REVIEW ARTICLE
Stamford Journal of Microbiology, 2025. Vol. 15, Issue 1, p. 6-12
ISSN: 2074-5346 (Print); 2408-8846 (Online) DOI: https://doi.org/10.3329/sjm.v15i1.86447

Gut-Brain Interaction: Microbiota and Mental Health

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Received 29 June 2025/Accepted 02 August 2025

The gut microbiome is the large community of bacteria that inhabits the human gastrointestinal system. They contribute significantly to our overall health. These microorganisms have a significant impact on brain function and behavior through the gut-brain axis. Our immune system is also influenced by these microorganisms. This review focuses on developing studies that connect gut microbial activity and composition to mental health outcomes, such as anxiety and depression. The microbiota can influence brain signaling by producing neuroactive substances such as serotonin, dopamine, and gamma-aminobutyric acid (GABA). The hypothalamic-pituitary-adrenal (HPA) axis and immunological responses are also regulated by them. Microbial imbalance has been associated with an increased risk of mental disease, reduced neurogenesis, and inflammation. Dietary factors and microbial exposure at the developing stage also have an impact on the gut microbiota's influence on emotional and cognitive development. The microbiome-based therapies, such as dietary modifications, for the prevention and treatment of mental disorders can be developed by utilizing these pathways.

Keywords: Gut microbiota, Gut-brain axis, Mental health, Dysbiosis, SCFA, Bi-directional pathway

INTRODUCTION

The human gut is populated with trillions of microorganisms comprised of bacteria, viruses, fungi, and archaea, which together form the gut microbiome. Historically linked with digestion, metabolism, and immune function, the gut microbiome is increasingly being identified as a critical component in modulating brain function and mental health (1). This two-way communication, also known as the gut-brain axis (GBA), encompasses an intricate network of neural, immune, endocrine, and metabolic pathways (2). Recent advances in the area of microbiome analysis, particularly by metagenomics and metabolomics, have recognized distinct microbial profiles in individuals with psychiatric disorders such as depression, anxiety, and autism spectrum disorder (ASD) compared with healthy controls (3). Dysbiosis, which refers to the disruption of microbial community, has been correlated with increased inflammation, impaired neurogenesis, and disrupted neurotransmitter production, all of which contribute to mental illness pathophysiology (4). Interestingly, bacteria in the gut have been demonstrated to produce significant neuroactive substances as serotonin, dopamine, gamma-aminobutyric acid (GABA), and short-chain fatty acids (SCFAs) (5).

The lack or imbalance of gut bacteria results in hyper-responsiveness to stress and impaired brain development, as demonstrated by animal models, including the groundbreaking work done on germ-free mice (6, 7). These findings are supported by parallel evidence from human research, which emphasizes the part that immunological regulation, vagal nerve transmission, and the hypothalamic-pituitary-adrenal (HPA) axis play in emotional reactivity and psychiatric risk. The microbial interaction with the gut-brain paradigm is further supported by emerging research that ties dietary patterns influencing the composition of the gut microbiome (8). These advances are accompanied by a growing interest in investigating microbiota-targeted interventions, such as probiotics, prebiotics, and nutritional strategies, as alternatives to traditional psychiatric treatments (4, 9). Despite the potential, more interdisciplinary study is necessary to fully understand the causal mechanisms driving these relationships.

This review aims to provide a summary of the current state of scientific understanding about the involvement of the gut microbiota in mental health, clarify the biological mechanisms involved, and suggest possible therapeutic implications. This review lays the groundwork for a more integrated approach to mental health treatment in the modern era of microbiome science by integrating the fields of microbiology, neurology, and clinical psychiatry.

Communication Pathways of Microbiome Gut- Brain Axis

The gut-brain axis is a dynamic, two-way communication system that includes neurological, hormonal, immunological, and metabolic pathways; connected by the brain with the gastrointestinal tract (GIT) (10). Various physiological and psychological processes, such as mood, cognition, and the stress response, are crucially regulated by this complex

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network (11). It ensures homeostasis and contributes to mental well-being; however, disruption of the balance may cause neuropsychiatric disorders. The gut-brain axis functions through multiple interconnected systems. The vagus nerve is vital for the interaction of the central and enteric nervous systems, while brain activity and behavior are influenced by immune pathways, hormonal signals from the hypothalamic pituitary adrenal (HPA) axis, and various microbial metabolites (12). The gut microbiota becomes an essential regulator of mental health through these mechanisms.

