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# Gut microbiome in serious mental illnesses: A systematic review and critical evaluation

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## ARTICLE INFO

## ABSTRACT

Schizophrenia and bipolar disorder (BD) are associated with debilitating psychiatric and cognitive dysfunction, worse health outcomes, and shorter life expectancies. The pathophysiological understanding of and therapeutic resources for these neuropsychiatric disorders are still limited. Humans harbor over 1000 unique bacterial species in our gut, which have been linked to both physical and mental/cognitive health. The gut microbiome is a novel and promising avenue to understand the attributes of psychiatric diseases and, potentially, to modify them. Building upon our previous work, this systematic review evaluates the most recent evidence of the gut microbiome in clinical populations with serious mental illness (SMI). Sixteen articles that met our selection criteria were reviewed, including cross-sectional cohort studies and longitudinal treatment trials. All studies reported alterations in the gut microbiome of patients with SMI compared to non-psychiatric comparison subjects (NCs), and beta-diversity was consistently reported to be different between schizophrenia and NCs. *Ruminococcaceae* and *Faecalibacterium* were relatively decreased in BD, and abundance of *Ruminococcaceae* was reported across several investigations of SMI to be associated with better clinical characteristics. Lactic acid bacteria were relatively more abundant in SMI and associated with worse clinical outcomes. There was very limited evidence for the efficacy of probiotic or prebiotic interventions in SMI. As microbiome research in psychiatry is still nascent, the extant literature has several limitations. We critically evaluate the current data, including experimental approaches. There is a need for more unified methodological standards in order to arrive at robust biological understanding of microbial contributions to SMI.

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## 1. Introduction

Schizophrenia and bipolar disorder (BD) are severe neuropsychiatric disorders, which combined have a lifetime prevalence of 3.5% (Perälä et al., 2007). Patients with these serious mental illnesses (SMI) face not only debilitating psychiatric and cognitive impairment but also worse physical health outcomes and considerably shorter life expectancies (Brown, 1997; Casey et al., 2009; Viron and Stern, 2010). SMI contribute substantially to the global burden of disease (Whiteford et al., 2013) and rank among the leading causes of disability (Chong et al., 2016) and mortality worldwide (Walker et al., 2015). Younger adults with SMI are prone to diseases associated with aging (Czepielewski et al., 2013; Hennekens et al., 2005; Soreca et al., 2008) and have twice the risk of dying from cardiovascular and gastrointestinal diseases compared to the general population (Saha et al., 2007). Physiological changes seen throughout the body with normal aging occur at earlier ages, including chronic inflammation and oxidative stress, which has led to the theoretical framework of SMI as disorders of accelerated biological aging (Jeste et al., 2011; Kirkpatrick et al., 2008; Nguyen et al., 2018a; Palmer et al., 2018; Rizzo et al., 2014). Given that lifespans are generally increasing for the general population (Christensen et al., 2009), while the mortality gap for schizophrenia is growing (Lee et al., 2018), understanding the mechanisms of potential accelerated aging in SMI is imperative.

Despite decades of research, our understanding of the pathophysiology of these disorders is still limited. Genomic research has identified

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susceptibility genes, but the results have not yet led to new therapies. The human gut microbiome is a dynamic population of microbes in our large intestine that form a symbiotic superorganism, with which we have co-evolved (Dinan et al., 2014). Containing $10^{13}$ microorganisms with over 1000 unique bacterial species containing 2 to 20 million unique genes, the gut microbiome is a complex genomic structure with 100 times more genes than the human genome (Gill et al., 2006; Human Microbiome Project Consortium, 2012; Qin et al., 2010; Turnbaugh et al., 2007). Unlike the human genome, which is fixed and unchangeable, the gut microbiome is highly dynamic and malleable. It can be shaped by various developmental and environmental influences, such as age, geography, cultural traditions and lifestyles (e.g., diet, cohabitation, travel), and medications (Caporaso et al., 2011; Koenig et al., 2011; Yatsunenko et al., 2012). In fact, the overall heritability of the microbiome is low, and the microbiomes of genetically unrelated, cohabiting individuals is more similar than of those who are members of the same family but living apart (Caussy et al., 2019; Cekanaviciute et al., 2017; Yatsunenko et al., 2012). Furthermore, the gut metagenome is a better predictor of many human physical phenotypes (e.g., body mass index [BMI], waist circumference, glucose and high-density lipoprotein [HDL] levels, lactose consumption) than the human genome (Rothschild et al., 2018). Both of these characteristics of the microbiome have important implications for the development of new therapeutic approaches.

The gut microbiome is critical in maintaining human physiology. It regulates many metabolic processes essential for optimal health that cannot be maintained by human cells, stimulates normal immune maturation, defends against pathogens, and stabilizes the gut barrier (Carroll et al., 2009). SMI are characterized by increased gut permeability (Severance et al., 2014, 2013, 2012). With a compromised intestinal lumen, enteric microbes are exposed to systemic circulation. Gut dysbiosis may underlie the pro-inflammatory milieu and other physiological abnormalities that have been implicated in SMI (Hsiao et al., 2013). Moreover, the microbiome plays a major role in the development and functioning of the central nervous system (Clarke et al., 2013; Cryan and Dinan, 2012; Diaz Heijtz et al., 2011; Neufeld et al., 2011). Recent preclinical investigations indicate that gut microbes can influence brain and behavior (Crumeyrolle-Arias et al., 2014; Hsiao et al., 2013; Jørgensen et al., 2015; Sampson et al., 2016; Sudo et al., 2004; Zheng et al., 2016), leading to a resurgent interest in the role of gut microbes in neuropsychiatric disorders and the potential ability to improve psychiatric and cognitive well-being through their manipulation.

Given the bidirectional communication between the gut and brain, via the "gut-brain axis," the concept of "psychobiotics" has emerged in recent years (Dinan et al., 2013; Sarkar et al., 2016; Wall et al., 2014; Zhou and Foster, 2015). Probiotics are live microorganisms that confer a beneficial health effect. Prebiotics are nondigestible food components that are selectively fermented by intestinal microflora, which are associated with health and wellbeing (Gibson et al., 2004). Much of psychobiotic research is based on animal models, which have demonstrated improvements in cognition, mood, and neurophysiology following probiotic and prebiotic treatment (Sarkar et al., 2016; Savignac et al., 2013). Human clinical investigations have begun only recently.

This article updates our prior systematic review of studies of the microbiome in schizophrenia and BD (Nguyen et al., 2018b). In the short time since, a number of additional empirical studies have been published, and more conceptual reviews and commentaries have been written on the gut-brain axis and its role in mental illnesses. However, aside from our own paper, we did not find other systematic reviews of the composition of the gut microbiome in SMI and its relationship to clinical, physical, and disease-related aspects of these disorders. This review is distinctly different from our previous article in that it is only focused on the gut microbiome (i.e., does not include studies of microbiomes of other tissues/organs) and includes 13 new studies. We provide a narrative synthesis of what can be a complex and seemingly contradictory field of knowledge, and we posit reasons for

seemingly discrepant findings across investigations. Although more useful insights may have been drawn from a meta-analysis of data across studies, considerable heterogeneity in study designs and methodologies to quantify and analyze the gut microbiome and few publicly available data from individual reports made this endeavor impractical. Instead, we highlighted commonalities and differences among these investigations.

## 2. Methods

### 2.1. Search strategy

We searched PubMed, PsycINFO, and Embase for articles published before March 7, 2019 using the following search string: microbiome AND (schizophrenia OR psychosis OR bipolar OR serious mental illness). Reference lists of the retrieved articles and relevant review articles were cross-referenced. We examined the titles and abstracts of all citations and selected empirical reports based on our inclusion/exclusion criteria.

### 2.2. Inclusion/exclusion criteria

Studies were selected if they met the following criteria: 1) were empirical studies of individuals clinically diagnosed with schizophrenia, schizoaffective disorder, BD, or related psychotic disorders, 2) utilized high-throughput sequencing methods to characterize microorganisms in the gut or distal large intestine, and 3) were published in English. Both cross-sectional and longitudinal studies were included. We excluded review papers, meta-analyses, abstracts, case reports, and studies exclusively using animal models.

### 2.3. Review process

Our database search yielded 184 articles, once duplicates were removed. The titles and abstracts of all articles were screened and, of these, 37 were assessed for eligibility. In total, 16 met all of the abovementioned criteria for review. The PRISMA flow chart depicting information through different stages of the systematic review is shown in Fig. 1.

Only three articles (Evans et al., 2017; Flowers et al., 2017; Schwarz et al., 2018) overlapped with our original review (Nguyen et al., 2018b), which included five papers on the microbiome; the other two investigations were of the oropharyngeal microbiome and did not qualify for the current review.

## 3. Results

### 3.1. Characteristics of reviewed studies

Detailed sample and methodology characteristics for each study are provided in Table 1. A summary of relevant data from the 16 reviewed studies is presented in Table 2. Five studies included individuals with schizophrenia and/or schizoaffective disorder, seven studies included persons with BD, one study comprised a mixed sample of patients with schizophrenia and BD, two included patients with first episode psychosis (FEP), and one article was of high-risk individuals. Most studies (62.5%) sampled outpatients, while three investigations recruited inpatients. A majority of studies were cross-sectional (75%). Four studies involved longitudinal assessment of the gut microbiome. All reviewed studies had at least one comparison group: 11 compared SMI to a non-psychiatric comparison (NC) group; five involved another psychiatric comparison group; four compared subjects pre-post treatment. Finally, studies were conducted worldwide, with 25% from the US, 44% from Asia, and 31% from Europe.

