Gut microbiome in schizophrenia and antipsychotic-induced metabolic alterations: a scoping review

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Abstract: Schizophrenia (SCZ) is a severe mental disorder with high morbidity and lifetime disability rates. Patients with SCZ have a higher risk of developing metabolic comorbidities such as obesity and diabetes mellitus, leading to increased mortality. Antipsychotics (APs), which are the mainstay in the treatment of SCZ, increase the risk of these metabolic perturbations. Despite extensive research, the mechanism underlying SCZ pathophysiology and associated metabolic comorbidities remains unclear. In recent years, gut microbiota (GMB) has been regarded as a ‘chamber of secrets’, particularly in the context of severe mental illnesses such as SCZ, depression, and bipolar disorder. In this scoping review, we aimed to investigate the underlying role of GMB in the pathophysiology of SCZ and metabolic alterations associated with APs. Furthermore, we also explored the therapeutic benefits of prebiotic and probiotic formulations in managing SCZ and AP-induced metabolic alterations. A systematic literature search yielded 46 studies from both preclinical and clinical settings that met inclusion criteria for qualitative synthesis. Preliminary evidence from preclinical and clinical studies indicates that GMB composition changes are associated with SCZ pathogenesis and AP-induced metabolic perturbations. Fecal microbiota transplantation from SCZ patients to mice has been shown to induce SCZ-like behavioral phenotypes, further supporting the plausible role of GMB in SCZ pathogenesis. This scoping review recapitulates the preclinical and clinical evidence suggesting the role of GMB in SCZ symptomatology and metabolic adverse effects associated with APs. Moreover, this scoping review also discusses the therapeutic potentials of prebiotic/probiotic formulations in improving SCZ symptoms and attenuating metabolic alterations related to APs.

Keywords: antipsychotics, fecal transplantation, gut microbiota, prebiotic, probiotic, schizophrenia

Introduction

Schizophrenia (SCZ) is a severe mental illness affecting 20 million people worldwide. Compared to the general population, patients with SCZ have a two- to three-fold higher mortality rate and 10–25 years reduced life expectancy, mainly due to the increased incidence of cardio-metabolic comorbidities such as cardiovascular disease and Type 2 diabetes mellitus (T2DM).1–3 Impaired glucose homeostasis in patients within the first episode of psychosis (FEP) affirms an intrinsic risk for developing T2DM. Unfortunately, antipsychotics (APs), which are the mainstay of treatment in SCZ spectrum disorders, have been found to further exacerbate this risk.4 Despite their clinical efficacy, all APs, and particularly second-generation APs (SGAs), induce severe metabolic adverse effects, including weight gain, adiposity, insulin resistance, and dyslipidemia.5–7 Studies show that SGAs in acute and chronic
treatment can disrupt glucose metabolism peripherally and centrally. Currently, the most common mechanistic insights behind AP-induced metabolic alterations (AIMA) include heterogeneous neurotransmitter–receptor interactions, impaired hypothalamic appetite-regulating pathways and energy-sensing, altered glucose and lipid metabolism, and aberrant adipose tissue homeostasis (increased lipogenesis and inflammatory state). However, despite years of research, it is still unclear how these mechanisms may interact to produce the metabolic perturbations associated with SCZ and AP medication.

The human gastrointestinal (GI) tract is considered the most diverse and densely populated microbial habitat. It contains approximately 100 trillion microorganisms, including bacteria, viruses, and yeast collectively called the ‘gut microbiota’ or ‘gut microbiome’ (GMB). The GMB encodes for more than three million genes, and orders more than the human genome (~23,000 genes). Major bacterial phyla comprising the GMB include Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. Firmicutes and Bacteroidetes represent 90% of the GMB. For the Bacteroidetes phylum, the major genera include Clostridium, Lactobacillus, Bacteroides, Enterococcus, and Ruminococcus. Bacteroides and Prevotella are the major genera of phylum Bacteroidetes, while Actinobacteria phylum (Bifidobacterium genus) is a less abundant component of GMB. Gut bacteria are essential for regulating digestion, immunity, and metabolic homeostasis. These bacteria play a pivotal role in the digestion, fermentation, and absorption of several nutrients and metabolites such as carbohydrates, lipids, protein, and amino acids while producing secondary metabolites such as short-chain fatty acids (SCFAs). Increased intestinal permeability and decreased epithelial integrity have been associated with an altered GMB. Similarly, the GMB has been shown to modulate blood-brain barrier (BBB) integrity.

The brain connects with the gut via bidirectional communication involving neuroendocrine and neuro-immune pathways. These connecting pathways are closely regulated by the GMB and together form the microbiota-gut-brain (MGB) axis. The bidirectional communication of the MGB axis is such that changes in GMB composition can affect behaviors or behavioral perturbations may alter the GMB. The vagus nerve is a chief mediator of the bidirectional communication along the gut-brain axis through cholinergic activation of nicotinic receptors. Sensory afferent neurons of the vagus nerve detect a diverse range of chemical and mechanical stimuli in the intestines and transmit messages to the nucleus tractus solitarius in the brainstem to initiate autonomic, endocrine, and behavioral responses. Working in the other direction, the vagus nerve also regulates gut functions including regional motility, secretion, permeability, and mucosal immune response which collectively can induce changes in GMB composition and activity. Furthermore, a functioning GMB is also required for the development and regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Altered GMB in early life plausibly impacts neuro-immuno-endocrine functions and predisposes an individual toward stress-related disorders in adulthood. Increased gut permeability due to intestinal barrier impairment has been associated with elevated corticosterone levels in early life stress. The neuro-immuno-endocrine functions of the MGB axis are regulated by GMB-derived molecules such as SCFAs, tryptophan metabolites, and secondary bile acids (e.g. deoxycholic acid, ursodeoxycholic acid, and lithocholic acid), which are derived from primary bile acids (cholic acid and chenodeoxycholic acid) primarily by gut bacteria. The GMB is also capable of secreting and utilizing neurotransmitters and neuroactive compounds such as serotonin (5-HT), dopamine, norepinephrine, and γ-aminobutyric acid (GABA), which under behavioral alterations. Likely, owing to these neuro-immuno-endocrine modulations (mainly HPA axis dysfunction), changes in GMB composition have been associated with severe mental illnesses such as major depression, bipolar disorder, and SCZ.

Accumulating evidence suggests that GMB alteration largely associated with SCZ pathogenesis and AIMA. AP treatment causes dysbiotic (i.e. obesogenic) shifts in the GMB, including an increased abundance of Firmicutes and decreased abundance of Bacteroidetes phyla in rodents and human studies. In addition, changes in GMB composition have been associated with altered glutamate neurotransmission, cognitive impairments in SCZ, and AP-induced increases in adiposity and alterations in glucose homeostasis and energy balance. Considering the potential role of GMB in the pathogenesis of SCZ and AIMA, several prebiotics and probiotics have been examined to improve disease symptoms and adverse metabolic effects associated with APs. The present scoping review synthesizes...
current clinical and preclinical evidence examining the role of the GMB in SCZ and AIMA, including the use of prebiotic/probiotic formulations as a therapeutic adjunct. Improved understanding of the links between GMB, SCZ, and AIMA and the therapeutic potential of prebiotic/probiotic formulations can provide further insight into the complex pathology of SCZ and holds important implications for improving metabolic outcomes in these patients.

Methods
The present study protocol was developed using the Joanna Briggs Institute’s scoping review methodological framework.51,52

Search strategy
A search strategy including three main concepts (illness/treatment, GMB, and metabolic alterations) was developed, discussed, and implemented by the authors (R.S., N.S., and E.S.). Ovid Medline, EMBASE, PsychINFO, EBSCO’s CINAHL, Scopus, and Google Scholar databases were searched from inception to December 2021. Specific search terms and syntax were adjusted as necessary for each database. The full search string is provided in Supplementary Table 1.

