2019)	Case-control, cross-sectional: SCZ (n = 25), HC (n = 25)	Negative symptoms, depressive symptom severity, CHD risk, self-reported mental well-being, age of disease onset
Zheng et al[3] (2019)	Cross-sectional: SCZ (n = 63), HC (n = 69)	Symptom severity
Li et al[36] (2020)	Case-control: SCZ (n = 82), HC (n = 80)	Overall symptom severity, general psychopathology, negative symptom severity
Chen et al[37] (2021)	Case-control, cross-sectional: SCZ with violence (n = 26), SCZ without violence (n = 16)	Violence
Manchia et al[38] (2021)	Case-control, cross-sectional: SCZ (n = 38, including 18 treatment-resistant and 20 responsive), HC (n=20)	Treatment resistance
Zhu et al[39] (2021)	Case-control, cross-sectional: acute (n = 42), remission (n = 40), HC (n = 44)	Negative symptom severity, excitement, cognition, and depression

CHD: coronary heart disease; FEP: first-episode psychosis; GAF: Global Assessment of Functioning scale; HC: healthy controls; SCZ: schizophrenia

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A healthy gut microbiome is associated with an increased diversity of bacteria present in the gut

healthy individuals, and can change quickly. Those who adopt new diets, for example, see drastic shifts in the gut microbiome within a few days.[27] Despite this variation, the main separation between a healthy and dysbiotic gut comes from the diversity of bacteria present in the gut—a healthy gut microbiome is associated with increased diversity. Numerous disease states have been associated with decreased bacterial diversity, including *Clostridium difficile* infection, Parkinson disease, depression, Crohn disease, and schizophrenia spectrum disorders.[28,29]

Although there are ethical limitations to studying causality in humans directly, animal models have provided a great deal of insight into the gut microbiome's role in the development of schizophrenia. A recent study used fecal transplant to provide the gut microbiome from patients with schizophrenia to a group of germ-free mice and compared these animals to a group of mice that received a fecal transplant from individuals with a healthy gut microbiome. The mice receiving the schizophrenia microbiome showed an increased startle response and hyperactivity.[3] This was consistent with mouse models of schizophrenia, although with obvious limitations.[30] In addition, the brains of these animals showed changes in glutamate, glutamine, and GABA in the hippocampus; these chemicals play a role in the neurophysiology of schizophrenia.[3,31] This study has not yet been replicated, and considerable variation remains within the schizophrenia biosignature.

Clinical symptoms of psychosis and the gut microbiome

Previous literature has grouped patients with schizophrenia spectrum disorders as 1 unified study group. But as is the case with many psychiatric conditions, there is a great deal of heterogeneity in neurobiology, genetics, and microbiome composition among individuals with schizophrenia.[32]

Researchers have begun to investigate ways in which the gut microbiome varies regarding the clinical symptoms of psychosis.[33] The ***Table***[3,34-39] provides an

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Related Resources

- Nocera A, Nasrallah HA. The association of the gut microbiota with clinical features in schizophrenia. Behav Sci. 2022;12(4):89.
- Nasrallah HA. It takes guts to be mentally ill: microbiota and psychopathology. Current Psychiatry. 2018;17(9):4-6.

overview of 7 human studies of gut microbiome changes relating to clinical features of schizophrenia. In these studies, researchers have found correlations between the gut microbiome and a tendency toward violence,[37] cognitive deficits,[34-36,39] depressive symptoms,[35,39] and numerous other clinical features of psychosis. Most of these correlations have not yet been replicated by further studies. But among studies with similar clinical questions, 3 reported changes in gut microbiome correlated with overall symptom severity, and 4 studies correlated changes with negative symptom severity. In 2 studies,[3,34] *Lachnospiraceae* was correlated with worsened symptom severity. However, this may have been the result of poor control for antipsychotic use, as 1 study in bipolar patients found that *Lachnospiraceae* was increased in those taking antipsychotics compared to those who were not treated with antipsychotics.[40] The specific shifts in bacteria seen for overall symptom and negative symptom severity were not consistent across studies. This is not surprising because the gut microbiome varies with diet and geographic region,[41] and patients in these studies were from a variety of regions. Multiple studies demonstrated gut microbiome alterations for patients with more severe negative symptoms. This is particularly interesting because negative symptoms are often difficult to treat and do not respond to antipsychotics.[42] This research suggests the gut microbiome may be helpful in developing future treatments for patients with negative symptoms that do not respond to existing treatments.