Below we summarize findings for different clinical populations (Tables 3–5). Within each, we highlight cross-sectional and longitudinal
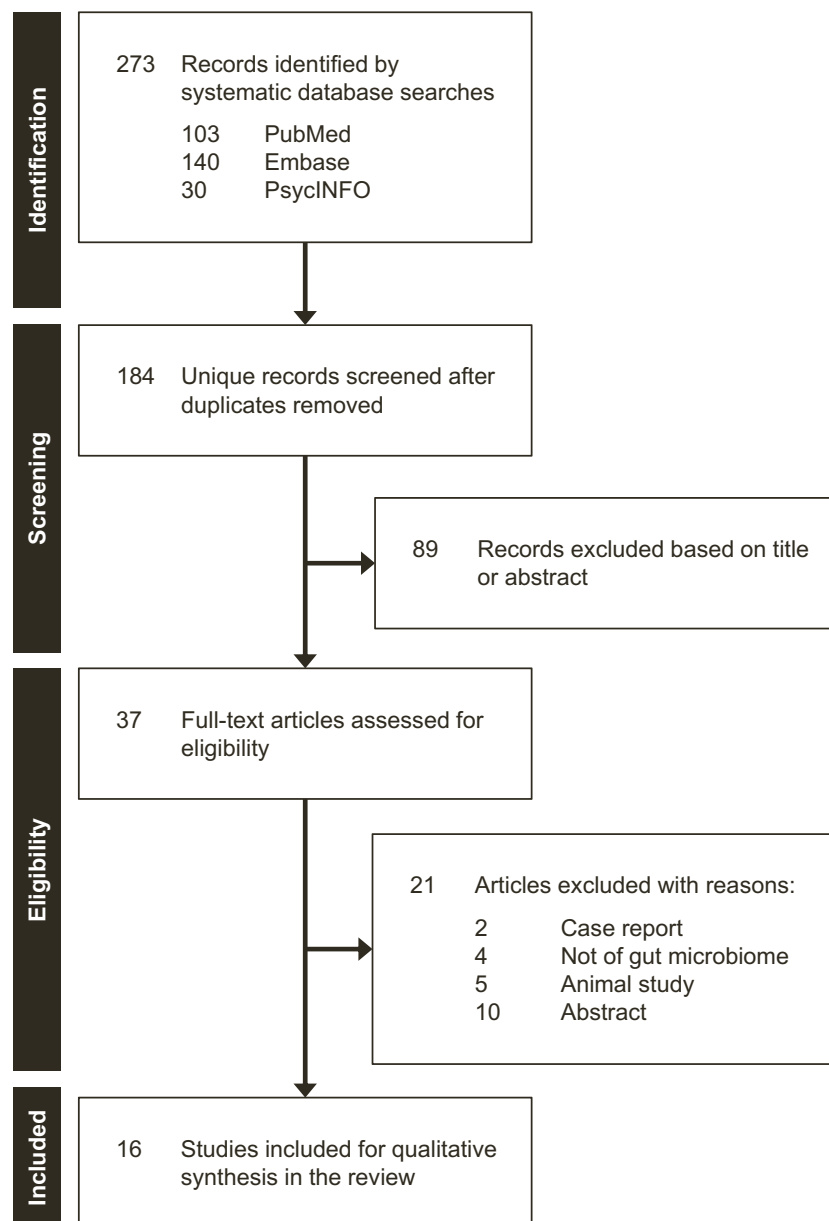
| | | |
|---|---|---|
| **Identification** | 273 Records identified by systematic database searches<br><br>103 PubMed<br>140 Embase<br>30 PsycINFO | |
| **Screening** | 184 Unique records screened after duplicates removed | 89 Records excluded based on title or abstract |
| **Eligibility** | 37 Full-text articles assessed for eligibility | 21 Articles excluded with reasons:<br><br>2 Case report<br>4 Not of gut microbiome<br>5 Animal study<br>10 Abstract |
| **Included** | 16 Studies included for qualitative synthesis in the review | |

**Fig. 1.** PRISMA flow diagram for selection of published articles for review.

findings related to 1) global community diversity, 2) taxonomic differences, 3) clinical characteristics associated with microbial biomarkers, and 4) functional potential (if applicable).

There are multiple levels on which the microbiome can be analyzed and characterized. We provide a brief summary of these techniques and measures to provide the reader context to understand and interpret the findings presented below (see Knight et al., 2018 for a more comprehensive review of best practices for analyzing microbiomes). Marker gene amplification and sequencing (e.g., 16S rRNA amplicon sequencing) uses primers that target a specific region of a gene of interest to determine microbial phylogenies of a sample. These methods are well-tested, fast, and cost-effective for obtaining a low-resolution view of microbial communities (often limited to a genus taxonomic level). Shotgun metagenomics is a method of sequencing all microbial genomes within a sample that yields more detailed genomic information than marker gene sequencing alone (Quince et al., 2017). It may be more expensive and is presently less streamlined than 16S sequencing, but captures all DNA present in a sample and allows for greater taxonomic resolution to species or strain level.

For each of these methods, various levels of analysis and statistical treatment can be used to extract meaningful results. Overall patterns in microbiome variation and community structure are typically assessed by alpha-diversity and beta-diversity (Fig. 2). Alpha-diversity quantifies feature diversity within individual samples, which can be compared across groups. Various indices of alpha-diversity characterize the number and distribution of species in a community, representing species richness and evenness. It is commonly observed that low alpha-diversity is a hallmark of dysbiosis (Yatsunenko et al., 2012). Beta-diversity captures dissimilarity between a pair of samples, generating a distance matrix based on either presence-absence of quantitative species abundance data. Another approach is to examine differentially abundant taxa or functional elements (e.g., genes and pathways) between groups. However, this approach to understanding differences between diagnostic groups versus controls can be challenging given that microbiome datasets are high-dimensional and compositional. The compositionality problem has been discussed in our previous review (Nguyen et al., 2018b), and is further mentioned in Section 4.

**Table 1**
Sample and methodology characteristics of reviewed studies.

| Publication | Country | Sample size | Mean age | Gender | Sample characteristics | Assessments | Sequencing | Data processing/analysis | Diversity assessments |
|---|---|---|---|---|---|---|---|---|---|
| **High-risk and first episode psychosis** | | | | | | | | | |
| He et al., 2018 | China | HR: 81<br>UHR: 19<br>NC: 69 | HR: 21.67 (SD = 5.75)<br>UHR: 20.47 (SD = 4.57)<br>NC: 23.13 (SD = 3.89) | HR: 41M/40F<br>UHR: 15M/4F<br>NC: 37M/32F | UHR: met one of following on SIPS: BIPS, APSS, GRDS; Outpatients; no AP, AD, anticonvulsants; no info on BMI<br>HR: one first-degree relative with SZ<br>NC: No info on matching; No info on BMI | DSM-IV; prodromal sx (SIPS, SOPS); global functioning (GAF) | 16S rRNA (V4 region, 515F/806R); Sequencing; Illumina MiSeq 250 bp paired-end | QIIME2 pipeline; sPLS-DA to cluster samples; PICRUSt with Greengenes and KEGG Databases (3 KEGG levels); LEfSe | α: observed OTUs, Shannon Index<br>β: PCoA, PLS-DA |
| Schwarz et al., 2018 | Finland | FEP: 28<br>NC: 16 | FEP: 25.9 (SD = 5.5)<br>NC: 27.1 (SD = 6.0) | FEP: 16M/12F<br>NC: 8M:8F | FEP: 14 SZ, 4 SZP, 1 SZA, 2 BD I, 1 UD, 6 PD NOS; AOS = 25.9 (SD = 5.5); outpatients; AP: 10 olanzapine, 7 risperidone, 8 quetiapine; BMI = 23.8 (SD = 4.3)<br>NC: Matched by age, sex and region of residence; BMI = 23.9 (SD = 3.1) | DSM-IV; positive and negative sx (BPRS, SANS); global functioning (GAF); medical hx; diet (Health Behavior and Health among the Finnish Adult Population survey); physical activity (Gothenburg scale) | qPCR for 16S primers; analysis of 7 bacterial groups [Lachnospiraceae (*Eubacterium rectale* group), Ruminococcaceae (*Clostridium leptum* group), *Bacteroides* spp., *Atopobium* group in addition to *Bifidobacteria* and *Lactobacillus*-group (comprising of the genera *Lactobacillus*, *Leuconostoc*, *Pediococcus*, and *Weissella*)]; NanoDrop 2000c Metagenomic; Illumina Hi Seq 2000 100 bp paired-end | CLC Genomics Workbench V6 pipeline; Sequences filtered to ≥60 bp, sequences matching human genome build 37 removed, remaining reads matched to Refseq Bacterial Database (length fraction = 0.8, similarity = 0.8); LEfSe | α: did not assess<br>β: did not assess |
| Yuan et al., 2018 | China | FESZ: 41 (pre-post)<br>NC: 41 | FESZ: 23.1 (SD = 8.0)<br>NC: 24.7 (SD = 6.7) | FESZ: 23M/18F<br>NC: 20M/21F | FESZ: AOS = 17.9 (SD = 3.2); DOI = 5.9 months (SD = 3.0 months); inpatients; AP naïve at baseline; BMI = 20.54 (SD = 2.52)<br>NC: No info on matching; BMI = 20.75 (SD = 2.85) | DSM-IV; positive and negative sx (PANSS); medical and psychiatric hx; physical exam; metabolic parameters (glucose, triglycerides, HDL, LDL, insulin, hs-CRP, SOD, HOMA-IR) | qPCR for 16S primers; analysis of 5 bacterial taxa [Bifidobacterium spp., Escherichia coli, Clostridium coccoides group, Lactobacillus spp., Bacteroides spp.] | SPSS v24.0 statistical analysis; qPCR quantification according to cycle threshold; | α: did not assess<br>β: did not assess |
| **Schizophrenia** | | | | | | | | | |
| Nagamine et al., 2018 | Japan | SZ: 16 (pre-post) | SZ: 63.0 (SD = 10.9) | SZ: 5M:11F | SZ: no info on AOS or DOI; inpatients, length of hospital stay = 3053 days (SD = 2805); CPZE = 729.7; BMI = 20.9 (SD = 3.7) (pre), 22.3 (SD = 4.3) (post) | Psychotic sx (BPRS); weight; metabolic parameters (glucose, triglycerides, total cholesterol, albumin); ADRs (fever, abdominal pain, constipation, diarrhoea) | Terminal restriction fragment length polymorphism analysis for 16S primers (no info on region, 516F/1492R) | Genemapper genotyping software; division into 29 OTUs, no information on OTU picking process | α: did not assess<br>β: did not assess |
| Nguyen et al., 2019 | USA | SZ: 25<br>NC: 25 | SZ: 52.9 (SD = 11.2)<br>NC: 54.7 (SD = 10.7) | SZ: 14M:11F<br>NC: 15M:10F | SZ: SZ or SZA; AOS = 21.5, DOI = 32.4; outpatients; WHO DDD = 2.01; BMI = 31.8 (SD = 5.4)<br>NC: Matched by age and sex; BMI = 28.9 (SD = 4.0) | DSM-IV; positive and negative sx (SAPS, SANS), depression sx (PHQ-9), psychiatric and medical hx; physical and mental well-being (SF-36), medical comorbidity (CIRS); CHD and CVD risk (Framingham) | 16S rRNA (V4 region, 501F/806RB) Sequencing: Illumina HiSeq 2000 150 bp paired-end | QIIME2 pipeline; sOTU definition with deblur; rarified to 7905 sequences per sample; | α: observed OTUs, Shannon Index, Faith's PD<br>β: unweighted UniFrac, Bray-Curtis dissimilarity |
| Okubo et al., 2019 | Japan | SZ: 29 (pre-post)<br>Tx responders: 12<br>Tx non-responders: 17 | SZ: 45 (median) (IQR = 16)<br>Tx responders: 46 (median) (IQR = 12)<br>Tx non-responders: 41 (median) (IQR = 16) | SZ: 11M:17F<br>Tx responders: 3M:8F<br>Tx non-responders: 8M:9F | SZ: no info on AOS or DOI; outpatients; HADS ≥ 10; CPZE = 600 (median) (IQR = 400); BMI = 25.7 (median) (IQR = 5.4)<br>Tx responders: CPZE = 600 (median) (IQR = 508); BMI = 26.5 (median) (IQR = 6.4)<br>Tx non-responders: CPZE = 643 (median); BMI = 23.6 (SD = 5.1) | DSM-V; anxiety and depression sx (HADS, PANSS); diet (semi-structured food frequency questionnaire); positive, negative, affective, and disorganized sx (BPRS); inflammatory markers (34 pro- and anti-inflammatory cytokines, related molecules, e.g. ligands and receptors) | 16S rRNA (V3–4 region, Tru357F/Tru806R); strain specific 16S PCR for *bifidobacterium breve A1* (A1F/A1R) Sequencing: Illumina MiSeq | QIIME pipeline; Sequences filtered to ≥150 bp; Open reference OTU picking with 97% threshold; | α: Shannon Index<br>β: UniFrac distances |
| Shen et al., 2018 | China | SZ: 64<br>NC: 53 | SZ: 42 (SD = 11)<br>NC: 39 (SD = 14) | SZ: 36M:28F<br>NC: 35M:18F | SZ: no info on AOS or DOI; outpatients; no info on medications; BMI = 23.49 (SD = 3.8)<br>NC: No info on matching; BMI = 23.14 (SD = 2.8) | ICD-10; psychiatric sx (PANSS); psychiatric and medical hx | 16S rRNA (V3–4 region, 341F/805R) Sequencing: Illumina HiSeq 2500 | QIIME pipeline; removal of low quality sequences; open reference OTU picking with 97% threshold; Rarefaction to 10,000 sequences per sample; LEfSe | α: number of reads, Faith's PD, observed OTUs, Shannon Index, Simpson, ACE, Chao1<br>β: unweighted |