Screening and study selection
All search results were imported to Covidence for screening and automatic deduplication. Three authors (R.S., N.S., and E.S.) independently completed the title/abstract and full-text screening according to prespecified inclusion and exclusion criteria (Supplementary Table 2). Conflicts were resolved by discussion and consensus among the authors, and consultation with senior authors (S.M.A. and M.H.).

Relevant data extracted from each study were presented in tables with the following headings: publication (reference), study design (country of origin, study design, and experimental techniques), significant outcomes, type of prebiotic/probiotic used, and change in the GMB composition.

Results and discussion

Search results
Our search from all the databases and gray literature search yielded 724 results, which upon deduplication reduced to 400. These 400 studies were subjected to the title and abstract screening, which excluded 323 studies, and 73 were assessed for full-text screening. In total, 27 studies were further removed in full-text screening, while 46 studies (13 preclinical and 33 clinical) included in quantitative synthesis (Figure 1).

Role of the GMB in SCZ and AIMA
Emerging evidence from preclinical and clinical studies suggests the putative role of the GMB in SCZ symptomatology22,36,53 and AIMA.22,44,54,55 The evidence supporting this line of thought is summarized in the following sections.

Preclinical evidence – GMB and SCZ (Table A). Preclinical studies in mice suggest that the GMB is important in modulating behavioral phenotypes resembling clinical symptoms of SCZ, such as social isolation and cognitive impairment. In one study, GMB depletion in adolescent mice using antibiotics was associated with SCZ-like behavioral phenotype, an altered tryptophan metabolic pathway, and reduced brain derived neurotrophic factor (BDNF) expression in the adult brain.56 Similar social and cognitive impairment has been observed in germ-free mice (GFM).22,56 Furthermore, fecal transplantation from SCZ patients to GFM has been shown to induce SCZ-like behavioral phenotypes, mainly psychomotor hyperactivity, learning and memory impairment, depression and anxiety-like behaviors, and increased startle response in the pre-pulse inhibition (PPI) test.42,57 These behavioral alterations were also associated with altered neurotransmitter levels, such as increased extracellular basal dopamine (in the prefrontal cortex), 5-HT (hippocampus), and elevation of the tryptophan degradation pathway (kynurenine-kynurenic acid pathway) in the brain and periphery, which play a pivotal role in SCZ pathogenesis.57 Hippocampal glutamate hypofunction and disruptions in the glutamate-glutamine-GABA cycle are majorly associated with SCZ pathophysiology, mainly negative symptoms, cognitive decline, and heightened dopamine neurotransmission in mesocortical pathways.58,59 Related to this, mice which received fecal transplants from SCZ patients displayed decreased glutamate and increased glutamine and GABA levels in the hippocampus compared to mice that received fecal transplants from HCs.42,57 These behavioral and neurochemical phenotypes of SCZ were also associated with altered GMB composition. Mice that received the SCZ fecal transplant
displayed an increased relative abundance of taxa such as *Parabacteroides*, *Bacteroides*, *Clostridium*, *Odoribacter*, and *Fusobacterium*, as well as families, including *Bacteroidaceae*, *Coriobacteriaceae*, *Prevotellaceae*, and *Veillonellaceae*. Together, this evidence suggests a possible role of the GMB in the pathogenesis of SCZ.

**Preclinical evidence – GMB and AIMA (Table 1B).** Rodent models have also been instrumental in characterizing AIMA and associated changes in the GMB. For example, in one study, olanzapine treatment in male and female rats increased body weight and adiposity, decreased locomotion, and increased the expression of interleukin (IL)-6 in adipose tissue and plasma levels of IL-8, IL-1β, leptin, and free fatty acids. Olanzapine also increased fatty acid synthase (FAS) expression in the liver and CD68 (a macrophage marker, which causes the release of proinflammatory cytokines from adipocytes) expression in adipose tissue. These metabolic alterations were associated with increased abundance of *Firmicutes* and decreased abundance of *Bacteroidetes*, which was reversed in rats receiving olanzapine with antibiotic cocktail treatment. In line with these findings, olanzapine treatment in female C57BL/6 J GFM shifted the GMB to an obesogenic profile characterized by increased abundance of phyla *Firmicutes*, *Proteobacteria*, and decreased *Bacteroidetes*. Olanzapine also exhibited antimicrobial activities against common enteric bacteria such as *Escherichia coli* and *Enterococcus faecalis*.

Similarly, risperidone treatment in female wild-type C57BL/6 J mice has been shown to cause significant weight gain, associated with decreased energy expenditure and altered GMB composition, with a notable increase in the relative abundance of *Firmicutes* versus *Bacteroidetes*. Although risperidone-induced weight gain was not attenuated by antibiotic treatment, risperidone differentially inhibited the growth of anaerobes in cultured gut microbes. Recently, metformin treatment was found to reverse olanzapine-induced metabolic alterations (increased body weight, serum glucose, triglycerides, LDL, and decreased HDL levels) and gut dysbiosis (increase in the *Firmicutes:* *Bacteroidetes* ratio) in rats. Taken together, these preclinical findings further support the interplay of the GMB and AIMA.

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**Figure 1.** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart. Literature search and selection process of included studies.
### A. GMB and SCZ

| SNo | Publication | Study details | Major outcomes | Change in GMB composition |
|-----|-------------|---------------|----------------|---------------------------|
| 1.  | Zhu et al.  | Fecal transplantation in antibiotic-treated mice showed behavioral phenotypes like SCZ (mainly psychomotor hyperactivity, learning, and memory impairment). Furthermore, fecal transplanted mice also showed abnormal neurotransmitter levels like increased extracellular basal dopamine in the prefrontal cortex, 5-HT (hippocampus), and elevated tryptophan degradation pathway [kynurenine-kynurenic acid pathway] in the brain and periphery as compared to the mice transplanted with fecal samples from HCs. | GMB of SCZ donor had 261 mOTU, 112 were seen in GMB of fecal transplanted mice, while 55 mOTUs were present in significantly different relative abundance in SCZ and HCs mice. In SCZ mice, majorly abundant taxa were Parabacteroides (distasonis and merdae), Bacteroides eggerthii, Clostridium (scindens and leptum), Odoribacter splanchnici, Fusobacterium ulcerans, and Holdemania filliformis. | |
| 2.  | Zhu et al.  | Mice fecal transplanted with SCZ GMB (S. vestibularis) overall increased distance traveled and rearing in the open field, reduced social interaction in three-chamber social test, exhibiting behavioral phenotype of SCZ. S. vestibularis treated mice showed significantly lower levels of dopamine in serum, intestinal contents, colon tissue and decreased GABA levels in intestinal content immediately after transplantation. Increased 5-HT levels in intestinal content were also observed in fecal transplanted mice. Levels of neurotransmitters were not affected in the brain except decreased tryptophan levels in the prefrontal cortex of the mice compared to control mice receiving saline gavage. | GMB characterization was not done in the mice transplanted with SCZ-rich microbiota [enrich in S. vestibularis]. But the clinical component of the study has shown the GMB characterization. | |
| 3.  | Zheng et al. | Fecal transplantation from SCZ in GFM showed locomotor hyperactivity, decreased depression and anxiety-like behaviors, increased startle response as compared to mice transplanted with the fecal sample from HCs. SCZ group mice also showed decreased glutamate, increased glutamine, and GABA in the hippocampus, which could be correlated with SCZ-like behaviors attributed to glutamatergic hypofunction. | GMB characterization was done in the FT-GFMs; however, the clinical subdivision of the study displayed GMB analysis. Increased relatively abundant families: Bacteroidaceae, Coriobacteriaceae, Prevotellaceae, and Veillonellaceae Decreased relatively abundant families: Acidaminococcaceae, Enterobacteriaceae, Lachnospiraceae, Rikenellaceae, and Ruminococcaceae in SCZ compared to HCs. | |