A wide variety of microorganisms make up the human gut microbiome, yet Actinobacteria, Proteobacteria, Bacteroidetes, and Firmicutes are the four main bacterial phyla essential for maintaining the gut–brain communication network. A balance in the number and diversity of these organisms is key for optimal gut homeostasis and overall well-being (13). When these microbial compositions are disrupted. This condition is known as dysbiosis, which results in several psychiatric and neurological conditions. The gut microbiota plays various vital functions, primarily categorized as protective and metabolic roles. Its defense mechanisms include preventing the colonization of pathogens, regulating the host immune system, and generating antimicrobial peptides like bacteriocins, which are mostly produced by lactic acid bacteria. The gut microbiota is also involved in promoting the development of both innate and adaptive immunity. These microorganisms produce short-chain fatty acids (SCFAs) by fermenting indigestible carbohydrates. SCFAs are critical for maintaining the integrity of the intestinal mucosal barrier and regulating the development of both local and systemic inflammation (14).

Neural Pathways

The vagus nerve serves as a key pathway for gut-brain signaling. It is the longest cranial nerve of the nervous system, responsible for transmitting sensory and motor signals between the brain and various organs, including the heart, lungs, and digestive tract (15). Being the primary communication channel between the gut and brain, it responds to mechanical, chemical, and hormonal signals through its diverse receptors. It is widely accepted that the metabolic activity of the gut microbiome has a great effect on host physiology. Among the various microbial metabolites that are crucial for maintaining gut-brain homeostasis, some of the most important metabolites include SCFAs, gut-derived neurotransmitters, and inflammatory mediators (16). The gut-brain axis integrates signals from the neuroendocrine system, enteric nervous system (ENS), autonomic nervous system (ANS), and other systems. The enteric nervous system (ENS), which is located in the digestive tract, has approximately 500 million nerve cells and most of the immune cells in the body, which allow it to communicate with the brain via the vagus nerve (17).

Cytokines and Inflammatory Pathways

Systemic immune responses are significantly influenced by the gut microbiota. Increased intestinal permeability (also known as "leaky gut") and dysbiosis, or an imbalance in the microbial community, enable the transfer of microbially derived molecules like lipopolysaccharide (LPS) into the bloodstream (18). Pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) are released when immune cells are activated by this translocation. These cytokines can reach the brain and influence areas involved in mood and thinking. Gut inflammation can impact mood and metabolism, suggesting a common immune-related mechanism underlying disorders like depression and obesity (19).

Endocrine Regulation

The Hypothalamic-Pituitary-Adrenal (HPA) axis is a central part of the body's stress response system (20). It is closely regulated by signals from the gut microbiome. Absence of gut microbiome leads the HPA axis to overreact to stress, causing unusually elevated levels of corticosterone (21, 22). Introducing certain beneficial microbes can help restore a balanced stress response, indicating that the microbiota help regulate both hormonal activity and inflammation (23). If this mechanism is interrupted, either by gut microbiota imbalances or persistent stress, it contributes to the risk of developing anxiety, depression, and other stress-related illnesses. Therefore, the gut microbiota regulates emotional and behavioral responses through its influence on the body's hormonal system (24).

Metabolic Signaling: Microbial Metabolites and Brain Function

Upon the breakdown of dietary fibers by gut microbiomes, short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate are formed. These compounds play a key role in gut-brain communication. SCFAs help strengthen the blood-brain barrier and support brain functions such as the growth of new neurons and the formation of connections between them (25). Butyrate, in particular, boosts the production of brain-derived neurotrophic factor (BDNF) and blocks enzymes like histone deacetylase (HDAC), which helps protect the brain and improve cognitive function. SCFAs also help microglia, which are the brain's immune cells, to develop properly, especially during early life, which is essential for keeping the brain's environment stable (21). Changes in SCFA-producing bacteria, such as lower levels of *Prevotella stercorea* and *Coprococcus* spp., have been linked to symptoms of depression, possibly due to their effects on inflammation and neurotransmitter balance (5).