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| Study | Country | Sample size | Age | Sex | Clinical characteristics | Diagnosis/assessment | Sequencing | Analysis | Diversity |
|---|---|---|---|---|---|---|---|---|---|
| Zheng et al., 2019 | China | SZ: 63 UD: 58 NC cohort 1: 69 NC cohort 2: 63 | SZ: 43.49 (SD = 1.68) UD: 40.6 (SD = 11.7) NC cohort 1: 39.99 (SD = 1.62) NC cohort 2: 41.8 (SD = 12.3) | SZ: 42M:21F UD: 22M:36F NC cohort 1: 36M:33F NC cohort 2: 23M:40F | SZ: no info on AOS or DOI; AP: 15 clozapine, 14 risperidone, 9 olanzapine, 5 chlorpromazine, 3 aripiprazole, 3 quetiapine, 9 2+ AP, 5 unmedicated; BMI = 22.90 (SD = 0.32) UD: 19 taking medications (no further info); BMI = 22.0 (SD = 2.4) NC cohort 1: Matched with SZ; BMI = 23.16 (SD = 0.33) NC cohort 2: Matched with UD; BMI = 22.6 (SD = 2.5) | DSM-IV; positive and negative sx (PANSS); depression sx (HAM-D); psychiatric and medical hx | 16S rRNA (V3–4 region, 338F/806R) Sequencing: Illumina MiSeq 250 bp paired-end | QIIME pipeline; removal of low quality and chimeric sequences; open reference OTU picking with 97% threshold; Taxonomy assignment with SILVA database; LEfSe | UniFrac, PCoA α: ACE, Chao, Shannon Index Beta: PLS-DA |
| **Bipolar disorder** | | | | | | | | | |
| Aizawa et al., 2018 | Japan | BD: 39 NC: 58 | BD: 40.3 (SD = 9.2) NC: 43.1 (SD = 12.9) | BD: 17M:22F NC: 22M:36F | BD: 13 BD I, 26 BD II; mood state: 23 depressed, 2 manic, 12 euthymic, 1 mixed; AOS = 28.2 (SD = 9.4); no info on DOI; outpatient; mean medication doses (n): CPZE = 182.9 (13); imipramine equivalence = 204 (12); lithium = 418.8 (16); valproate = 725.0 (8); lamotrigine = 186.5 (13); carbamazepine = 325.0 (4); no meds (3); BMI = 23.9 (SD = 4.7) Comparison: Matched by age and sex; BMI = 22.4 (SD = 3.8) | DSM-IV; depression sx (HAM-D); mania sx (YMRS); psychiatric and medical hx | RT-qPCR for 16S or 23S primers; analysis of only *Bifidobacterium* and *Lactobacillus* subgroups; Yakult Intestinal Flora-SCAN | ANCOVA adjusted for age and sex and BMI to compare *Bifidobacterium* and *Lactobacillus* abundance; partial correlation analysis against continuous variables | α: did not assess β: did not assess |
| Bengesser et al., 2019 | Austria | BD depressed: 13 BD euthymic: 19 | BD (both sub-cohorts): 41.67 (SD = 17.51) | BD (both sub-cohorts): 25M:7F | BD depressed (HAM-D > 10); BD euthymic (HAM-D < 10); subtype not indicated; outpatients; no info on AOS or DOI; no info on medications; BMI = 27.99 (SD = 6.45) | DSM-IV; psychiatric and medical hx; HAM-D; YMRS; BDI | 16S rRNA (V1-V2 region); Ion Torrent One Touch 2.0 Kit | Sequence processing: DeconSeq, Acacia tool, Usearch algorithm; analysis: QIIME 1.8; Rarified to 8000 sequences per sample | α: Simpson Index and Evenness Index β: did not assess |
| Coello et al., 2019 | Denmark | BD: 113 UR: 39 NC: 77 | BD: 31 (no SD provided; range 26–39) UR: 28 (no SD provided; range 22–34) NC: 29 (no SD provided; range 24.5–40.5) | BD: 43M:70F UR: 18M:21F NC: 30M:47F | BD: 44 BD I, 65 BD II; newly diagnosed; mood states: 68 euthymic, 26 depressed, 4 manic, 8 hypomanic, 6 mixed; AOS = 17; DOI = 11; BMI = 24.8 (no SD provided; range 22.2–27.8) UR: unaffected first-degree relatives; BMI = 24.4 (no SD provided; range 21.8–26.4) NC: age- and sex-matched; BMI = 24.2 (no SD provided; range 22.0–26.3) | ICD-10; depression sx (HAM-D); mania sx (YMRS); psychiatric and medical hx; physical activity (IPAQ) | 16S rRNA (V3-V4 region); Sequencing: Illumina MiSeq (MiSeq Reagent Kit V3, 2 × 300 bp paired-end) | USEARCH 10.0, mothur 1.38 and inhouse script pipeline; removal of low quality and chimeric sequences; closed reference OTU picking with 97% threshold; Taxonomy assignment with SINTAX | α: observed OTUs, Shannon Index β: weighted and unweighted UniFrac distances |
| Evans et al., 2017 | USA | BD: 115 NC: 64 | BD: 50.2 (SD = 12.8) NC: 48.6 (SD = 16.6) | BD: 32M:83F NC: 24M:40F | BD: 76 BD I, 29 BD II, 10 BD NOS; outpatients; most on more than one psychiatric medication; no info on AOS or DOI; BMI = 29.3 (SD = 7.2) NC: No info on matching; BMI = 26.0 (SD = 4.6) | DSM-IV, DIGS; depression sx (PHQ-9); mania sx (ASRM); anxiety sx (GAD-7); psychiatric and medical hx; physical and mental well-being (SF-12); sleep (PSQI) | 16S rRNA (V4 region) Sequencing: Illumina MiSeq | mothur 1.36.1 pipeline; sequence alignment to SILVA database; OTU picking with 97% threshold; | α: did not assess β: Yue and Clayton distance |
| Flowers et al., 2017 | USA | BD on AP treatment: 46 BD off AP treatment: 69 | BD on AP treatment: 46.0 (SD = 12.0) BD off AP treatment: 51.7 (SD = 13.5) | BD on AP treatment: 12M:34F BD off AP treatment: 21M:48F | BD I, BD II, BD NOS (ns not provided); outpatients AP group: inclusion defined by use of an atypical AP (clozapine, olanzapine, risperidone, quetiapine, asenipine, ziprasodone, lurasidone, aripiprazole, paliperidone, and iloperidone). Other medications: 26 AD, 32 MS, 20 lithium, 13 BZ; groups did not differ in treatment with MS or AD, though the AP group used | DSM-IV, DIGS; psychiatric and medical hx | 16S rRNA (V4 region) Sequencing: Illumina MiSeq V2 | mothur 1.36.0 pipeline; removal of low quality and chimeric sequences; OTU picking with 97% threshold; LEfSe | α: Simpson Diversity Index β: Yue and Clayton distance |

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**Table 1** (continued)

| Publication | Country | Sample size | Mean age | Gender | Sample characteristics | Assessments | Sequencing | Data processing/analysis | Diversity assessments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | more BZ; no info on AOS or DOI; BMI = 31 (SD = 7)<br>Non-AP group: matched for previous hospitalizations and other metabolic comorbidities; BMI = 27.5 (SD = 6) | | | | |
| Flowers et al., 2019 | USA | SZ/BD on AP: 21 (19 pre-post) SZ/BD not on AP (on MS): 16 | SZ/BD on AP: 54 (SD = 10) SZ/BD not on AP (on MS): 50 (SD = 15) | SZ/BD on AP: 12M:9F SZ/BD not on AP (on MS): 9M:7F | BD I, BD II, BD NOS, BD with psychosis, SZA, or SZA; outpatients; inclusion was defined by the use of an atypical AP (clozapine, olanzapine, risperidone, quetiapine, or ziprasidone) or lithium and/or lamotrigine for at least 6 months; no info on AOS or DOI; BD subjects may overlap with Flowers et al. (2017) AP group: 9 BD I, 3 BD II, 4 SZ, 5 SZA; other medications: 9 AD, 5 BZ, 12 for hypertension, 2 for diabetes, 10 for hyperlipidemia; BMI = 30.6 Non-AP group: 10 BD I, 6 BD II; other medications: 12 AD, 4 BZ, 4 for hypertension, 2 for hyperlipidemia; BMI = 31.1 | DSM-IV; psychiatric and medical hx; physical and mental well-being (SF-36); 24 h dietary recall (ASA24); anthropometric measurements (height, weight, blood pressure) | 16S rRNA (V4 region); Sequencing: Illumina MiSeq 250 bp paired-end | mothur 1.36.0 pipeline; removal of low quality and chimeric sequences; OTU picking with 97% threshold; LEfSe | α: Inverse Simpson Index β: Bray-Curtis dissimilarity |
| Painold et al., 2019 | Austria | BD: 32 NC: 10 | BD: 41.31 (SD = 14.73) NC: 31.4 (SD = 7.61) | BD: 18M:14F NC: 4M:6F | BD: BD I; inpatients hospitalized for depressive episode; all on medications: 24 atypical AP, 8 lithium, 11 anticonvulsants, 23 antidepressants; DOI = 17.5; BMI = 28.44 (SD = 6.08) NC: No info on matching; BMI = 24.26 (SD = 3.76) | DSM-IV; depression sx (BDI; HAM-D); psychiatric and medical hx; metabolic parameters (triglycerides, HDL cholesterol, fasting plasma glucose); anthropometric measurements (waist-to-hip ratio, waist-to-height ratio) | 16S rRNA (V1-V2 region); Sequencing: Ion Torrent One Touch 2.0 Kit | QIIME pipeline; Sequences filtered to ≥100 bp; removal of low quality and chimeric sequences; OTU picking with 97% threshold | α: observed OTUs, Chao1, Shannon Index, Simpson Index β: weighted and unweighted UniFrac distances |
| Vinberg et al., 2019 | Denmark | MZT Affected: 71 MZT HR: 32 MZT LR: 25 | MZT Affected: 37.7 (CI = 8.9) MZT HR: 38.2 (CI = 9.4) MZT LR: 37.2 (CI = 7.7) | MZT Affected: 18M:53F MZT HR: 9M:23F MZT LR: 5M:20F | Affected: twins in remission (HAM-D, YMRS < 14); 27 BD, 45 UD; outpatients; 44 medications: 22 antidepressants, 15 AP, 11 anticonvulsant, 4 lithium, 7 BZ; BMI = 26.5 (SD = 7.0) HR: unaffected twins with co-twin history of affective disorder; 10 BD, 22 UD; 1 on medication (not specified); BMI = 23.9 (SD = 3.1) LR: no personal of family history of affective disorder; BMI = 24.5 (SD = 3.1) | ICD-10; depression sx (HAM-D); mania sx (YMRS); psychiatric and medical hx; fasting samples (urine, blood) | 16S rRNA (V3-V4 region); Sequencing: Illumina MiSeq, 2 × 300 bp paired-end | USEARCH 9.2 and mothur 1.38.1 pipeline; removal of low quality and chimeric sequences; OTU picking with 97% threshold; rarified to 5244 sequences per sample | α: observed OTUs, Shannon Index β: generalized UniFrac distances |