### B. GMB and AIMA

| SNo | Publication | Study details | Major outcomes | Change in GMB composition |
|-----|-------------|---------------|----------------|---------------------------|
| 4.  | Luo et al.  | Thirty-five days of olanzapine treatment showed significantly increased body weight, serum glucose, and lipids [increased triglycerides and LDL; decreased HDL] levels, reversed with metformin treatment. Olanzapine treatment also showed increased adipocytes and liver fibrosis, which was reversed by metformin treatment. | Olanzapine treatment increased the Firmicutes: Bacteroidetes ratio. In species levels, olanzapine treatment showed a decreased relative abundance of Ruminococcus bromii compared with the control group. However, metformin co-administration increased the relative abundance of Bacteroides uniformis and acidifaciens), Ruminococcus bromii, Desulfovibrio simplex, and Arcobacter butzleri. Still, it decreased the abundance of Lactobacillus reuteri and Bacteroides pectinophilus compared with the olanzapine-treated group. | |
Table 1.

| No. | Publication | Study details | Change in GMB composition |
|-----|-------------|---------------|--------------------------|
| 5.  | Bahr et al. | Risperidone treatment caused significant weight gain, and decreased energy expenditure and physical activity. | Risperidone-induced changes include increased Firmicutes (phylum Bacteroidetes) and decreased relative abundance of Firmicutes. Fecal transplantation from the risperidone-treated group failed to alter GMB composition significantly. Risperidone treatment increased the relative abundance of class Gammaproteobacteria and class Bacteroidetes. These changes contributed to altered GMB and subsequent weight gain. | Risperidone treatment caused significant weight gain, and decreased energy expenditure and physical activity. | Risperidone-induced changes include increased Firmicutes (phylum Bacteroidetes) and decreased relative abundance of Firmicutes. Fecal transplantation from the risperidone-treated group failed to alter GMB composition significantly. Risperidone treatment increased the relative abundance of class Gammaproteobacteria and class Bacteroidetes. These changes contributed to altered GMB and subsequent weight gain. |
| 6.  | Morgan et al. | Olanzapine treatment increased the relative abundance of class Actinobacteria and class Bacteroidetes. These changes contributed to weight gain. Olanzapine treatment also showed direct antimicrobial activity. | Olanzapine treatment resulted in increased food intake, adiposity, body weight, and decreased locomotion. Olanzapine also showed direct antimicrobial activity. | Olanzapine treatment increased the relative abundance of class Actinobacteria and class Bacteroidetes. These changes contributed to weight gain. Olanzapine treatment also showed direct antimicrobial activity. | Olanzapine treatment resulted in increased food intake, adiposity, body weight, and decreased locomotion. Olanzapine also showed direct antimicrobial activity. |
| 7.  | Davey et al. | Rats treated with olanzapine had increased body weight gain, plasma free fatty acids, and reversed liver adipogenesis markers. Olanzapine significantly increased food intake, adiposity, body weight, and decreased locomotion. Olanzapine also showed direct antimicrobial activity. | Olanzapine treatment resulted in increased food intake, adiposity, body weight, and decreased locomotion. Olanzapine also showed direct antimicrobial activity. | Rats treated with olanzapine had increased body weight gain, plasma free fatty acids, and reversed liver adipogenesis markers. Olanzapine significantly increased food intake, adiposity, body weight, and decreased locomotion. Olanzapine also showed direct antimicrobial activity. | Olanzapine treatment resulted in increased food intake, adiposity, body weight, and decreased locomotion. Olanzapine also showed direct antimicrobial activity. |
| 8.  | Davey et al. | Male and female rats were treated with olanzapine for 7 weeks. Female C57BL/6 J germ-free mice were treated with olanzapine and a high-fat diet (HFD, 50 mg/kg of diet) and only an HFD placebo diet. Experimental method(s): 16s rRNA sequencing. 30 min locomotor activity was performed in open field test. | Olanzapine treatment resulted in increased food intake, adiposity, body weight, and decreased locomotion. Olanzapine also showed direct antimicrobial activity. | Male and female rats were treated with olanzapine for 7 weeks. Female C57BL/6 J germ-free mice were treated with olanzapine and a high-fat diet (HFD, 50 mg/kg of diet) and only an HFD placebo diet. Experimental method(s): 16s rRNA sequencing. 30 min locomotor activity was performed in open field test. | Olanzapine treatment resulted in increased food intake, adiposity, body weight, and decreased locomotion. Olanzapine also showed direct antimicrobial activity. |
Clinical evidence – GMB and SCZ (Table 2). A plethora of evidence from human studies supports the involvement of the GMB in SCZ pathogenesis and metabolic alterations. A dysregulated MGB axis may explain the role of the GMB in SCZ pathogenesis, presenting as altered inflammatory processes and immune responses in SCZ patients. Microbial translocation across the gastrointestinal tract (GIT) barrier, mediated by soluble CD14 (sCD14) and LPS-binding proteins (LBP), causes low-grade inflammation and immune reaction. Patients with SCZ exhibit altered patterns of these serological bacteria translocation markers including increased sCD14 serum and fecal concentrations of SCFAs, which was negatively correlated with cognitive function. Patients with SCZ showed increased CRP, IL-6, soluble IL-2R, and sCD14 SCFAs showed immune activation evidenced by higher circulating SCFAs, compared with HCs, and decreased abundance of phylum Lentinisphaerae compared with AP-naïve first-episode SCZ patients. These GMB alterations were associated with abnormal right middle frontal gyrus volume. Another study which examined the association of the GMB with brain structural and functional changes found that low gray matter volume (GMV) and regional homogeneity and high amplitude of low-frequency fluctuation were observed in several brain regions of SCZ patients compared with HCs. These patients had lower abundance of genera Ruminococcus and Roseburia, and lower abundance of genus Veillonella.

Differential abundance of microbial taxa also appears to be associated with varying psychopathology of SCZ including (1) an inverse relation between abundance of family Ruminococcaceae and severity of negative symptoms, (2) a positive relation between abundance of genus Bacteroides and severity of depressive symptoms, and (3) a positive relation between phylum Verrucomicrobia and self-reported mental well-being. Lower alpha diversity was observed in SCZ patients receiving SGAs, while changes in abundance of taxa such as Veillonellaceae and Lachnospiraceae were associated with SCZ severity. Another study has reported the difference in GMB composition among the acute SCZ and remission SCZ patients. The remission SCZ group had enriched phyla (Desulfovibrion, Mitsuokella, Lactobacillus, and Succinivibrio). Furthermore, the abundance of Haemophilus was positively correlated with negative symptoms, cognition, excitement, and depression, whereas Coprococcus was found to be negatively correlated with negative symptoms. In line with this, Pan et al. have reported that compared with acute SCZ, remission SCZ patients had increased abundances of family Clostridiaceae-1 and genus Clostridium sensu-stricto-1 and unclassified family Peptostreptococcaceae. Moreover, there was positive correlation between Succinivibrion abundance and total and general Positive and Negative Symptom Scale (PANSS) scores, while Corynebacterium was negatively correlated with the negative scores of PANSS.