Research of probiotic supplementation for ameliorating symptoms of schizophrenia has yielded mixed results.[43] It is possible that studies of probiotic supplementation have failed to consider the variations in the gut microbiome among individuals with schizophrenia. A better understanding of the variations in gut microbiome may allow for the development of more personalized interventions.

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Three studies found changes in gut microbiome correlated with overall symptom severity, and 4 linked changes with negative symptom severity

Recommendations for a healthy gut microbiome

In addition to antipsychotics, many other evidence-based interventions can be used to help restore a healthy gut microbiome in patients with schizophrenia. To improve the gut microbiome, we suggest discussing the following changes with patients:

- **Quitting smoking.** Smoking is common among patients with schizophrenia but decreases gut microbiome diversity.[44]
- **Avoiding excessive alcohol use.** Excessive alcohol use contributes to dysbiosis and increased intestinal permeability.[45] Moderate alcohol consumption does not appear to have the same harmful effects on the microbiome.[46]
- **Avoiding the use of recreational drugs,** including marijuana, which impact the gut microbiome.[47]
- **Consuming a diet rich in fiber.**[48] Presently, there is not enough evidence to recommend probiotic supplementation to reduce

Bottom Line

The gut microbiome is connected to the clinical symptoms of psychosis via a variety of hormonal, neuroimmune, and metabolic mechanisms active across the lifespan. Despite advances in research, there is still much to be understood regarding this relationship. Clinicians should discuss with patients ways to promote a healthy gut microbiome, including consuming a diet rich in fiber, avoiding use of recreational drugs, and exercising regularly.

symptoms of schizophrenia.[41] Similar to probiotics, fermented foods contain *Lactobacillus*, a bacterial species that produces lactic acid.[49] *Lactobacillus* is enriched in the gut microbiome in some neurodegenerative diseases, and lactic acid can be neurotoxic at high levels.[50-52] Therefore, clinicians should not explicitly recommend fermented foods under the assumption of improved brain health. A diet rich in soluble fiber has been consistently shown to promote anti-inflammatory bacteria and is much more likely to be beneficial.[53,54] Soluble fiber is found in foods such as fruits, vegetables, beans, and oats.

- **Exercising** can increase microbiome diversity and provide anti-inflammatory effects in the gut.[55,56] A recent review found that steady-state aerobic and high-intensity exercise interventions have positive effects on mood, cognition, and other negative symptoms in patients with schizophrenia.[55]
- **Minimizing stress.** Psychological stress and physiological stress from untreated medical conditions are toxic to healthy gut bacteria and weaken the gut barrier.[57]
- **Mitigating exposure to pollution.** Environmental pollution, including exposures to air pollution, heavy metals, and pesticides, disrupts the gut microbiome.[58]

The American Heart Association publishes lifestyle recommendations for individuals with heart disease and the National Institutes of Health publishes lifestyle recommendations for patients with chronic kidney disease. This leads us to question why the American Psychiatric Association has not published lifestyle recommendations for those with severe mental illness. The effects of lifestyle on both the gut microbiome and symptom mitigation is critical. With increasingly shortened appointments, standardized guidelines would benefit psychiatrists and patients alike.

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Studies of probiotic supplementation to ameliorate symptoms of schizophrenia have yielded mixed results

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Exercising, minimizing stress, and eating a diet rich in fiber can help restore a healthy gut microbiome

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