ACE = Abundance-based Coverage Estimator; AD = antidepressant medication; ADR = adverse drug reactions; ANCOVA = analysis of covariance; APSS = Attenuated Positive Symptom Syndrome; ASA24 = Automated Self-Administered 24-Hour Dietary Assessment Tool; ASRM = Altman Self-Rating Mania Scale; AOS = age of onset; AP = antipsychotic medication; BD (I/II) = bipolar disorder (type I/II); BDI = Beck depression index; BIPS = Brief Intermittent Psychotic Syndrome; BMI = Body Mass Index; bp = base pair; BPRS(−E) = Brief Psychiatric Rating Scale(−Extended); BZ = benzodiazepine; CHD = coronary heart disease; CVD = cardiovascular disease; CI = confidence interval; CIRS = Cumulative Illness Rating Scale; CPZE = chlorpromazine equivalence; DIGS = Diagnostic Interview for Genetic Studies; DOI = duration of illness; DSM-IV/V = Diagnostic and Statistical Manual of Mental Disorders - Fourth/Fifth Edition; F = female; Faith's PD = Faith's phylogenetic diversity; FEP = first-episode psychosis (all primary psychotic disorders include); FESZ = first-episode schizophrenia; GAD-7 = Generalized Anxiety Disorder 7-item scale; GRDS = Genetic Risk and Deterioration Syndrome; GAF = Global Assessment of Functioning; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Depression Scale; HDL = high density lipoprotein; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; HR = high-risk; hs-CRP = high-sensitivity C-reactive protein; hx = history; ICD-10 = International Classification of Diseases 10th edition; IPAQ = The International Physical Activity Questionnaire; IQR = interquartile range; KEGG = Kyoto Encyclopedia of Genes and Genomes; LDL = low-density lipoproteins; LEfSe = linear discriminant analysis effect size; LR = low-risk; M = male; MS = mood stabilizer; MZT = monozygotic twins; NC = non-psychiatric comparison group; NOS = not otherwise specified; (s)OTU = (sub) operational taxonomic unit; PANSS = positive and negative syndrome score; PCoA = principal coordinates analysis; (q)PCR = (quantitative real-time) polymerase chain reaction; PD = Psychotic Disorder; PHQ-9 = Patient Health Questionnaire 9; (s)PLS-DA = (sparse) partial least-squares discriminant analysis; PSQI = Pittsburgh Sleep Quality Index; QIIME(2) = quantitative insights into microbial ecology (2); rRNA = ribosomal ribonucleic acid; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation; SF-12/36 = 12/36-Item Short-Form Health Survey; SOD = superoxide dismutase; spp. = species; SIPS = Structured Interview for Prodromal Symptoms; SOD =;SOPS = Scale of Prodromal Syndromes; SPSS = Statistical Package for Social Sciences; SZ = schizophrenia; SZA = schizoaffective disorder; SZP = Schizophreniform Disorder; Tx = Treatment; UD = Unipolar Affective Disorder; UHR = ultra-high-risk individuals; UR = unaffected relative; WHO DDD = World Health Organization antipsychotic defined daily dose; y = years; YMRS = young mania rating scale.

**Table 2**
Summary of study characteristics for reports in review.

| Sample characteristics | Clinical sample | | | Comparison sample | | |
|---|---|---|---|---|---|---|
| | Mean (SD) | Median | Range | Mean (SD) | Median | Range |
| Number of participants | 46.5 (31.7) | 35.5 | 12–115 | 42.3 (23.7) | 41.0 | 10–77 |
| Mean age (years) | 39.6 (12.1) | 41.3 | 20–63 | 37.9 (10.3) | 37.9 | 23–55 |
| Minimum age (years) | 19.6 (5.2) | 19.0 | 13–30 | 21.2 (5.3) | 21.0 | 13–30 |
| Maximum Age (years) | 49.9 (16.4) | 52.0 | 30–76 | 44.8 (16.5) | 40.3 | 30–76 |
| Gender ratio (M/F) | 1.2 (1.0) | 1.2 | 0–4 | 0.92 (0.4) | 0.98 | 0–2 |
| Body mass index | 26.0 (3.5) | 25.7 | 21–32 | 24.7 (2.7) | 24.2 | 21–31 |
| Age of onset (years) | 22.1 (4.9) | 21.5 | 17–28 | – | – | – |
| Duration of illness (years) | 15.3 (14.1) | 14.3 | 0–32 | – | – | – |

F = females; M = males; SD = standard deviation.

Knowing the taxonomic composition of a microbial community tells only one part of the story. The research field is increasingly moving toward understanding the functions of specific strains of these communities, which offers biotechnological promise in therapeutic discovery and provides greater insight into the contributions of microorganisms to human health. This can be done by facilitating additional analysis of current sequencing techniques and/or integrating other omics data, including metatranscriptomics, metaproteomics, and metabolomics. Although marker gene analysis does not provide direct evidence of a community's functional capabilities, PICRUSt (phylogenetic investigation of communities by reconstruction of unobserved states) is a computational approach that can use 16S data to predict the functional composition of a metagenome (Langille et al., 2013). Metagenomic sequencing can also produce detailed metabolic and functional profiles of microbial communities by giving access to all genes, which can then be mapped onto known functional annotations. Metabolomics and genome-scale metabolic modelling can identify bacterial metabolites and predict metabolic pathways and products from genomic and transcriptomic data, respectively (Kim et al., 2017; Ursell et al., 2014). These methods capture microbially produced metabolites, which can signal neighboring microorganisms and influence host physiology, and highlight potential metabolic pathways by which gut microbes may meaningfully impact human health and function.

### 3.2. High-risk and first episode psychosis

Three articles met our inclusion criteria, including one of individuals at high-risk (HR) and ultra-HR for schizophrenia and two of persons with FEP. Each study used different methods for quantifying the gut microbiome, including 16S sequencing, quantitative real-time polymerase chain reaction (qPCR) analyses using 16S rRNA primers, and metagenomics sequencing.

#### 3.2.1. Cross-sectional findings

Only one study reported community-level characteristics and found no differences in alpha-diversity among HR, ultra-HR, and NCs (He et al., 2018). However, beta-diversity analysis revealed that ultra-HR and HR had significantly different global microbiome composition than NCs, with ultra-HR showing greater heterogeneity in clustering across the principal coordinate analysis space compared to other groups.

All studies reported on taxonomic differences between groups. Together, these investigations revealed 25 taxa that were significantly different among FEP, HR groups, and NCs. Between the two studies using qPCR analysis, the single common finding was that *Bacteroides* spp. was not significantly different between FEP and NC groups. Yuan et al. (2018) reported reduced numbers of *Bifidobacterium* spp., *Escherichia coli*, and *Lactobacillus* spp. and increased numbers of *Clostridium coccoides* group in FEP compared to NCs, while Schwarz et al. (2018) found no differences in bacterial numbers between FEP and NCs. On differential abundance testing, family *Lactobacillaceae* was overrepresented among the taxa that were most strongly increased in FEP

(Schwarz et al., 2018). Similarly, order Lactobacillales was differentially increased in ultra-HR compared to HR and NCs (He et al., 2018).

*Lactobacillus* group was associated with increased severity of psychotic symptoms and worse global functioning in FEP patients at the time of hospitalization (Schwarz et al., 2018). These studies also showed an association between the microbiome and systemic inflammation. *Bifidobacterium* spp. was correlated with lower serum low-density lipoprotein (LDL), while *Escherichia coli* correlated with lower serum triglycerides and high-sensitivity C-reactive protein (Yuan et al., 2018). Finally, one study explored possible functional pathways using PICRUSt to infer genetic potentials based on 16S sequences, with no differences in any KEGG pathways to three levels (He et al., 2018).

#### 3.2.2. Longitudinal findings

Two studies assessed the microbiome longitudinally, tracking patient outcomes following initial hospitalization (Schwarz et al., 2018) and a period of risperidone treatment (Yuan et al., 2018). FEP patients who showed the greatest abnormalities in microbial composition from NCs at hospitalization showed lower rate of disease remission at one-year follow-up, even after considering potential confounders such as baseline level of global functioning, level of physical activity, BMI, duration of antipsychotic treatment, and food intake (Schwarz et al., 2018). Following 24 weeks of risperidone treatment, FEP patients showed increases in *Bifidobacterium* spp. and *Escherichia coli* and decreases in *Clostridium coccoides* group and *Lactobacillus* spp. Notably, increases in *Bifidobacterium* spp. predicted increases in weight and BMI over the treatment period.

### 3.3. Schizophrenia

There were five articles of the gut microbiome in patients with schizophrenia. Three studies were cross-sectional investigations, and two studies sampled the microbiome longitudinally. All studies utilized 16S sequencing.