Interconnected Pathways and Their Clinical Importance

The communication pathways in the gut–brain axis are closely linked and do not work independently. For example, when the immune system activates the stress response (HPA axis), it can change the balance of gut microbes (26). Likewise, substances produced by gut bacteria can affect the vagus nerve. Having a healthy and balanced gut microbiome early in life is important for proper emotional development and long-term mental well-being. Conditions like melancholy, anxiety, autism, and post-traumatic stress disorder (PTSD) may occur upon the loss of balance (24).

Dietary Influence on Microbiome and Mental Health

Diet is one of the most significant factors capable of influencing human health and the gut microbiota. There is a strong connection between our diet and the composition of our gut microbiota (27). Dietary substances that promote the growth of gut bacteria include glycans (which include inulin, lignin, pectin, cellulose, and fructo-oligosaccharides) that are indigestible by both humans and animals. These components, however, can be broken down by gut bacteria such as *Bacteroides, Bifidobacterium,* and *Ruminococcus*. Additionally, diet can affect the host's immune system and metabolism, which can alter the gut microbiome. Microbiological metabolites such as short-chain fatty acids (SCFAs), precursors of neurotransmitters (including tryptophan, GABA, and dopamine), and B vitamins affect brain signaling, neuro-inflammatory regulation, and the mental stress response (28). As a consequence, what we eat and how frequently we eat can influence the composition and function of our gut microbial community, as well as brain function and cognitive control (29).

A balanced diet that is high in fiber, unsaturated fats, antioxidants, like whole grains, fruits, vegetables, fermented foods, and healthy fats, will increase beneficial bacteria while reducing the pathogens (30).

These foods are known to increase short-chain fatty acids (SCFAs) produced within the microbiome, which can be used as an energy source by the cells of the colon and have an anti-inflammatory effect within the brain (Figure 1). Conversely, diets high in saturated fat, animal protein, sugar, and processed food increase the members of Bacteroidetes, while decreasing bacteria like *Lactobacillus* (31). This type of diet has been associated with chronic inflammation, obesity, and metabolic diseases due to increased production of toxic metabolites such as LPS and TMAO, and decreased SCFAs (32). It decreases microbial diversity and enhances the growth of pathogenic or opportunistic organisms in the gut. Dysbiosis also prevents the microbial production of neuroactive compounds and contributes to increased inflammation, reduced communication between the gut and brain, and overall compromised mental health. Vegetarian diets are more likely to have a *more* diverse and beneficial gut microbiome than non-vegetarian diets. In addition, the ketogenic diet (KD), which is high in fat and low in carbs, causes ketosis and