The increased relative abundance of Proteobacteria and decreased relative abundance of Firmicutes was also observed in SCZ patients receiving APs. The abundance of some genera (such as Blautia, Coprococcus, and Roseburia) was positively correlated with specific metabolic pathways (vitamin B6, taurine, and hypotaurine). In contrast, the abundance of some genera was negatively correlated.
| No. | Publication | Study design | GMB composition | Change in GMB composition |
|-----|-------------|--------------|-----------------|--------------------------|
| 1.  | Yuan et al. | A 24-week follow-up study involving 107 drugs-naive FEP patients and 107 HCs | Twenty-four weeks of risperidone treatment showed increased alpha diversity compared with that of HCs at baseline. Significantly increased dynamic changes were observed in the levels of hs-CRP and homocysteine and BMI after 24 weeks of risperidone treatment. SCZ patients showed lower alpha diversity at baseline compared with HCs, while a significant difference in beta diversity between SCZ and HC groups was also observed. | Twenty-four weeks of risperidone treatment showed increased alpha diversity compared with that of HCs at baseline. Significantly increased dynamic changes were observed in the levels of hs-CRP and homocysteine and BMI after 24 weeks of risperidone treatment. SCZ patients showed lower alpha diversity at baseline compared with HCs, while a significant difference in beta diversity between SCZ and HC groups was also observed. |
| 2.  | Chen et al. | GMB profiling in 28 SCZ patients with violence (V.SCZ) and compared with 16 SCZ patients without violence (NV.SCZ). | This study profiled differences in the GMB composition between V.SCZ and NV.SCZ followed by data analysis using R Version 3.3.2 and R Studio (Version 1.0.136) to explore the microbial diversities. Principal coordinate analysis (PCoA) was used for identification of OTUs. | Functional pathway analysis revealed alterations in pyrimidine pathways related to trimethylamine-N-oxide reductase and kynurenine metabolic pathways. These metabolic pathways were linked to inflammatory cytokines associated with the risk of coronary heart diseases in SCZ. |
| 3.  | Zhu et al. | A Pilot study comprising 42 acute SCZ patients, 48 chronic SCZ patients and 48 matched (age, sex, BMI, antibiotic use, and sequencing plate) nonpsychiatric controls. | The abundance of Lactobacillus was positively correlated with negative symptoms. 16s rRNA sequencing was used for GMB analysis, followed by data analysis using R Version 3.2.2. Principal coordinate analysis (PCoA) was used for identification of OTUs. | Data analysis using R Version 3.2.2 and R Studio (Version 1.0.136) was used for microbial taxa and functional pathways analysis. |
| 4.  | Marabelli et al. | A cross-sectional study. SCZ patients were also tested for response to APs [20 responders and 18 with treatment-resistant SCZ (TR)] and HCs. | No change in alpha diversity was observed. Functional pathway analysis revealed alterations in pyrimidine pathways related to trimethylamine-N-oxide reductase and kynurenine metabolic pathways. These metabolic pathways were linked to inflammatory cytokines associated with the risk of coronary heart diseases in SCZ. |
| 5.  | Nguyen et al. | A cross-sectional study. SCZ patients and 48 matched, age, sex, BMI, and sequencing plate matched controls were recruited. Comparison of HCs were recruited for the study. | Functional pathway analysis revealed alterations in pyrimidine pathways related to trimethylamine-N-oxide reductase and kynurenine metabolic pathways. These metabolic pathways were linked to inflammatory cytokines associated with the risk of coronary heart diseases in SCZ. | Data analysis using R Version 3.2.2 and R Studio (Version 1.0.136) was used for microbial taxa and functional pathways analysis. |
| SNo. | Publication | Study details | Major outcomes | Change in GMB composition |
|------|-------------|---------------|----------------|--------------------------|
| 6.   | Li et al. 73 | Country: China; Study design: 38 SCZ patients and 38 demographically matched HCs were recruited for the study. In total, 35 SCZ patients were receiving AP treatment. Experimental method(s): 16s rRNA sequencing was used for GMB analysis. To elucidate the brain structural and functional differences, structural magnetic resonance imaging (sMRI) and resting-state functional (rs-fMRI) were used. | GMB alteration was associated with brain structure and functional changes. Low gray matter volume (GMV) and regional homogeneity, but the higher amplitude of low-frequency fluctuation in several brain regions of SCZ patients compared with HCs. | A significantly lower abundance of genera Ruminococcus and Roseburia and a lower abundance of genus Veillonella were observed in SCZ patients compared with HCs. |
| 7.   | Zhu et al. 49 | Country: China; Study design: 197 SCZ patients and 200 HCs were enrolled in a two-stage cross-sectional study to compare short-chain fatty acid levels, systemic immune activation Experimental method(s): 16s rRNA sequencing was used for GMB analysis. Microbial diversity and differential OTU identification were done by R (Version 3.3.2) and R Studio (Version 1.0.136), and PCA analysis, respectively. | SCZ patients showed significantly higher acetate, propionate, butyrate, and total SCFAs concentrations than HCs. SCFA levels were negatively correlated with cognitive function. | Bacteria producing SCFAs were enriched in the GMB of the SCZ patients. SCZ GMB alpha diversity was increased in SCZ patients, which was positively associated with SCFA concentration in serum but not in feces. Patients with higher circulating SCFAs also showed immune activation (increased CRP, IL-6, soluble IL-2R, and sCD14 in serum). |
| 8.   | Li et al. 76 | Country: China; Study design: 82 SCZ patients and 80 demographically matched HCs were enrolled to evaluate the correlation between GMB composition and symptom severity in SCZ. Experimental method(s): 16 s rRNA sequencing was used for GMB analysis. Raw sequences were processed using QIIME 2, while DADA2 algorithm was performed to demultiplexing raw sequences and identifying the microbial features. | No significant difference in alpha diversity was found, but significant differences in beta diversity were observed between SCZ and HC. | Significantly increased abundance of phylum: Actinobacteria and genera: Collinsella, Corynebacterium, Lactobacillus, Mogibacterium, Succinivibrio, and undefined Eubacterium, and undefined Ruminococcus, whereas decreased abundance of phylum: Firmicutes and genera: Adlercreutzia, Anaerostipes, Faecalibacterium, and Ruminococcus were observed in SCZ group compared with HCs. In the SCZ group, the abundance of Succinivibrio was positively correlated with total and general PANSS scores, while Carylernbacterium was negatively correlated with the negative scores of PANSS. |
| 9.   | Li et al. 75 | Country: China; Study design: 97 SCZ patients and 69 matched HCs were recruited in the study. Experimental method(s): 16 s rRNA sequencing was used for GMB analysis and metagenomic for microbial enterotypes identification. Participants whose GMB was enriched with Prevotella and Bacteroides were marked as enterotype-P and enterotype-B, respectively. | SCZ patients had significantly higher BMI than the HCs. Patients with enterotype-P had higher BMI. | SCZ group with enterotype-P had a significantly higher abundance of phyla Proteobacteria and Firmicutes, whereas HCs with enterotype-P had a significantly higher abundance of phylum Bacteroidetes. |
| 10.  | Pan et al. 74 | Country: China; Study design: 29 SCZ patients’ fecal samples were collected at two time points (onset and remission periods) and 29 samples from HCs. Experimental method(s): 16 s rRNA Miseq was used for GMB analysis. OTU clustering and taxonomic analysis was done using Usearch software (V.7.0). | Bacterial taxonomic composition analysis showed no significant difference between SCZ patients and HCs at phylum and genus levels. However, there were differences in the GMB composition of SCZ patients with acute onset and remission (aSCZ and rSCZ, respectively). Furthermore, three genera, i.e., Eisenbergiella, norank-f Ruminococcaceae, and Turicibacter were found to be the best biomarker in aSCZ patients. | In the SCZ patients, aSCZ GMB was found to be enriched with 15 taxa such as families (Ruminococcaceae, Actinomycetaceae, and Desulfovibrionales), class: Deltaproteobacteria, orders (Desulfovibrionales and Actinomycetales), genera (Turbibacter, Anaerotruncus, Bilophila, Intestinalbacter, Ruminococcaceae UCG-004, Flavonifractor, Ruminiclostridium-9, Actinomyces, and Acetanaerobacterium). On the other hand, the rSCZ group was found to be enriched in 19 genera such as Anaerostilb, Anaerotruncus, Atopobium, Actinomyces, Bilophila, Clostridium sensu-stri-to-1, Conomonas, Intestinalbacter, Flavonifractor, Eubacterium, Parabacteroides, Turricibacter, norank f-Ruminococcaceae, Ruminococcaceae UCG-004, Lactobacillus, norank f-Christensenellaceae, Solobacterium, Prevotella, and Holdemania. Furthermore, compared with aSCZ, rSCZ patients had increased abundances of family Clostridaceae-1, genera Clostridium sensu-stri-to-1, and unclassified f-Peptostreptococcaceae. |
| No. | Publication | Major outcomes | Study details |