#### 3.3.1. Cross-sectional findings

All studies analyzed diversity metrics, but findings were mixed. Zheng et al. (2019) observed reduced microbial richness and evenness in schizophrenia relative to NCs, while two other studies found no differences in alpha-diversity using similar indices (Nguyen et al., 2019; Shen et al., 2018). Nevertheless, all studies revealed beta-diversity differences between schizophrenia and NC groups.

All investigations reported taxonomic differences between schizophrenia and NCs, although the drivers of community separation varied considerably across studies. Combining these studies, 130 taxa were significantly different between schizophrenia and NCs. At the phylum level, two studies found Proteobacteria to be different between groups; however, it was relatively decreased in schizophrenia in one (Nguyen et al., 2019) but relatively increased in another (Shen et al., 2018). Divergent findings were also reported for genus *Clostridium* (Nguyen et al., 2019; Shen et al., 2018). Six genera were relatively increased in schizophrenia: Anaerococcus, *Succinivibrio*, *Megasphaera*, *Collinsella*,

**Table 3**
Studies of the microbiome in individuals at high-risk for and with first episode psychosis.

| Publication | Diversity patterns | Taxonomic differences[a] | Association with clinical features | Functional potential | Longitudinal changes | Limitations |
|---|---|---|---|---|---|---|
| He et al., 2018 | α: no difference between HR, UHR, and NC (observed OTUs, Shannon Index) β: HR and UHR different from NC (PCoA) with increased heterogeneity in clustering in UHR compared to HR and NC (PLS-DA) | Orders: UHR ↑ Clostridiales, Lactobacillales, and Bacteroidales compared to HR and NC Genera: UHR ↑ *Lactobacillus* and *Prevotella* compared to HR and NC Species: UHR ↑ *Lactobacillus ruminis* compared to HR and NC | N/A | No differences in KEGG pathways into 3 levels; UHR ↑ acetyl coenzyme A synthesis pathway compared to HR and NC using KEGG Orthology database | N/A | — Small sample size for UHR group — Did not examine relationship of community diversity/specific taxa to demographic or clinical/disease-specific features in groups — No data on BMI or diet — Functional profiling performed on the basis of 16S rRNA gene data is limited; only inferences can be made about the genome corresponding to the specific marker gene sequence, as well as about the functional potential of a given genome |
| Schwarz et al., 2018 | N/A | qPCR: numbers of bacteria not different between FEP and NC Metagenomic sequencing: Families: FEP ↑ *Lactobacillaceae*, *Halothiobacillaceae*, *Brucellaceae*, and *Micrococcineae*, ↓ *Veillonellaceae* Genera: FEP ↑ *Lactobacillus*, *Tropheryma*, *Halothiobacillus*, *Saccharophagus*, *Ochrobactrum*, *Deferribacter*, and *Halorubrum*, ↓ *Anabaena*, *Nitrosospira*, and *Gallionella* | *Lachnospiraceae*, *Bacteroides* spp., *Lactobacillus* correlated with ↑ psychotic symptoms. *Lachnospiraceae*, *Bacteroides* spp., and predominant bacteria associated with ↑ negative symptoms. *Lactobacillus* correlated with ↑ positive symptoms. *Ruminococcaceae*, *Bacteroides* spp., *Lactobacillus*, and predominant bacteria associated with ↓ GAF. Duration of AP treatment not correlated with bacteria. Subgroup of FEP with greatest differences in composition from NCs showed ↑ negative symptoms and ↓ GAF but not with positive symptoms. | N/A | Microbiota clustering at intake associated with ↑ remission at 12-month follow-up; 70% FEP that clustered with NCs showed remission, compared to only 28% of patients with "abnormal," even after controlling for baseline GAF | — Small sample size — No community-level characteristics reported (alpha- and beta-diversity) — qPCR analysis limited to only 5 bacterial groups — Model predicting remission only used top 5 families rather than the entire population — More specific information about/examination of the impact of AP medication use — Further examination of relationship with metabolic and inflammatory biomarkers collected — No information regarding diet — No analyses of functional potential |
| Yuan et al., 2018 | N/A | FESZ ↓ *Bifidobacterium* spp., *Escherichia coli*, *Lactobacillus* spp., and ↑ *Clostridium coccoides* group. No difference in *Bacteroides* spp. between groups | At baseline, *Bifidobacterium* spp. correlated with ↓ serum LDL; *Escherichia coli* correlated with ↓ serum triglycerides and hs-CRP, after controlling for age, gender, smoking status, and DOI | N/A | After 24 weeks of risperidone treatment, ↑ *Bifidobacterium* spp. and *Escherichia coli* and *Clostridium coccoides* group and *Lactobacillus* spp. No change in *Bacteroides* spp. Hierarchical multiple linear regression analysis shows that only △*Bifidobacterium* spp. was correlated with △weight over 24 weeks, after controlling for age, gender, smoking status, and DOI. No other relationships between changes in fecal bacteria and changes in metabolic parameters. | — Single arm study: lack of non-treatment control group, no follow-up in NC — No community-level characteristics reported (alpha- and beta-diversity) — Limited microbiome investigation to qPCR analysis of only 5 bacteria, rather than performing OTU analysis |

AP = antipsychotic medication; DOI = duration of illness; F = female; FEP = first-episode psychosis (all primary psychotic disorders include); FESZ = first-episode schizophrenia; GAF = Global Assessment of Functioning; HR = high-risk individuals; hs-CRP = high-sensitivity C-reactive protein; KEGG = Kyoto Encyclopedia of Genes and Genomes; LDL = low-density lipoproteins; M = male; NC = non-psychiatric comparison group; OTU = operational taxonomic unit; PCoA = principal coordinates analysis; PLS-DA = partial least-squares discriminant analysis; qPCR = quantitative real-time polymerase chain reaction; rRNA = ribosomal ribonucelic acid; SD = standard deviation; spp. = species, SZ = schizophrenia; UHR = ultra-high-risk individuals.

[a] ↑↓ arrows indicate increase or decrease in *relative* abundance, when referring to taxonomic differences.

*Klebsiella*, *Methanobrevibacter*, while five genera were decreased in schizophrenia: *Haemophilus*, *Sutterella*, *Blautia*, *Coprococcus*, and *Roseburia*. At the family level, *Veillonellaceae*, *Prevotellaceae*, *Bacteroidaceae*, and *Coriobacteriaceae* were increased in schizophrenia, whereas *Lachnospiraceae*, *Ruminococcaceae*, *Norank*, and *Enterobacteriaceae* were decreased. One study evaluated the specificity of its findings in schizophrenia, comparing results to a previous study of patients with major depressive disorder (Zheng et al., 2016), and found that only a minority of taxa overlapped, suggesting that schizophrenia has a somewhat distinct microbial signature.

Psychosis symptom severity was positively correlated with *Bacteroidaceae*, *Streptococcaceae*, and *Lachnospiracea* and negatively with Veillonellaceae (Zheng et al., 2019). Findings for *Ruminococcaceae* were mixed. One study observed two different operational taxonomic units correlated with psychosis symptoms severity, one positively and the other negatively (Zheng et al., 2019). Another study reported *Ruminococcaceae* to be inversely associated with severity of negative symptoms (Nguyen et al., 2019). *Bacteroides* was positively related to depressive symptoms, and Verrucomicrobia with self-reported mental well-being. These studies also reported relationships with other clinical and health variables. Cyanobacteria correlated with increased age of onset, *Coprococcus* with greater risk for developing coronary heart disease, and Actinobacteria with greater number of years of smoking (Nguyen et al., 2019).

Finally, several functional metabolic pathways differed between schizophrenia and NCs, including vitamin B6, fatty acid, starch and sucrose, tryptophan, cysteine, methionine, and linoleic acid metabolism, as well as degradation of some xenobiotics (e.g., foreign substances to the body or ecological system) (Shen et al., 2018). Specific taxa were associated with these differential metabolic pathways: *Blautia*, *Coprococcus*, and *Roseburia* were negatively associated with vitamin B6, taurine, hypotaurine metabolic pathways and positively associated with the methane metabolic pathway (Shen et al., 2018).

### 3.3.2. Longitudinal findings

Two studies evaluated changes in the gut microbiome following probiotic and prebiotic administration. Nagamine et al. (2018) explored whether 6-month supplementation of prebiotic 4G-β-D-galactosylsucrose, an oligosaccharide that is selectively utilized by *Bifidobacterium* and has been reported to be beneficial in chronic inflammatory bowel disease (Teramoto et al., 1996), could improve low body weight in schizophrenia. They observed that *Bifidobacterium* was increased and *Clostridium* subcluster XIVa was reduced. Changes in microbial composition were also accompanied by significant increases in weight and BMI. On the other hand, there were no changes in *Bifidobacterium* following 4-week administration of probiotic *Bifidobacterium breve* A-1, despite improved depression and anxiety symptoms (Okubo et al., 2019). When the baseline microbial compositions were evaluated, there was no significant difference in alpha-diversity, beta-diversity, or relative abundances at the phylum level between treatment responders compared to non-responders; at the genus level, treatment non-responders had higher levels of *Parabacteroides*.

## 3.4. Bipolar disorder

Eight articles investigated the gut microbiome in BD. All studies were cross-sectional except for one longitudinal investigation, which explored intestinal microbial changes following prebiotic administration. Seven studies utilized 16S sequencing, and one utilized qPCR (examining only *Bifidobacterium* and *Lactobacillus* subgroups).

### 3.4.1. Cross-sectional findings

Six articles reported on measures of alpha- and beta-diversity. Monozygotic twins concordant for affective disorders had reduced species richness compared to unaffected twins, but richness did not differ between concordant and discordant pairs (Vinberg et al., 2019). Two articles reported no differences between BD and NCs or their unaffected first-degree relatives (Coello et al., 2019; Painold et al., 2019). Differences in alpha-diversity within BD subgroups suggested that diversity patterns may vary depending on mood state and gender; species evenness was reduced in depressed BD compared to euthymic BD (Bengesser et al., 2019), and species richness was decreased in women with schizophrenia or BD who were treated with antipsychotic medications, compared to those not-treated with antipsychotics (Flowers et al., 2019). With regards to beta-diversity differences, reports were mixed. One study found that community membership differed between BD and NCs (Coello et al., 2019), while another investigation using the same measure did not (Painold et al., 2019). Likewise, one article revealed community structure differences (Evans et al., 2017), while two investigations found no differences (Coello et al., 2019; Painold et al., 2019). Beta-diversity was also not different among monozygotic twins concordant or discordant for affective disorders and those without affective disorders (Vinberg et al., 2019).

Combining these studies, seven taxa were different between BD and NCs. At the phylum level, only Actinobacteria was found to be significantly different between groups, with abundance relatively increased in BD (Painold et al., 2019). At the family and genus levels, two studies revealed *Ruminococcaceae* and *Faecalibacterium* to be relatively decreased in BD (Evans et al., 2017; Painold et al., 2019). Other significantly different taxa included *Coriobacteriaceae* and *Flavonifractor*, which were increased in BD, and *Christensenellaceae*, which was decreased. Neither *Bifidobacterium* nor *Lactobacillus* was found to be different between BD and NCs (Aizawa et al., 2018).