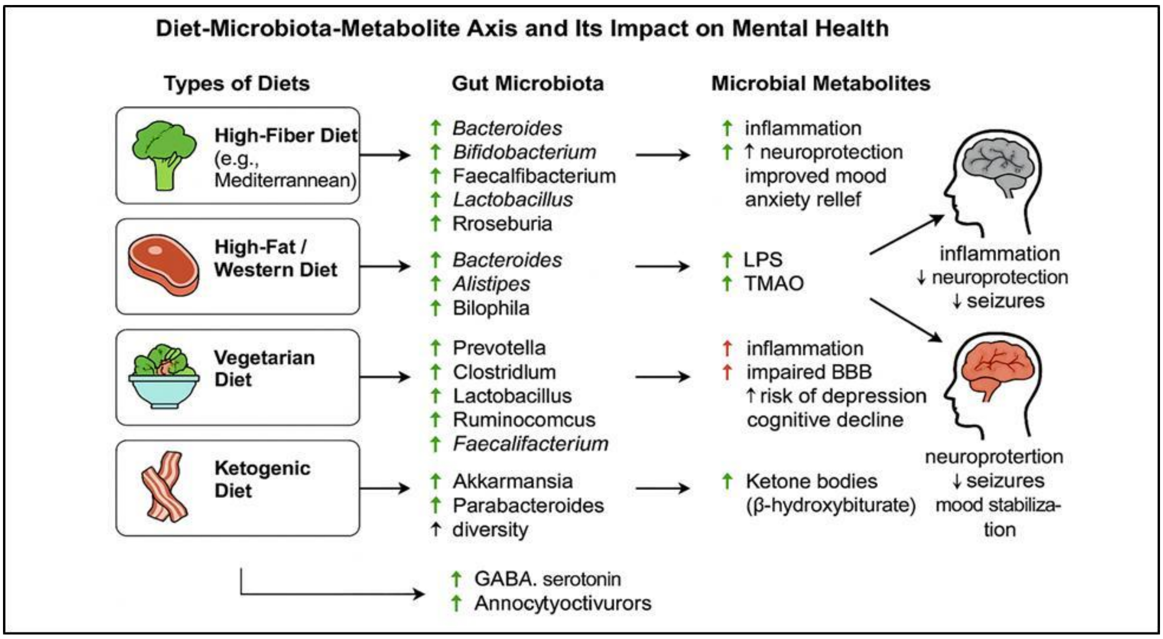

Figure 1: Relationship between diet and gut microbiota. This is an overview of how different dietary patterns influence gut microbiota composition and their impact on mental health. ↑ indicates an increase in abundance or effect and ↑ indicates an increase in harmful outcomes. A high-fiber diet (e.g., Mediterranean) increases beneficial bacteria such as *Bacteroides, Bifidobacterium, Faecalibacterium,* and *Roseburia*, leading to higher production of short-chain fatty acids (SCFAs), reduced inflammation, enhanced neuroprotection, improved mood, and anxiety relief. A high-fat/Western diet promotes *Bacteroides, Alistipes,* and *Bilophila*, resulting in increased lipopolysaccharides (LPS) and trimethylamine N-oxide (TMAO), contributing to pro-inflammatory states and detrimental SCFA profiles. Vegetarian diets increase *Prevotella, Clostridium, Lactobacillus, Ruminococcus,* and *Faecalibacterium*, but may also elevate inflammation, impair blood–brain barrier (BBB) integrity, and heighten risks of depression and cognitive decline. Ketogenic diets enrich *Akkermansia, Parabacteroides,* and microbial diversity, while increasing ketone bodies (β-hydroxybutyrate), thereby conferring neuroprotection, seizure reduction, and mood stabilization. Across dietary patterns, gut microbiota also influences neurotransmitters (e.g., GABA, serotonin), linking diet–microbiota interactions to brain function.

raises ketone bodies, which are beneficial to the brain and metabolic health. A ketogenic diet may help alleviate the symptoms of metabolic and psychological disorders by regulating oxidative stress, mitochondria, and neurotransmitters such as GABA and glutamate (33).

Breastfeeding in infants promotes the formation of healthy gut bacteria, such *as Bifidobacterium, Lactobacillus, Streptococcus*, etc., by supplying nutrition, antibodies, and prebiotics. Formula-fed newborns have a distinct gut microbiota, which includes more *Clostridium, Enterobacter, and Escherichia coli.* (33) Solid foods during infancy increase microbial diversity and alter the intestinal condition, resulting in increased *Ruminococcus*, *Faecalibacterium prausnitzii*, and *Roseburia* spp. populations. However, babies that quit breastfeeding prematurely have more *Akkermansia muciniphila* and *Bilophila wadsworthia*, but those who breastfeed longer have more bacteria of the genus *Collinsella* spp., *Lactobacillus intestinalis*, and *Veillonella* spp.. By age 2-3, the gut flora has stabilized and grown more comparable to that of adults. These microbial variations have a substantial impact on mental function. A healthy microbiome facilitates the formation of the immune system and improves mental health, which may decrease the likelihood of mental disorders in adolescents. Some studies suggest that alcohol consumption can lead to inflammation, alteration in the microbiota, and an increased risk of psychological disorders (28, 29). In addition, it can cause local intestinal irritation that compromises gut integrity, as well as developmental problems in the neural system. Lastly, it has been demonstrated that drinking alcohol increases the populations of pro-inflammatory bacteria like Proteobacteria and decreases the number of beneficial gut bacteria (34).