|-----|-------------|----------------|---------------|
| 11. | Zhu et al.11 | SCZ patients had greater alpha and beta diversity than HCs. DM alteration was functionally associated with SCFAs production, and increased relative abundance of various taxa in SCZ compared with HCs: order (Deltaproteobacteria, Actinobacteria), class (Sphingomonadaceae, Actinomycetales and Sphingomonadales), family (Sphingomonadaceae), genera (Anaerococcus, Blautia, Megasphaera, Ruminococcus) and species (Akkermansia muciniphila, Eggerthella lenta, Megasphaera intestinalis). | There was no significant difference in alpha diversity (alpha diversity index was calculated using the Bray-Curtis distance and richness (Simpson index) was calculated using QIIME 2, followed by Deblur algorithm for microbial sOUTs). On the Illumina platform, Metagenomic shotgun sequencing was done. Furthermore, SCZ-associated GMB composition was determined using pathway/module analysis (KEGG). Chronic AP-treated SCZ patients had increased relative abundance of Bacteroides, Clostridiales, Enterococcus, Enterobacteriaceae, Fusobacterium, Peptostreptococcus, Prevotella, Porphyromonas, Parabacteroides, and Pseudomonas genera as compared with HCs. Reduced relative abundance of various taxa in SCZ compared with HCs: order (Deltaproteobacteria, Actinobacteria), class (Sphingomonadaceae), family (Sphingomonadaceae), genera (Anaerococcus, Blautia, Megasphaera, Ruminococcus) and species (Akkermansia muciniphila, Eggerthella lenta, Megasphaera intestinalis). | | 12. | Zhang et al.12 | SCZ patients had greater alpha and beta diversity than HCs. DM alteration was functionally associated with SCFAs production, and increased relative abundance of various taxa in SCZ compared with HCs: order (Deltaproteobacteria, Actinobacteria), class (Sphingomonadaceae, Actinomycetales and Sphingomonadales), family (Sphingomonadaceae), genera (Anaerococcus, Blautia, Megasphaera, Ruminococcus) and species (Akkermansia muciniphila, Eggerthella lenta, Megasphaera intestinalis). | There was no significant difference in alpha diversity (alpha diversity index was calculated using the Bray-Curtis distance and richness (Simpson index) was calculated using QIIME 2, followed by Deblur algorithm for microbial sOUTs). On the Illumina platform, Metagenomic shotgun sequencing was done. Furthermore, SCZ-associated GMB composition was determined using pathway/module analysis (KEGG). 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DM alteration was functionally associated with SCFAs production, and increased relative abundance of various taxa in SCZ compared with HCs: order (Deltaproteobacteria, Actinobacteria), class (Sphingomonadaceae, Actinomycetales and Sphingomonadales), family (Sphingomonadaceae), genera (Anaerococcus, Blautia, Megasphaera, Ruminococcus) and species (Akkermansia muciniphila, Eggerthella lenta, Megasphaera intestinalis). | There was no significant difference in alpha diversity (alpha diversity index was calculated using the Bray-Curtis distance and richness (Simpson index) was calculated using QIIME 2, followed by Deblur algorithm for microbial sOUTs). On the Illumina platform, Metagenomic shotgun sequencing was done. Furthermore, SCZ-associated GMB composition was determined using pathway/module analysis (KEGG). Chronic AP-treated SCZ patients had increased relative abundance of Bacteroides, Clostridiales, Enterococcus, Enterobacteriaceae, Fusobacterium, Peptostreptococcus, Prevotella, Porphyromonas, Parabacteroides, and Pseudomonas genera as compared with HCs. Reduced relative abundance of various taxa in SCZ compared with HCs: order (Deltaproteobacteria, Actinobacteria), class (Sphingomonadaceae), family (Sphingomonadaceae), genera (Anaerococcus, Blautia, Megasphaera, Ruminococcus) and species (Akkermansia muciniphila, Eggerthella lenta, Megasphaera intestinalis). | | 14. | Xu et al.14 | SCZ patients had greater alpha and beta diversity than HCs. DM alteration was functionally associated with SCFAs production, and increased relative abundance of various taxa in SCZ compared with HCs: order (Deltaproteobacteria, Actinobacteria), class (Sphingomonadaceae, Actinomycetales and Sphingomonadales), family (Sphingomonadaceae), genera (Anaerococcus, Blautia, Megasphaera, Ruminococcus) and species (Akkermansia muciniphila, Eggerthella lenta, Megasphaera intestinalis). | There was no significant difference in alpha diversity (alpha diversity index was calculated using the Bray-Curtis distance and richness (Simpson index) was calculated using QIIME 2, followed by Deblur algorithm for microbial sOUTs). On the Illumina platform, Metagenomic shotgun sequencing was done. Furthermore, SCZ-associated GMB composition was determined using pathway/module analysis (KEGG). Chronic AP-treated SCZ patients had increased relative abundance of Bacteroides, Clostridiales, Enterococcus, Enterobacteriaceae, Fusobacterium, Peptostreptococcus, Prevotella, Porphyromonas, Parabacteroides, and Pseudomonas genera as compared with HCs. Reduced relative abundance of various taxa in SCZ compared with HCs: order (Deltaproteobacteria, Actinobacteria), class (Sphingomonadaceae), family (Sphingomonadaceae), genera (Anaerococcus, Blautia, Megasphaera, Ruminococcus) and species (Akkermansia muciniphila, Eggerthella lenta, Megasphaera intestinalis). | | 15. | Nguyen et al.15 | SCZ patients had greater alpha and beta diversity than HCs. DM alteration was functionally associated with SCFAs production, and increased relative abundance of various taxa in SCZ compared with HCs: order (Deltaproteobacteria, Actinobacteria), class (Sphingomonadaceae, Actinomycetales and Sphingomonadales), family (Sphingomonadaceae), genera (Anaerococcus, Blautia, Megasphaera, Ruminococcus) and species (Akkermansia muciniphila, Eggerthella lenta, Megasphaera intestinalis). | There was no significant difference in alpha diversity (alpha diversity index was calculated using the Bray-Curtis distance and richness (Simpson index) was calculated using QIIME 2, followed by Deblur algorithm for microbial sOUTs). On the Illumina platform, Metagenomic shotgun sequencing was done. Furthermore, SCZ-associated GMB composition was determined using pathway/module analysis (KEGG). Chronic AP-treated SCZ patients had increased relative abundance of Bacteroides, Clostridiales, Enterococcus, Enterobacteriaceae, Fusobacterium, Peptostreptococcus, Prevotella, Porphyromonas, Parabacteroides, and Pseudomonas genera as compared with HCs. Reduced relative abundance of various taxa in SCZ compared with HCs: order (Deltaproteobacteria, Actinobacteria), class (Sphingomonadaceae), family (Sphingomonadaceae), genera (Anaerococcus, Blautia, Megasphaera, Ruminococcus) and species (Akkermansia muciniphila, Eggerthella lenta, Megasphaera intestinalis). |
| Study design | Country | Study details | Experimental methods | Change in GMB composition |
|-------------|---------|---------------|-----------------------|--------------------------|
| 16. Zheng et al. | China | Increased relatively abundant families (Bacteroidaceae, Coriobacteriaceae, and Veillonellaceae) were observed in SCZ patients. Taxa such as Akkermansia, Fusobacterium, Prevotellaceae, Veillonellaceae, Acidaminococcaceae, Megasphaera, Prevotella genera was associated with SCZ. Acme such as Bacteroides, Enterobacteriaceae, Lachnospiraceae, and Ruminococcaceae, and species such as Bacteroides fragilis were observed in SCZ patients. | Demultiplexing the raw FASTQ files, and chimeric sequences are filtered using UCLUST method was used for clustering the sequencing data to OTUs. QIIME (Version 1.17) was used for analyzing the sequencing data. | No significant difference in alpha diversity was observed, while a significant difference in beta diversity was observed. The abundance of bacterial groups between the two groups were found to be significantly different. | 
| 17. Shen et al. | China | Glutamic acid, pyruvate, acetyl-CoA, and fatty acid were observed in SCZ patients as compared with HCs. The abundance of bacterial groups was positively correlated with symptom severity. | Demultiplexing the raw FASTQ files, and chimeric sequences are filtered using UCLUST method was used for clustering the sequencing data to OTUs. QIIME (Version 1.9.1) was used for analyzing the sequencing data. | No significant difference in alpha diversity was observed, while a significant difference in beta diversity was observed. | 
| 18. Schwarz et al. | Germany | The abundance of bacterial genera such as Bacteroides, Enterobacteriaceae, Lachnospiraceae, Rikenellaceae, and Ruminococcaceae was positively correlated with negative symptoms. | Demultiplexing the raw FASTQ files, and chimeric sequences are filtered using UCLUST method was used for clustering the sequencing data to OTUs. QIIME (Version 1.17) was used for analyzing the sequencing data. | No significant difference in alpha diversity was observed, while a significant difference in beta diversity was observed. |
with metabolic pathways of tyrosine (Collinsella), phenylalanine, and beta-alanine (Clostridium). Furthermore, SCZ patients with or without violent behavior had different GMB profiles, which are highly enriched (phylum Bacteroidetes) and poorly enriched composition (phylum Actinobacteria). Hence, in the light of the evidence presented, the GMB has a noticeable association with SCZ symptoms and pathophysiology.