All these studies examined the relationship of the gut microbiome with clinical variables, including disease severity, psychiatric symptoms, medication use, and health variables. Longer duration of illness was associated with decreased alpha-diversity (Painold et al., 2019). Depression symptom severity was positively correlated with *Enterobacteriaceae* and negatively with *Faecalibacterium*, *Clostridiaceae* and *Roseburia* (Painold et al., 2019), whereas sleep was positively associated with *Faecalibacterium* (Evans et al., 2017). Atypical antipsychotic treatment was associated with reduced gut biodiversity, particularly in women (Flowers et al., 2019, 2017). Patients on atypical antipsychotics had relatively increased levels of *Lachnospiraceae*, while non-treated individuals had preferentially higher levels of *Akkermansia* and *Alistipes*. Smoking correlated with increased presence of *Flavonifractor* (Coello et al., 2019), and better self-reported physical health was associated with increased *Faecalibacterium*, *Anaerostipes* and *Ruminococcaceae* and decreased *Enterobacteriaceae* (Evans et al., 2017). BD patients with higher BMI and metabolic syndrome showed increased *Lactobacillaceae*, *Lactobacillus*, and *Coriobacteriaceae* (Painold et al., 2019). Microbiome composition was also related to serum inflammatory and metabolic biomarkers (Painold et al., 2019). BD with higher IL-6 had increased Lactobacillales, *Lactobacillaceae*, *Lactobacillus*, *Streptococcaceae*, and *Streptococcus*, compared to BD with lower IL-6. Similarly, higher total cholesterol was associated with increased *Clostridiaceae* and lower LDL was associated with increased *Prevotellaceae* and *Prevotella*. Increased thiobarbituric acid reactive substances, a parameter of oxidative stress, were associated with increased *Eubacterium*, and higher tryptophan levels were associated with *Lactobacillus*, *Lactobacillaceae*, *Coriobacteriaceae*, and *Clostridiaceae*.

### 3.4.2. Longitudinal findings

One article evaluated changes in the gut microbiome in patients with schizophrenia and BD following administration of resistant starch (Flowers et al., 2019), based on evidence from prior studies that have shown an inverse association between diets consisting of resistant starch and occurrence of obesity and diabetes mellitus in the general population (Higgins et al., 2004; Johnston et al., 2010). Nondigestible plant fibers, such as resistant starches, are selectively fermented by bacterial species in the large intestine and lead to the production of short-

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**Table 4**
Studies of the microbiome in patients with schizophrenia.

| Publication | Diversity patterns | Taxonomic differences[a] | Association with clinical features | Functional potential | Longitudinal changes | Limitations |
|---|---|---|---|---|---|---|
| Nagamine et al., 2018 | N/A | N/A | N/A | N/A | After 6 months of treatment with 4G-β-D-galactosylsucrose (prebiotic treatment for underweight patients), ↑ *Bifidobacterium* and ↓ *Clostridium* subcluster XIVa, which was accompanied by increase in weight/BMI in underweight SZ | — Small sample size<br>— Lack of non-treatment control group, cannot exclude a placebo effect<br>— No community-level characteristics reported (alpha and beta diversity)<br>— Further investigation of whether gut microbiome composition could predict changes in weight/BMI and other targeted outcomes |
| Nguyen et al., 2019 | α: no difference between SZ and NC (observed OTUs, Shannon Index, Faith's PD)<br>β: different between SZ and NC (unweighted UniFrac, Bray-Curtis dissimilarity), with tighter clustering in NC than SZ (unweighted UniFrac, Bray-Curtis dissimilarity) | Phyla: SZ ↓ Proteobacteria<br>Genera: SZ ↑ Anaerococcus, and ↓ Haemophilus, Sutterella, Clostridium<br>Across all taxonomic levels: 35 OTUs different between SZ and NC (33 order Clostridiales, 1 class Gammaproteobacteria, 1 class Erysipelotrichi) | Cyanobacteria correlated with ↑ age of onset; *Bacteroides* associated with ↑ depressive symptoms; *Ruminococcaceae* correlated with ↓ negative psychosis symptoms; *Coprococcus* associated with ↑ Framingham CHD risk; Verrucomicrobia correlated with ↑ mental well-being; Actinobacteria correlated with ↑ greater number of years of smoking in SZ | N/A | N/A | — Small sample size<br>— Did not assess relationship with AP medications<br>— Heterogeneous sample including patients with SZA and some chronic disease |
| Okubo et al., 2019 | α: at baseline, no difference between responders and non-responders (Shannon Index)<br>β: no difference between responders and non-responders (UniFrac distances) | Phlyla: at baseline, no differences in relative abundances between responders and non-responders<br>Genera: at baseline, non-responders ↑ *Parabacteroides* | N/A | N/A | No change in the genus *Bifidobacterium* after 4 weeks of *Bifidobacterium breve* A-1 treatment or 8 weeks (post-observation), although anxiety and depressive symptoms were improved | — Open-label, single arm study: lack of non-treatment control group, cannot exclude a placebo effect<br>— Further investigation of whether gut microbiome composition could predict changes in anxiety and depressive symptoms and cytokines |
| Shen et al., 2018 | α: no difference between SZ and NC (number of reads, Faith's PD, observed OTUs, Shannon Index, Simpson, ACE, Chao1)<br>β: different between SZ and NC (unweighted UniFrac, PCoA), with tighter clustering in NC than SZ (unweighted UniFrac) | Phyla: SZ ↑ Proteobacteria<br>Genera: SZ ↑ *Succinivibrio, Megasphaera, Collinsella, Clostridium, Klebsiella, Methanobrevibacter*; NC ↑ *Blautia, Coprococcus*, and *Roseburiawere*<br>Species: SZ ↑ *Collinsella aerofaciens, Bacteroides fragilis*, and ↓ *Roseburia faecis, Blautia producta, Collinsella plebeius* | N/A | Vitamin B6, fatty acid, starch and sucrose, tryptophan, cysteine, methionine, and linoleic acid metabolism; and degradation of xenobiotics different between SZ and NC. *Blautia, Coprococcus*, and *Roseburia* associated with ↓ vitamin B6, taurine, hypotaurine metabolic pathways and ↑ methane metabolic pathway | N/A | — Excluded patients with chronic disease, which is less representative of the SZ population<br>— Excluded patients with SZA and other SZ spectrum disorders<br>— No indication of whether samples were matched on demographic variables<br>— Validation of a microbiome-based schizophrenia classifier based on small sub-sample<br>— Did not examine relationship of community diversity/specific taxa to demographic or clinical/disease-specific features in groups<br>— Functional profiling performed on the basis of 16S rRNA gene data is limited; only inferences can be made about the genome corresponding to the specific marker gene sequence, as well |

| Study | α/β diversity | Taxonomic findings | Correlations | Limitations |
|---|---|---|---|---|
| Zheng et al., 2019 | α: microbial richness (Chao) and diversity (Shannon Index) ↓ SZ β: different between SZ and NC (PLS-DA) from order to species levels; results not clustered by sex or AP use or type | Families: 77 differential OTUs between SZ and NC; 23 OTUs ↑ SZ: Veillonellaceae (5 OTUs), Prevotellaceae (4 OTUs), Bacteroidaceae (3 OTUs), Coriobacteriaceae (2 OTUs); 54 OTUs ↓ SZ: Lachnospiraceae (16 OTUs), Ruminococcaceae (12 OTUs), Norank Ruminococcaceae (5 OTUs), Enterobacteriaceae (4 OTUs); Families most predictive of SZ diagnosis, based on stepwise regression, were Aerococcaceae, Bifidobacteriaceae, Brucellaceae, Pasteurellaceae, and Rikenellaceae. Compared to NC, only Ruminococcaceae, Acidaminococcaceae, Bacteroidaceae, and Veillonellaceae were similarly up- or down-regulated in SZ and UD | Veillonellaceae correlated with ↓ psychosis symptom severity; Bacteroidaceae, Streptococcaceae, and 2 Lachnospiraceae OTUs correlated ↑ psychosis symptom severity. 2 different OTUs from Ruminococcaceae correlated with ↑ and ↓ psychosis symptom severity. | as about the functional potential of a given genome<br>– Uneven read lengths between sequences (arbitrary trimming of sequences) might create systematic biases in downstream analyses<br>– Differential abundance testing performed only on the basis of supervised method (LefSe) and no unsupervised tests (for beta-diversity and differential abundance) reported. Likely over-estimating the observed effects |
| | | N/A | N/A | |

ACE = Abundance-based Coverage Estimator; AOS = age of onset; AP = antipsychotic medication; BMI = body mass index; CHD = coronary heart disease; DOI = duration of illness; F = female; Faith's PD = Faith's phylogenetic diversity; LefSe = linear discriminant analysis effect size; M = male; NC = non-psychiatric comparison group; PCoA = principal coordinates analysis; PLS-DA = partial least-squares discriminant analysis; OTU = operational taxonomic unit; rRNA = ribosomal ribonucleic acid; SD = standard deviation; SZA = schizoaffective disorder; Tx = treatment; UD = unipolar affective disorder.

[a] ↑↓ arrows indicate increase or decrease in relative abundance, when referring to taxonomic differences.

chain fatty acids (SCFA) that have the potential to improve health (Louis et al., 2007; Nugent, 2005). One particular SCFA, butyrate, has been found to be associated with improved depression-related behaviors in a mouse model by increasing serotonin concentration and brain-derived neurotrophic factor (BDNF) expression as well as restoring blood-brain barrier impairments (Sun et al., 2016). Although alpha-diversity remained unchanged, beta-diversity differences were observed following 14-day supplementation of resistant starch. Specifically, the relative abundances of phylum Actinobacteria increased, genera Bacteroides and Parabacteroides decreased, and resistant starch–degrading species Bifidobacterium faecale and Bifidobacterium adolescentis increased.

## 4. Discussion

The microbiome revolution has opened new frontiers for examining host-microbe associations in the context of understanding brain and behavioral health and better conceptualizing psychiatric disorders. Indeed, there have been more conceptual reviews and opinion papers on the gut-brain axis and its potential role in psychiatric disorders than there are empirical, data-driven investigations examining the composition of the microbiota in SMI and its role in disease presentation and treatment. This paper provides a detailed summary of the evidence regarding alterations of the gut microbiome in people with SMI, including FEP, schizophrenia, and BD, building upon our previous study (Nguyen et al., 2018b). We did not find any other published paper that systematically reviewed the available data on the gut microbiome in SMI. In our previous review, there were five studies, only three of which were focused on the gut microbiome. Since then, in just under two years, 13 additional papers on the gut microbiome have been published. Although multiple papers were published from the same groups of investigators, presumably using overlapping participant cohorts, the studies reviewed here represent a broader range of patient types and reflect individuals with a wider geographical spread across the US, Europe, and Asia, compared to our earlier article.