While differing compositions of diets can affect the composition of the gut microbiome, timing of meals and following consistent eating times are also crucial to support the gut microbiota and good mental health. The disturbances in gut microbiome caused by irregular meal timing and late-night meals may disrupt gut bacterial rhythms and decrease the biosynthesis of serotonin in the gut (35). In contrast, dietary composition following regular eating schedules and consistently timing meals may help reset microbial activity, improve brain-gut communication, and increase the production of beneficial metabolites that positively influence mood, cognition, and resilience to stress (24). Recent technologies in metagenomics and multi-omics have illustrated how quickly the microbiota can change in response to types of dietary changes; for example, simply switching of diet from animal-based to plant-based (or vice versa) proved to alter the abundance of key bacterial groups in a very short timeframe (Firmicutes, Bacteroidetes, and Actinobacteria). These changes not only affect the gut microbiome composition but also influence the gene expression, impacting neurotransmitter production and inflammatory responses (36). Moreover, inflammation and dysbiosis impact brain development and function, resulting in the emergence of gastrointestinal symptoms like diarrhea, bloating, and abdominal pain in autistic children (37).

Role of Gut Microbiome in Mental Disorders

The gut microbiome regulates brain function and psychological stability through the microbiota-gut-brain axis. Microbial populations in the gut generate neuroactive substances that affect neuronal signaling, stress responses, and behavior (38). Modifications in microbial community composition, known as dysbiosis, have been strongly attributed to the onset and development of several mental disorders, including depression, anxiety, autism spectrum disorders, schizophrenia, and neurodegenerative diseases like Parkinson's and Alzheimer's. These variations can affect the blood-brain barrier, immunological activation, and neuroinflammation, all of which can contribute to these disorders (36, 39). The table (Table 1) summarizes clinical descriptions and associated bacterial taxa associated with each psychiatric disorder.

Therapeutic Approaches: Effectiveness of Probiotics, Prebiotics, and Antibiotics

Growing evidence suggests that targeting the gut microbiome may offer new ways to improve mental health. Among the most explored approaches are the use of probiotics, prebiotics, and antibiotics (9). These therapies aim to restore or maintain a healthy microbial balance in the gut, which in turn may positively influence brain function and emotional well-being.

Probiotics are live organisms that help the host's health when consumed in sufficient amounts. They are known for supporting gut health by restoring and maintaining a balanced intestinal microbiota. Probiotics can help improve digestion, enhance immune function, reduce inflammation, and may even influence mental well-being through the gut-brain axis. Common probiotic strains include species from the genera *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* have demonstrated potential in lowering stress, anxiety, and depressive symptoms (48). Their potential mechanisms of action include reducing inflammation, generating neuroactive compounds such as gamma-aminobutyric acid (GABA), and strengthening the intestinal barrier, which keeps toxic substances from getting to the brain. Probiotics are rich in fermented foods like yogurt, kefir, and sauerkraut, as well as in dietary supplements (49).

Prebiotics refer to food components that are not digestible in nature, typically dietary fibers, that selectively promote the growth and activity of beneficial microorganisms in the gut. Prebiotics are sources of nutrients for these beneficial microbes, as opposed to probiotics, which are living microbes (50). They promote immune function, improve digestion, improve gut health, and may even have an impact on mood and mental health through the gut-axis of the brain (51). Common prebiotics include inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), pectin, resistant starch, which are naturally found in foods such as garlic, onions, bananas, leeks, asparagus, and whole grains.

Table 1: Gut Dysbiosis in Mental Diseases and Disorders.