Clinical evidence – GMB and AIMA (Table 3). Chronic AP-treated SCZ patients with metabolic comorbidities, including diabetes, weight gain, and hypertension, have also shown altered GMB composition. For example, in one study, first-episode SCZ patients were found to have decreased abundance of spp. such as Bifidobacterium, E. coli, and Lactobacillus compared with HCs. Twenty-four weeks of risperidone treatment significantly increased body weight, BMI, serum glucose and lipids, antioxidant markers (i.e. superoxide dismutase), and high-sensitivity C-reactive peptide (hs-CRP). These metabolic changes were accompanied by an increased abundance of Bifidobacterium spp. and E. coli, and a decreased abundance of Lactobacillus spp. and the Clostridium cocoide group compared with baseline. Change in the abundance of Bifidobacterium was associated with a change in body weight. In another study, adolescents receiving risperidone treatment were found to have increased BMI, a lower Bacteroidetes: Firmicutes ratio, and an increased abundance of Proteobacteria and Actinobacteria and decreased abundance of Verrucomicrobia compared with an AP-naïve psychiatric control group.

Another study reported that risperidone treatment for 24 weeks caused a significant change in the abundance of Bacteroidetes, Christensenellaceae, Enterobacteriaceae, and Proteobacteria, which was associated with the changes in metabolic parameters such as increased BMI, HOMA-IR, and serum lipids. On the contrary, 6 weeks of olanzapine treatment in an observational study caused significant weight gain but did not change the GMB composition in SCZ patients. In a nutshell, the GMB could be regarded as a potential player in metabolic perturbations associated with AP treatment.

Probiotic/prebiotic formulations as therapeutic adjuncts in SCZ and AIMA
Probiotics are live organisms, mainly bacteria, that exert therapeutic benefits when taken in adequate quantities. Prebiotics are the complex and indigestible food material (such as oligosaccharides), which upon fermentation in the colon, produces metabolites (such as SCFAs) that nourish the GMB and promote health benefits. When probiotics and prebiotics are taken together, they are termed ‘synbiotics’; when they are intended to produce therapeutic benefits in patients suffering from mental illnesses, they are referred as ‘psychobiotics’.

Preclinical evidence (Table 4A). The present review includes five preclinical studies investigating the preventive role of prebiotic/probiotic formulations against AP-induced gut dysbiosis, metabolic alterations, and dysregulated expression of different neurotransmitter receptors in rodents. Two studies reported protective effects of the probiotic formulation VSL#3 (a freeze-dried mixture of Bifidobacterium spp., Lactobacillus spp., and Streptococcus thermophilus) in rats and in mice treated with olanzapine. Specifically, VSL#3 reversed olanzapine-induced metabolic alterations (increased body weight, fasting glucose, serum total cholesterol and triglycerides, and decreased HDL levels) in Wistar rats. VSL#3 treatment restored olanzapine-induced GMB disarrangement (decreased Bacteroidetes, Akkermansia muciniphila, Enterobacteriaceae, and increased Firmicutes). VSL#3 also restored the olanzapine-induced oxidative stress and inflammatory aberrations in mice. Recently, a probiotic formulation containing Akkermansia muciniphila was found to reverse olanzapine-induced metabolic alterations, mainly increased serum markers (insulin, total cholesterol, triglycerides), systemic inflammation (increased serum IL-6, and TNF-α levels), gluconeogenesis and adipocyte deposition markers in the liver, and insulin resistance. A different group used the prebiotic formulation BimunoTM galacto-oligosaccharides (B-GOS) to attenuate olanzapine-induced weight gain in female Sprague Dawley rats. In addition to preventing weight gain, B-GOS treatment reduced mRNA expression of 5-HT2A receptors, and increased expression of GlnN1 protein and GlnN2A mRNA (glutamate receptor subunits) in the cortex. B-GOS treatment also increased the abundance of Bifidobacteria spp. and decreased Coprococcus spp., Escherichia Shigella spp., Oscillibacter spp., Clostridium, Coccoides spp., Rosbeuria Intestinalis Cluster, and Clostridium XVIII cluster. In a separate study, B-GOS and sodium acetate (a prebiotic) treatment increased and decreased plasma acetate levels in control and olanzapine-treated rats, respectively. These changes were associated with a decrease in brain histone deacetylase (HDAC) and histone acetyltransferase.

In summary, the GMB composition can be altered by AP treatment, which may contribute to the pathogenesis of SCZ and AIMA. Prebiotics and probiotics play a potential role in the alleviation of AP-induced GMB disarrangement, which could be used as a new therapeutic approach for SCZ and AIMA.
Twenty-four weeks of risperidone treatment in SCZ patients showed significant changes in the abundance of Christensenellaceae and Enterobacteriaceae, which was associated with the changes in metabolic parameters. At the baseline, the abundance of these microbial species was significantly increased over BMI, HOMA-IR, serum levels compared with baseline levels.

At baseline, glucose levels were significantly higher in the SCZ group compared with HCs. Twenty-four weeks of risperidone treatment significantly increased the BMI, HOMA-IR, serum levels, and beta diversity were estimated by Shannon diversity using QIIME version 1.7.0.

At baseline, glucose levels were significantly higher in the SCZ group compared with HCs. Risperidone treatment significantly increased body weight, BMI, fasting serum glucose, low-density lipoproteins, triglycerides, antioxidant marker superoxide dismutase (SOD), inflammatory marker high-sensitivity C-reactive protein (hs-CRP), and HOMA-IR, compared with HCs.