All the reviewed studies found alterations of the gut microbiome in patients with SMI compared to NCs. However, specific microbial metrics reported to be anomalous across articles varied, and there was minimal consensus with regards to microbial diversity patterns, relative abundance, or directionality of differences in taxa. Even within specific patient populations, there were more differences in findings across investigations than similarities. The most consistent finding was among studies of schizophrenia, all of which reported differences in beta-diversity between patients and NCs. Yet, when looking at the taxonomic drivers of these global community differences, 130 taxa were found to be different across five studies, with little consistency across investigations. Two studies revealed Ruminococcaceae and Faecalibacterium to be relatively decreased in BD. Abundance of Ruminococcaceae was also reported across several investigations of schizophrenia and BD to be associated with better clinical characteristics, including reduced psychosis symptom severity (and specifically negative symptoms) and improved self-reported physical health (Evans et al., 2017; Nguyen et al., 2019; Zheng et al., 2019), suggesting that this taxon may be protective.

Another notable finding was that lactic acid bacteria (i.e., order Lactobacillales, family Lactobacillaceae, genus Lactobacillus) were relatively more abundant in SMI and associated with worse outcomes, including increased severity of psychotic symptoms, poorer global functioning (He et al., 2018; Schwarz et al., 2018), higher BMI and metabolic syndrome, and higher serum levels of pro-inflammatory IL-6 (Painold et al., 2019). These results are consistent with prior studies of the oropharyngeal microbiome, in which Lactobacillus gasseri, along with a bacteriophage that preferentially infects Lactobacillus gasseri, were relatively increased in schizophrenia (Castro-Nallar et al., 2015; Yolken et al., 2015). Transmission of microbes from the mouth to the gut is a constant process, and oral-fecal transmission is an important

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**Table 5**
Studies of the microbiome in patients with bipolar disorder.

| Publication | Diversity patterns | Taxonomic differences[a] | Association with clinical features | Functional potential | Longitudinal changes | Limitations |
|---|---|---|---|---|---|---|
| Aizawa et al., 2018 | N/A | No difference in *Bifidobacterium* or *Lactobacillus* counts between BD and NC, even when BDI/BDII patients and males/females examined separately and controlling for BMI. | *Bifidobacterium* and *Lactobacillus* counts correlated with ↓ sleep symptoms. No association with overall depressive or manic symptoms. *Bifidobacterium* counts associated with ↓ cortisol levels. No relationship between bacteria counts and dose of AP or between those on/off MS. | N/A | N/A | — qPCR analysis limited to only 2 bacterial groups<br>— Mixed sample of BD (different sub-diagnoses, mood states) may have diluted findings<br>— Did not account for length/-type of medication use |
| Bengesser et al., 2019 | α: BD depressed ↓ evenness (Simpson Index) compared to BD euthymic | N/A | Methylation of cg05733463 of the clock gene *ARNTL* correlated with ↓ alpha-diversity (both richness and evenness) in BD. Neither depressive nor manic symptoms were associated with any measure of alpha-diversity. | N/A | N/A | — Small sample size<br>— Did not report on beta-diversity or taxonomic differences<br>— Did not examine patients in manic or mixed states<br>— Did not account for medication use or diet |
| Coello et al., 2019 | α: no difference among BD, UR, and NC (observed OTUs, Shannon Index)<br>β: unweighted UniFrac different between BD and NC (but not weighted UniFrac); weighted UniFrac different between BD and UR; no difference between UR and NC (unweighted and weighted UniFrac) | BD ↑ *Flavonifractor* compared to UR and NC, even after controlling for age, sex, smoking, waist circumference, and physical activity; Non-smoking BD ↑ *Flavonifractor* compared to non-smoking NC | *Flavonifractor* associated with smoking and female sex, but not age, waist circumference, physical activity, DOI, depressive and manic symptoms, medication, and hs-CRP; no difference in *Flavonifractor* among BD subtype or mood states | N/A | N/A | — Most BD and UR were smokers, although statistically controlled for this variable, cannot rule out potential confounding effect<br>— Mood states evaluated as a dichotomous variable (euthymic vs. affective state), rather than individual states, which may have diluted findings<br>— No data on diet |
| Evans et al., 2017 | β: different between BD and NC (Yue and Clayton distance) | BD ↓ *Faecalibacterium* and an unclassified member from the *Ruminococcaceae* family | *Faecalibacterium* associated with ↑ physical health, ↓ depression, ↑ sleep quality; *Anaerostipes* and *Ruminococcaceae* associated with ↑ physical health, *Enterobacteriaceae* associated with ↓ physical health. | N/A | N/A | — Did not report alpha-diversity<br>— Requires further examination of associations with disease-specific features (e.g., duration of illness, number of mood episodes)<br>— Did not quantify the amount of or investigate the effects of medication use among BD<br>— Used mean scores on self-report scales rather than assessment(s) most temporally related to time of stool collection |
| Flowers et al., 2017 | α: AP-treated women ↓ diversity (Simpson Diversity Index); no differences between BD men<br>β: different between BD medication groups (Yue and Clayton distance). OTUs identified for differing directions of the medication groups: *Lachnospiraceae*, *Alistipes*, and *Akkermansia*. | AP-treated patients ↑ *Lachnospiraceae* Non-AP-treated patients ↑ *Akkermansia* and *Sutterella* | *Akkermansia* ↓ in non-obese AP-treated patients. | N/A | N/A | — Further examination of relationship with duration of illness or other indicators of disease or symptom severity<br>— Further investigation of relationship of comorbid medical conditions or other metabolic biomarkers on microbiome, given the relationship between atypical APs and metabolic disease<br>— No information regarding diet, which is an important environmental factor that drives |

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| Study | α/β diversity | Taxonomic differences | Correlations/other | | Intervention | Limitations |
|---|---|---|---|---|---|---|
| Flowers et al., 2019 | α: at baseline, no difference between AP and non-AP groups (Inverse Simpson Index) β: at baseline, no difference between AP and non-AP groups (Bray-Curtis) | non-AP ↑ *Alistipes* compared to AP group | AP-treated women ↓ alpha-diversity (Simpson Diversity Index); no differences between men. | N/A | Following 14-day prebiotic (resistant starch) administration, no changes in alpha-diversity; significant beta-diversity differences (Bray-Curtis); ↑ phylum Actinobacteria and ↓ genera *Bacteroides* and *Parabacteroides*. 4.2-fold ↑ resistant starch–degrading species *Bifidobacterium faecale* and *Bifidobacterium adolescentis*. No changes to phyla Firmicutes, Bacteroidetes, and Proteobacteria; other *Bifidobacteria*; *Ruminococcus bromii* (resistant starch–degrading species); or *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Eubacterium hallii* (butyrate-producing species) | gut microbial composition and as atypical APs could increase appetite — Single arm study: lack of non-treatment control group; no follow-up in non-AP treated group — No data on adherence, which may contribute to variability in results — Differences in represented diagnoses within the AP group, with increased numbers of SZ and SZA patients — Further analyses between diagnostic groups (SZ vs. BD) |
| Painold et al., 2019 | α: no difference between BD and NC (observed OTUs, Chao1, Shannon Index, Simpson Index), even after patients with diabetes and severe obesity (BMI > 35) excluded β: no difference between BD and NC (unweighted and weighted UniFrac), even after excluding patients with diabetes and severe obesity | Phyla: BD ↑ Actinobacteria, compared to NC Class: BD ↑ Coriobacteria Order: BD ↑ Coriobacteriales Family: BD ↑ *Coriobacteriaceae* and ↓ *Ruminococcaceae* Genus: BD ↓ *Faecalibacterium* | Alpha-diversity (observed OTUs) correlated with ↓ DOI. No relationship between alpha-diversity and serum concentrations of CRP, IL-6, total cholesterol, HDL, LDL, TRP, KYN, oxidative stress parameters, depression levels, or anthropometric measurements. Sample median split of BD with high/low values of serum biomarkers: BD with high IL-6 ↑ *Lactobacillales, Lactobacillaceae, Lactobacillus, Streptococcaceae*, and *Streptococcus* compared to BD with lower IL-6; high total cholesterol ↑ *Clostridiaceae*; low LDL cholesterol ↑ *Prevotellaceae* and *Prevotella*. No difference between high and low HDL groups. High TRP differed significantly in the *Lactobacillus, Lactobacillaceae, Coriobacteriaceae* and *Clostridiaceae*; no difference in KYN; high TBARS ↑ *Eubacterium*; low MDA ↑ *Faecalibacterium*. BD with high BMI ↑ *Lactobacillus, Lactobacillaceae*, and Bacilli. BD with metabolic syndrome ↑ *Lactobacillaceae, Lactobacillus*, and *Coriobacteriaceae*. BD with clinically relevant depressive symptoms (BDI ≥ 18) ↑ *Enterobacteriaceae* and ↓ *Clostridiaceae* and *Roseburia* | N/A | N/A | — BD had significant higher BMI values; although analyses were repeated with severely obese patients excluded, sub-sample size is considerably smaller — BD patients acutely ill and on different medications, which may have contributed to variability — Did not examine or account for medication differences |
| Vinberg et al., 2019 | α: difference between affected, HR, and LR MZT (observed OTUs); LR ↑ richness than affected group; no difference between affected and HR β: no difference between affected, HR, and LR (generalized UniFrac) | At phylum, class, order, family, and genus levels, unclassified Firmicutes was only predictive taxa of 'disease.' At OTU level, single OTU *Christensenellaceae* ↓ in affected and HR compared to LR. *Christensenellaceae* ↓ in UD affected/HR and BD affected/HR, compared to LR. In only discordant MZT, no differences in *Christensenellaceae* between affected and HR when looking at UD, BD, or both combined. | *Christensenellaceae* not associated with difference in depressive symptoms between MZT | N/A | N/A | — Unclear if lower *Christensenellaceae* due to decreased relative abundance or detection limitations — Uneven group sizes — Affected and HR MZT smoked had higher prevalence of smoking and higher BMI; LR had higher rates of alcohol consumption — Further investigation of medication use in affected group |