Mental Disease/ Disorder	Clinical Overview	Microbial Changes	References
Parkinson's Disease	Tremors, stiffness, slow movement	↓ *Prevotella*, *Blautia, Roseburia* ↑ *E. coli, Ralstonia, Oscillospira, Bacteroides*	(40-42)
Alzheimer's Disease	Memory loss, confusion, poor judgment	↑ *E. coli, Salmonella, Klebsiella, Bacillus subtilis* ↓ *Bifidobacterium*	(24, 40-43)
Huntington's Disease	Involuntary movements, mood swings	↑ *Bacteroides, Proteobacteria, Actinobacteria* ↓ *Firmicutes, Deferibacteres*	(41)
Dementia	Memory loss, confusion	↓Actinobacteria, Bacteroides ↑*Escherichia, Bifidobacterium, Streptococcus, Lactobacillus*	(41-43)
Amyotrophic Lateral Sclerosis (ALS)	Muscle weakness, difficulty speaking/swallowing	↑ glucose- metabolizing microbes *Dorea* ↓ *Butyrivibrio fibrisolvens, E. coli, Oscillibacter, Lachnospira*	(41, 44)
Epilepsy	Seizures, loss of consciousness	↓*Bifidobacterium, E. rectale, Dialister* ↑ *E. coli*	(40)
Anorexia Nervosa	eating disorder, intense fear of gaining weight	↑ *Methanobrevibacter smithii*, *Proteobacteria*, *Enterobacteriaceae* ↓ *Lactobacillus, Clostridium* spp.	(24, 40)
Anxiety	Excessive worry, Restlessness	↑*Ruminococcaceae*, *Ruminiclostridium, Clostridiaceae* ↓ *Bacteroides, Faecalibacterium* spp.	(24, 39, 40, 42, 44-46)
Generalized Anxiety Disorder (GAD)	a constant feeling of being overwhelmed	↑*Fusobacteria*, *Bacteroides* ↓ *Faecalibacterium, Eubacterium, Butyricicoccus*	(39, 44)
Depression	Sadness, fatigue, loss of interest	↓ *Fusicatenibacter, Dialister, Lachnospira, Coprococcus* spp. ↑*Prevotella*, *Eggerthella, Holdemania, Gelria, Turicibacter, Paraprevotella*	(24, 39, 40, 42, 44)
Major Depressive Disorder (MDD)	Persistent low mood, sleep/appetite change	↓*Bacteroides, Dialister, Faecalibacterium* ↑*Lactobacillus, Clostridium,*	(24, 43, 44, 47)
Autism Spectrum Disorder (ASD)	Communication issues, repetitive behavior	↑ *Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, Bacillus* spp. ↑*Faecalibacterium*, *Agathobacter*	(39, 40, 42-44)
Schizophrenia	Hallucinations, delusions, disorganized thinking	↑*Acetanaerobacterium,Haemophilus, Turicibacter* ↓*Adlercreutzia, Anaerostipes, Ruminococcus*	(24, 39, 43, 44)
Bipolar Disorder	Mood swings between mania and depression	↓ *Faecalibacterium, Ruminococcaceae* ↑ *Clostridiaceae, Collinsella, Flavonifractor*	(24, 39, 43)
ADHD	Inattention, hyperactivity, impulsiveness	↓ Firmicutes ↑*Bifidobacterium, Agathobacter, Anaerostipes, Lachnospiraceae*	(39, 40, 43)
PTSD	Flashbacks, anxiety, emotional numbness	↑*Mitsuokella, Odoribacter, Catenibacterium* ↓*Fusicatenibacter, Eubacterium*	(24, 42)

Note: ↑ represents increase, ↓ represents decrease. Abbreviations: ADHD, Attention-deficit hyperactivity disorder; PTSD, Post-traumatic stress disorder.

The combined use of probiotics and prebiotics, often referred to as synbiotics, may offer a more effective strategy by both introducing beneficial bacteria and creating a favorable environment for them to thrive (52).

Antibiotics, although necessary for treating bacterial infections, can have a detrimental effect on the gut microbiota by eliminating both beneficial and harmful microbes (53). Repeated or prolonged use of antibiotics has been associated with disruption of the gut microbiota, which has been connected to a higher risk of mood disorders, cognitive abnormalities, and other neurological problems (54). As a result, using antibiotics carefully is crucial. Probiotics and antibiotics may occasionally work together to lessen the adverse effects on the gut.

CONCLUSIONS

The connection between the gut microbiome and mental health is no longer speculative due to extensive studies on both human and animal models. Considerable evidence supports the therapeutic potential of addressing the gut microbiota to enhance mental health outcomes. Interventions such as probiotics, prebiotics, and dietary changes have been demonstrated to boost microbial balance and reduce psychiatric symptoms. It is challenging to draw firm conclusions from limited research on this field since most of these studies are preclinical or involve small sample numbers. Microbial diversity makes it more complicated for profiling and selecting diagnostic criteria. The integration of artificial intelligence and machine learning could facilitate microbiome profiling and precision-based mental health treatments.

CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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