These changes were not altered by 6 weeks of olanzapine therapy. However, GMB was not associated with increased BMI and the clinical efficacy of olanzapine.
### Table 4. Effect of probiotic/prebiotic in SCZ and AIMA.

| S No. | Publication | Study design | Pro/Prebiotics used | Major outcomes |
|-------|-------------|--------------|---------------------|----------------|
| A. Preclinical evidence | | | | |
| 1. | Huang et al. | Country: China  
Study design: Female C57BL/6 mice were fed with HFD for 8 weeks followed by 16 weeks of olanzapine (5 mg/kg/day, twice a day) treatment orally in phosphate buffer saline (PBS), and 200 µL of Akkermansia muciniphila® (5×10^9 CFU) twice a day. Bile weekly food intake and body weight were measured, and locomotor activity was measured in the last week.  
Experimental methods: Oral glucose tolerance test, olanzapine tolerance test, serum markers [glucose, insulin, total cholesterol, triglycerides, TNF-α, IL-6, IL-β, Alanine transaminase (ALT) and Aspartate transaminase (AST) levels], hepatic PEPC and G6Pase activity, and fat deposition by oil-red staining. | Probiotic formulation containing A. muciniphila® [Akk I subtype, GP01 strain]. | A. muciniphila® colonization was confirmed after 16 weeks of treatment. Probiotic did not suppress the olanzapine-induced weight gain but increased the locomotion. Probiotic treatment reversed the olanzapine-induced increase in serum markers [insulin, total cholesterol, triglycerides, ALT, and AST]. It also alleviated olanzapine-induced gluconeogenesis, insulin resistance, and systemic inflammation [serum IL-6 and TNF-α levels]. |
| 2. | Syed and Nayak | Country: India  
Study design: 36 Wistar rats were treated with olanzapine [2 mg/kg/day] and probiotic formulation VSL#3 [two doses, 0.6 mg/kg/day and 1.2 mg/kg/day] for 28 days.  
Experimental methods: Estimation of body weight and serum parameters [fasting glucose, lipid profile, total cholesterol, HDL, and triglycerides] was done. | Probiotic: VSL#3 [Sun Pharma, Indial] is a freeze-dried mixture containing 112.5 billion CFU/capsule of *Bifidobacterium longum*, *Lactobacillus acidophilus*, *plantarum*, *casei*, and *bulgaricus* spp., and *Streptococcus thermophilus*. | VSL#3 treatment in low and high doses has significantly reduced the body weight, total cholesterol, triglycerides, fasting glucose, and increased HDL cholesterol in olanzapine-treated rats. GMB composition was not analyzed. |
| 3. | Kao et al. | Country: UK  
Study design: 48 female SD rats were treated with B-GOS®/saline and B-GOS®/olanzapine [10 mg/kg/day], and further acetic acid/saline, acetic/olanzapine.  
Experimental method(s): Rats were treated for 2 weeks. Brain histone deacetylase (HDAC) and histone acetyltransferase (HAT) activity were measured in the brain. HDAC 1–4 and NMDA receptor subunits expression was measured in the cortex and hippocampus. GMB analysis was done with 16 S rRNA sequencing. | Prebiotic: Bimuno™ galacto-oligosaccharides (B-GOS®; 500 mg/kg/day) and sodium acetate (500 mg/kg/day). | B-GOS® treatment decreased the HDAC activity in the cortex and hippocampus and increased HDAC-1 and HDAC-3 mRNA expression in the cortex in olanzapine-treated rats. B-GOS® and acetate treatment increased plasma acetate levels in saline-treated rats but decreased plasma acetate levels in olanzapine-treated rats. Acetate treatment showed decreased body weight, but it was not significant as compared with the olanzapine-treated group. Olanzapine and acetate treatment did not significantly change GMB, mainly in *Coprococcus* spp., *Escherichia/Shigella* spp., *Oscillibacter* spp., *Clostridium* Cocoides spp., *Roseburia Intestinalis* Cluster, and *Clostridium* XVIII cluster. |
| 4. | Dhaliwal et al. | Country: India  
Study design: Female Swiss albino mice were treated with olanzapine [3 mg/kg, oral gavage] and VSL#3 probiotic formulation [20 × 10^9 CFU/day]. Oxidative stress, inflammatory markers, oral glucose tolerance test, serum glucose, adiponectin, and triglyceride were estimated.  
Experimental method(s): GMB analysis was done using QIAamp® DNA stool mini kit (Qiagen) following qPCR. | Probiotic: VSL#3 formulation contains *Bifidobacterium* (longum, breve, and infantis spp.), *Lactococcus acidophilus*, *plantarum*, *casei*, and *bulgaricus* spp., and *Streptococcus thermophilus*. | VSL#3 treatment reversed the metabolic alteration, oxidative stress, and elevated proinflammatory cytokines in olanzapine-treated mice. VSL#3 treatment also restored the GMB disarrangement viz. increased the abundance of Bacteroidetes, Akkermansia muciniphila, Enterobacteriaceae [decreased in olanzapine-treated group], and decreased the abundance of Firmicutes [increased in olanzapine-treated group]. |
| 5. | Kao et al. | Country: UK  
Study design: Female SD rats were treated with B-GOS®/saline and B-GOS®/olanzapine [10 mg/kg/day].  
Experimental method(s): Rats were treated for 2 weeks. Immunoblotting, in situ hybridization, RT-PCR, and gut microbiota analysis with 16 S rRNA sequencing. | Prebiotic: B-GOS®, 500 mg/kg/day | B-GOS® treatment attenuated olanzapine-induced weight gain. Olanzapine and B-GOS® cotreatment reduced the mRNA expression of the 5-HT_3_ receptor in the cortex of rats. B-GOS® treatment increased the cortical expression of GluN1 protein and GluN2A mRNA. B-GOS® treatment increased the acetate level in the saline-treated group, while showed reduced levels in the olanzapine-treated group. Furthermore, B-GOS® treatment increased the composition of *Bifidobacteria* spp. and decreased the genera such as *Caprooccus* spp., *Escherichia/Shigella* spp., *Oscillibacter* spp., *Clostridium* Cocoides spp., *Roseburia Intestinalis* Cluster, and *Clostridium* XVIII cluster. |

(Continued)
Table 4. (Continued)