AOS = age of onset; AP = antipsychotic medication; ARNTL = Aryl hydrocarbon receptor nuclear translocator-like protein 1; BD (I/II) = bipolar disorder (type I/II); BDI = Beck Depression Index; BMI = body mass index; CHD = coronary heart disease; CRP = C-reactive protein; DOI = duration of illness; F = female; Faith's PD = Faith's phylogenetic diversity; HDL = high-density lipoprotein; hs-CRP = high sensitivity C-reactive protein; IL = interleukin; KYN = kynurenine; LDL = low-density lipoprotein; LR = low risk; M = male; MDA = malondialdehyde; MS = mood stabilizer; MZT = monozygotic twin; NC = non-psychiatric comparison group; qPCR = quantitative real-time polymerase chain reaction; rRNA = ribosomal ribonucleic acid; SD = standard deviation; SZ = schizophrenia; SZA = schizoaffective disorder; TBARS = thiobarbituric acid reactive substances; TRP = tryptophan; UD = unipolar affective disorder; UR = unaffected relative.
[a] ↑↓ arrows indicate increase or decrease in *relative* abundance, when referring to taxonomic differences.
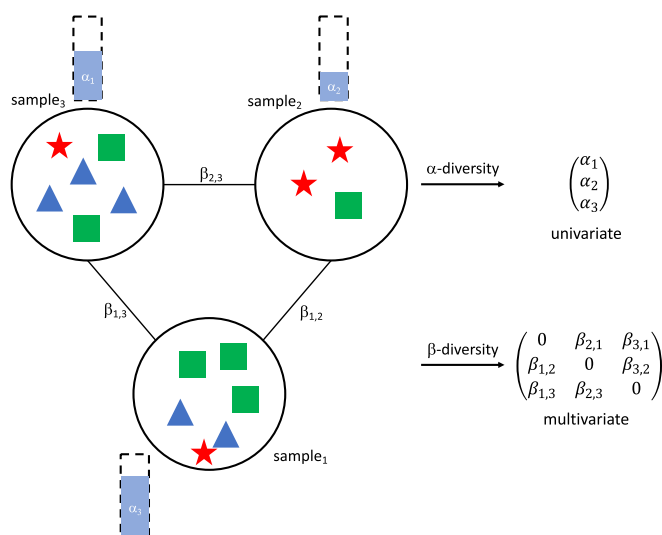
**Fig. 2.** Schematic representation of alpha- and beta-diversity. Three samples from different populations are present, each containing different numbers and proportions of taxa (blue triangles, green squares, and red stars). Alpha-diversity quantifies microbial diversity within a sample by characterizing species number, distribution, etc. and represents within-sample diversity. Hence, each sample receives a single numeric value representing its α-diversity (i.e., univariate variable); the exact numeric values will depend on the metric used (e.g. Shannon diversity, number of observed features, or Faith's phylogenetic diversity). Beta-diversity represents between-sample diversity and compares microbial dissimilarity between each pair of samples. In this case, each pair of samples has a numeric value representing their β-diversity (i.e., multivariate variable), which may be represented as a matrix of values. Similar to alpha-diversity, the exact numeric values will depend on the metric used (e.g., Bray-Curtis dissimilarity, or UniFrac [phylogenetic] distance).

factor that can determine gut composition (Schmidt et al., 2019). The increased presence of lactic acid bacteria in this population and its association with worse clinical, inflammatory, and metabolic profiles is surprising given that lactic acid bacteria are often considered health-promoting and anti-inflammatory (Ménard et al., 2004). These taxa are commonly found in the composition of probiotics (Naidu et al., 1999) and have been shown to enhance immunity following supplementation (Schiffrin et al., 1997; Sheih et al., 2001). Schizophrenia and BD have been associated with chronic inflammatory states (Berk et al., 2011; Kirkpatrick and Miller, 2013), so reduced abundance of these taxa might have been expected. Findings of lactic acid bacteria among other psychiatric and neurological disorders have also been mixed, with lower levels reported in major depressive disorder (Aizawa et al., 2016) and increased levels in autism spectrum disorders (Tomova et al., 2015).

Although findings hint at the possibility that psychotropic medications may impact gut microbial composition, the data are still too limited to draw definitive conclusions. Only six studies examined antipsychotic treatment. Two cross-sectional studies, reporting on overlapping cohort of patients, showed that atypical antipsychotic treatment may be associated with reduced gut biodiversity, particularly in women (Flowers et al., 2019, 2017). Another longitudinal study found that risperidone treatment may result in increased *Bifidobacterium* spp. and *Escherichia coli* and decreased in *Clostridium coccoides* group and *Lactobacillus* spp. (Yuan et al., 2018). Three articles did not find any association between microbial composition or taxa with antipsychotic dose or treatment duration (Aizawa et al., 2018; Nguyen et al., 2018a, 2018b; Schwarz et al., 2018).

Discrepancies across articles may be explained, at least partly, by heterogeneity in study designs, methodologies, and study participant characteristics. Although a strength of some investigations included strict within-sample classification and characterization, between-sample variability across studies likely contributed to differences in comparability. For example, Shen et al. (2018) excluded participants

with certain chronic diseases, including hypertension and diabetes, that may affect the stability of the gut microbiota, while Nguyen et al. (2019) did not exclude patients with these diseases, as physiological and metabolic changes are inherent to the disorder and its associated lifestyle (Mitchell et al., 2011). Articles on BD tended to be most heterogeneous in terms of patient samples, with many studies including patients with various subtypes and in different mood states. Indeed, alpha-diversity was decreased in depressed compared to euthymic patients, suggesting that diversity patterns may also vary depending on mood state (Bengesser et al., 2019).

The potential clinical implications of gut microbiome research are exciting. Despite decades of pharmacological treatment development, many patients with SMI do not respond to medications and experience many adverse side effects (Lally and MacCabe, 2015). The available medications reduce symptoms and prevent relapse but do not affect the underlying etiopathology. Modulation of the gut microbiota may be a tractable strategy for developing novel treatments without major side effects or high costs. Probiotic bacteria may exert health-promoting effects through various mechanisms that may be strain-specific (e.g., lactic acid bacteria) or widespread across a diversity of strains, including normalization of perturbed microbiota, inhibition of potential pathogens, production of useful metabolites or enzymes, and immunomodulation (Hill et al., 2014). Trials of probiotics have reported to improve symptoms of depression and psychological distress in patients with major depression (Akkasheh et al., 2016; Chahwan et al., 2019), multiple sclerosis (Kouchaki et al., 2017), chronic fatigue syndrome (Rao et al., 2009), and irritable bowel syndrome (Pinto-Sanchez et al., 2017). However, the findings are far from conclusive and there is very limited evidence for the efficacy of probiotic or prebiotic interventions on changing microbial composition in SMI (Okubo et al., 2019). Conversely, prebiotics led to changes in microbial composition but without changes in mood or psychiatric symptoms (Flowers et al., 2019; Nagamine et al., 2018). These investigations shared a major weakness in that they were all open-label, single-arm treatment studies without a non-treatment control group. Thus, we cannot determine whether observed microbial changes are due to treatment or other potential sources of bias. Earlier randomized, double-blinded, placebo-controlled trials investigating probiotic interventions in SMI have reported to improve bowel function (Dickerson et al., 2014), reduce levels of intestinal inflammatory indices (Severance et al., 2017), and increase levels of systemic immunomodulatory proteins (Tomasik et al., 2015), but the findings with regards to psychiatric outcomes are still mixed (Dickerson et al., 2018, 2014; Severance et al., 2017). These studies did not assess microbial biomarkers pre- or post-treatment, so the relationship of the immune and clinical responses to gut microbial composition remains unclear.

In light of significant discrepancies, particularly as they relate to differences and directionality of specific taxa, we find it important to highlight the issue of compositionality. All microbiome data are compositional, meaning that they are relative and, on their own, carry no information about absolute abundances, regardless of normalization steps taken (e.g., rarefaction or differential expression analysis, such as DESeq) (Gloor et al., 2017). Relevant statistical methods that account for the compositional nature of the data (e.g., based on log-ratios) must be used, otherwise large numbers of false-positive data are likely (Knight et al., 2018; Mandal et al., 2015; Weiss et al., 2017). Also, this calls for caution in language determining the directionality of differential abundance changes. For example, it may be misleading to state that a genus of bacteria has increased without specifying a point of reference (i.e., another genus) in relation to which this has happened (Christensen et al., 2009; Morton et al., 2019, 2017). Thus, the compositionality problem may partially explain inconsistencies and sparse overlap in the results of specific microbial investigations.

The studies discussed represent a variety of experimental approaches to analyze the microbiome (e.g., 16S rRNA marker gene

sequencing, shotgun metagenomics, qPCR). They all provide a varying degree of complementary, but not easily integratable information. Moreover, the microbiome is known to vary by geography. Western and Eastern populations have distinct microbiomes (Yatsunenko et al., 2012), but differences have also been shown between countries sharing similar lifestyles (e.g., USA and UK) and even among different regions in the same country (McDonald et al., 2018). Hence, it is important to scrutinize those experimental approaches in order to arrive at robust biological understanding of microbial contributions to SMI. It should be emphasized, however, that despite differences across investigations, participants within each study were more homogeneous and less likely confounded by geographical and methodological variations, and the findings of altered gut microbiome reported in each study are more likely driven by disease-related factors rather than geographical or technical variations. The problem occurs when trying to compare studies across different laboratories (and regions, etc.) and drawing confident and generalizable conclusions about microbial contributions to SMI, which calls for more unified methodological standards. It is understandable that various groups across the globe employ experimental techniques at hand. To make findings translatable and useful across different disciplines, cohorts, and geographic regions, there is an imperative need for using consensus-based methodology for such studies. Some of the technical or geographical variation in detected specific taxa may be mitigated through the use of functional profiles, rather than taxonomic ones (Cheung et al., 2019). Adoption of standard processing techniques is the only viable solution, arguably more feasible and reasonable than conducting a single worldwide multi-billion dollar massive-scale study.

An advantage of using specialized techniques, such as qPCR to quantify bacteria of interest or specific 16S rRNA primer sets, is that it helps to address specific hypothesis-driven questions posed by psychiatry researchers. On the other hand, the use of case-specific techniques makes integrating studies difficult or impossible due to systematic variations (Debelius et al., 2016). In the microbiome field, there has been a consistent push for unification through the use of standardized primers and sample preparation protocols (Caporaso et al., 2012; Knight et al., 2018; Minich et al., 2018; Thompson et al., 2017). These universal procedures result in less specificity but have been shown to provide most versatility. The advantage of such an approach is the possible effect of scale that may be exemplified by the Earth Microbiome Project (Thompson et al., 2017). This project crowd-sourced samples from the entire planet attempting to characterize microbial biodiversity across all possible environments. Standardized procedures allowed for the integration of samples from diverse environments including soil, oceans, and human gut onto a single communal catalogue spanning over 20,000 samples.

Another facet crucial to making substantial progress in understanding how the gut microbiome contributes to SMI is the availability of data. Many researchers are justifiably hesitant to share raw data that they have accumulated at great time, effort, and expense; nonetheless, it is necessary for reproducibility and integration efforts (Knight et al., 2018). Tools such as Qiita (qiita.ucsd.edu), which is free and open-source, make the upload, storage, processing, analysis, and sharing of data feasible (Gonzalez et al., 2018). It is a standard and requirement for many journals that researchers deposit data in long-term repositories (e.g., NCBI-SRA, EBI-ENA, or GSA). Once those necessary steps are widely adopted, using key resources like Qiita, it will it be possible to conduct meta-analyses across different studies and arrive at robust conclusions providing the community with insights and hypotheses on the impact of the gut microbiome in SMI.

## Contributors

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## Declaration of Competing Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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