| No. | Clinical evidence | Study design | Probiotic used | Prebiotics used | Major outcomes |
|-----|-------------------|--------------|----------------|----------------|---------------|
| 6.  | Yamamura et al. 85 | Country: Japan, SCZ or Bipolar disorder patients were treated with probiotics and/or prebiotics (SGA) | Probiotic formulation containing Bifidobacterium breve (Probiotic formulation containing MCC1274) containing 5.0 × 10^7 CFU/g | Prebiotic raw unmodified potato starch or resistant starch (~50% by weight) | Increased abundance of five functional genes responsible for higher lipids and energy metabolism were found in the responders compared with non-responders. GMB composition was not analyzed. |
| 7.  | Li et al. 86 | Country: China, SCZ patients with more than 20% weight gain after 6 months of conventional treatment or those who did not achieve a sustained remission. | Probiotic Bifido® containing B. breve, L. plantarum, and E. faecium in a concentration of 2.0 × 10^9 CFU/g and Prebiotic dietary fiber maltodextrin and perfect dietary fiber drink (30 g twice daily). | Biochemical parameters such as fasting plasma glucose, insulin, C-peptide, HOMA-IR, and HOMA-β were measured. | A significant difference in weight gain and BMI was observed at the fourth week (decreased in the olanzapine and probiotic cotreatment group); however, it was not at the eighth and twelfth weeks. No difference was observed in appetite assessment. |
| 8.  | Jamilian and Ghaderi 87 | Country: Iran, SCZ patients with the first episode of psychosis (FEP) having not used APs for at least 3 months before enrollment in the study. Patients were randomized for olanzapine (15–20 mg/day) or olanzapine plus probiotic formulation Bifico treatments for 12 weeks. | Probiotic: LactoCare® containing L. acidophilus, L. lactis, and E. faecalis in a concentration of 200 μg/day, and Prebiotic: inulin in a capsule. | Biochemical parameters such as plasma glucose, insulin, C-peptide, HOMA-IR, and HOMA-β were measured. | A significant difference in weight gain and BMI was observed at the fourth week in the olanzapine and probiotic cotreatment group; however, it was not at the eighth and twelfth weeks. No difference was observed in GMB composition. |
| 9.  | Kang et al. 88 | Country: China, SCZ patients with SCZ or schizoaffective disorder were assigned to olanzapine (840 mg twice daily), olanzapine plus probiotic cotreatment also reduced BMI and body weight compared with olanzapine alone, but the effects were not statistically significant. GMB composition was not analyzed. | Probiotic cotreatment with selenium significantly reduced the fasting insulin and HOMA-IR compared with the olanzapine alone treated group. | Biochemical parameters such as fasting plasma glucose, insulin, C-peptide, HOMA-IR, and HOMA-β were measured. | A significant difference in weight gain and BMI was observed at the fourth week in the olanzapine and probiotic cotreatment group; however, it was not at the eighth and twelfth weeks. No difference was observed in GMB composition. |
| 10. | Yang et al. 89 | Country: China, SCZ patients with SCZ or schizoaffective disorder were assigned to olanzapine (840 mg twice daily), olanzapine plus probiotic cotreatment also reduced BMI and body weight compared with olanzapine alone, but the effects were not statistically significant. GMB composition was not analyzed. | Probiotic cotreatment with selenium significantly reduced the fasting insulin and HOMA-IR compared with the olanzapine alone treated group. | Biochemical parameters such as fasting plasma glucose, insulin, C-peptide, HOMA-IR, and HOMA-β were measured. | A significant difference in weight gain and BMI was observed at the fourth week in the olanzapine and probiotic cotreatment group; however, it was not at the eighth and twelfth weeks. No difference was observed in GMB composition. |
| 11. | Flowers et al. 90 | Country: China, SCZ patients with SCZ or schizoaffective disorder were assigned to olanzapine (840 mg twice daily), olanzapine plus probiotic cotreatment also reduced BMI and body weight compared with olanzapine alone, but the effects were not statistically significant. GMB composition was not analyzed. | Probiotic cotreatment with selenium significantly reduced the fasting insulin and HOMA-IR compared with the olanzapine alone treated group. | Biochemical parameters such as fasting plasma glucose, insulin, C-peptide, HOMA-IR, and HOMA-β were measured. | A significant difference in weight gain and BMI was observed at the fourth week in the olanzapine and probiotic cotreatment group; however, it was not at the eighth and twelfth weeks. No difference was observed in GMB composition. |
| S No. | Publication | Study design | Pro/Prebiotics used | Major outcomes |
|-------|-------------|--------------|--------------------|---------------|
| 12.   | Okubo et al.| Country: Japan | Probiotic formulation containing *Bifidobacterium breve* A-1 (10^11 CFU/day) for 4 weeks, and blood cytokines and GMB composition was investigated. Hospital Anxiety and Depression Scale (HADS) and PANSS scores were used. | After 4 weeks of treatment, HADS and PANSS scores improved in SCZ patients (responders) with a higher relative abundance of *Parabacteroides* than non-responders. Responders showed significantly increased IL-22 and TNF-related activation-induced cytokine (TRANCE) expression while non-responders did not. |
| 13.   | Severance et al. | Country: USA | Probiotic formulation containing *Lactobacillus rhamnosus* strain GG (10^9 CFUs) and *Bifidobacterium animalis* subsp. *lactis* Bb12 (10^9 CFUs). | No difference in PANSS score was observed in probiotic supplemented SCZ patients. Furthermore, it had no effect on SCZ symptoms (PANSS score), but greater effects were seen for positive symptoms rather than negative symptoms. *C. albicans* IgG levels were significantly reduced by the probiotic formulation in males but not in females. Seronegativity for *C. albicans* in males showed improvement in positive symptoms and bowel movement. |
| 14.   | Tomasik et al. | Country: USA | Probiotic formulation containing *Lactobacillus rhamnosus* strain GG (10^9 CFUs) and *Bifidobacterium animalis* subsp. *lactis* Bb12 (10^9 CFUs). | Probiotics supplementation had no effects on SCZ symptoms (PANSS score). Probiotic supplementation significantly decreased acute-phase reactant von Willebrand factor and increased the levels of MCP-1, BDNF, T-cell specific protein RANTES, Macrophage inflammatory protein 1 beta. In silico analysis suggested that probiotics regulated the immune functions via IL-17. GMB composition was not analyzed. |
| 15.   | Dickerson et al. | Country: USA | Probiotic formulation containing *Lactobacillus rhamnosus* strain GG (10^9 CFUs) and *Bifidobacterium animalis* subsp. *lactis* Bb12 (10^9 CFUs) for 14 weeks. | No difference in PANSS score was observed in probiotics supplemented SCZ patients; however, they were less likely to develop bowel difficulty. GMB composition was not analyzed. |
(HAT) activities in the cortex and hippocampus. Recently, these findings suggest a preventive role of prebiotic/probiotics in olanzapine-induced weight gain and gut dysbiosis.

Clinical evidence (Table 4B). In the last decade, several clinical studies have been conducted to explore the therapeutic potentials of prebiotics/probiotics in SCZ and AIMA. In human studies, a probiotic formulation containing *Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. *lactis* Bb12 has been used in SCZ patients in three different clinical trials (list studies). Although probiotic treatment did not affect the total PANSS scores, one study found that it decreased both positive and negative symptom severity, with a greater effect for the former. Other effects of probiotic treatment in these patients included less difficulty in bowel movement, decreased inflammatory factors (acute-phase reactant von Willebrand), increased BDNF, T-cell specific protein RANTES and macrophage inflammatory protein 1 beta, and reduced *Candida albicans* IgG levels. These findings support the immunomodulatory effects of probiotics in SCZ patients. In a different study, a probiotic formulation containing *Bifidobacterium breve* A-1 was found to improve Hospital Anxiety and Depression Scale (HADS) and PANSS scores in SCZ patients. This was accompanied by increased levels of IL-22 and TNF-related activation-induced cytokines and an increased relative abundance of *Parabacteroides*. More recently, probiotic supplementation (combination of *Bifidobacterium*, *Lactobacillus*, and Enterococcus) was shown to attenuate olanzapine-induced weight gain at the 4-week mark, although this was not sustained after 8 and 12 weeks of treatment.

Prebiotic formulations have also been investigated for modifying the GMB in SCZ patients receiving SGA treatment. For example, one study found that potato starch (resistant starch), a prebiotic, increased the abundance of *Actinobacteria*. Currently, a prospective study using a combination of probiotics (combination of *Bifidobacterium*, *Lactobacillus*, and Enterococcus)
Conclusion
The GMB has been regarded as a ‘chamber of secrets’, particularly in severe mental illness and the associated metabolic comorbidities. Based on evidence from human and rodent studies, the GMB may serve as a mechanistic link between metabolic dysfunction and cognitive decline in SCZ, given its involvement in energy metabolism and glucose regulation, as well as the programming of social behaviors and cognition, all of which are impaired in SCZ. GMB alterations also correspond to SCZ symptomatology clinically and can induce SCZ-like behavioral and neurochemical phenotypes when fecal microbiota from SCZ patients is transplanted into rodents. The major characteristics of gut dysbiosis are increased systemic and enteric inflammatory cytokine levels; disrupted gut membrane and BBB integrity and permeability; altered neurotransmitter (mainly dopamine, GABA, 5-HT, glutamate) biosynthesis, activity, and metabolism; and decreased SCFA synthesis. These alterations have been associated with SCZ pathophysiology and AIMA (as summarized in Figure 2), and therefore, the GMB should be a point of consideration in current psychopharmacotherapy. Early GMB characterization in a large group of patients with SCZ, both pre- and post-AP treatment, could help in understanding the mechanisms underlying these findings and aid in the discovery of biomarkers and inform future therapeutics. Furthermore, psychobiotic adjuncts could be of great interest in improving psychiatric symptoms and minimizing severe metabolic adverse effects associated with AP use.

Ethical Approval/Patient consent
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Author contribution(s)
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