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Compositional and Functional Alterations in Intestinal Microbiota in Patients with Psychosis or Schizophrenia: A Systematic Review and Meta-analysis

Nuala Murray[1], Sukainah Al Khalaf[2,3], Thomaz F. S. Bastiaanssen[4,5], David Kaulmann[2], Edgar Lonergan[6], John F. Cryan[4,5], Gerard Clarke[1,5], Ali S. Khashan[2,3], and Karen O'Connor[*,1,6]

[1]Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland; [2]School of Public Health, University College Cork, Cork, Ireland; [3]INFANT Research Centre, University College Cork, Cork, Ireland; [4]Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland; [5]APC Microbiome Ireland, University College Cork, Cork, Ireland[6]RISE, Early Intervention in Psychosis Service, South Lee Mental Health Services, Cork, Ireland;

*To whom correspondence should be addressed; tel: 0214233164, e-mail: karen.oconnor3@hse.ie

***Background and Hypothesis*: Intestinal microbiota is intrinsically linked to human health. Evidence suggests that the composition and function of the microbiome differs in those with schizophrenia compared with controls. It is not clear how these alterations functionally impact people with schizophrenia. We performed a systematic review and meta-analysis to combine and evaluate data on compositional and functional alterations in microbiota in patients with psychosis or schizophrenia. Study design: Original studies involving humans and animals were included. The electronic databases PsycINFO, EMBASE, Web of Science, PubMed/MEDLINE, and Cochrane were systematically searched and quantitative analysis performed. *Study results*: Sixteen original studies met inclusion criteria (1376 participants: 748 cases and 628 controls). Ten were included in the meta-analysis. Although observed species and Chao 1 show a decrease in diversity in people with schizophrenia compared with controls (SMD = −0.14 and −0.66 respectively), that did not reach statistical significance. We did not find evidence for variations in richness or evenness of microbiota between patients and controls overall. Differences in beta diversity and consistent patterns in microbial taxa were noted across studies. We found increases in *Bifidobacterium*, *Lactobacillus*, and *Megasphaera* in schizophrenia groups. Variations in brain structure, metabolic pathways, and symptom severity may be associated with compositional alterations in the microbiome. The heterogeneous design of studies complicates a similar evaluation of functional readouts. Conclusions: The microbiome may play a role in the etiology and symptomatology of schizophrenia. Understanding how the implications of alterations in microbial genes for symptomatic expression and clinical outcomes may contribute to the development of microbiome targeted interventions for psychosis.**

Key words: microbiome/psychosis/schizophrenia/microbiota

Introduction

The gut microbiota is a complex ecological community of microbes which are diverse and personalized[1] and includes bacteria, fungi, and viruses.[2] The collective microbial gene repertoire of these microorganisms is termed the microbiome and is often considered a second modifiable genome in the human body, greatly expanding the range of functions that can be carried out by the host alone.[3] This gastrointestinal ecosystem is intrinsically linked to human health and recent studies suggest a direct link with brain function and implications for mental health.[4] Gut microorganisms communicate with the brain by recruiting the gut–brain axis, a two-way communication system.[5,6] This axis describes key pillar physiological systems including the endocrine, nervous, immune, and metabolic systems facilitating behavioral responses.[7,8] Several processes have been investigated as mechanisms underpinning communication along this axis, including tryptophan metabolism,[9,10] the hypothalamic-pituitary-adrenal axis,[11] the production of microbial metabolites such as short-chain fatty acids,[12] and the vagus nerve.[6] A healthy microbiome supports effective signaling along these bidirectional gut–brain pathways.[13] These pathways may impact on a broad range of neurological and psychiatric conditions. Compositional and functional microbiome alterations have been associated with central nervous system disorders including depression,[14,15] Parkinson's disease,[16] autistic spectrum disorder,[17,18] and attention deficit hyperactivity disorder.[19,20] Emerging preclinical and clinical evidence suggests that the composition and function of intestinal microbiome differs in those with schizophrenia as compared with controls.[21–23]

Psychosis is a condition that affects the way the brain processes information. It is associated with an array of mental illnesses including schizophrenia, schizoaffective disorder, bipolar disorder, and depression. Impaired cognition, delusions, and hallucinations are typical symptoms of acute psychosis. Those with chronic illness may experience social withdrawal, anhedonia, and struggle with motivation. The etiology of psychosis is thought to be multifactorial and the result of interactions between genetic and environmental factors.[24] Several theories have attempted to explain its pathogenesis, and alterations in neurotransmitter pathways involving dopamine, glutamate, and γ-aminobutyric acid have been implicated.[25–27] Converging evidence suggests that psychosis is associated with chronic systemic and gastrointestinal inflammation, oxidative stress, and metabolic dysfunction.[28] Metabolic and gut disturbances are highly prevalent in psychosis and schizophrenia, with comorbidities including celiac disease, colitis, and irritable bowel syndrome.[29] Gastrointestinal diseases are one of the factors linked to increased mortality risk in schizophrenia.[30] Physiological dysfunctions implicated in psychosis, such as inflammation and oxidative stress, may be associated with changes in the gut microbiome.[21]

Whilst empirical investigations have focused on elucidating compositional aspects of intestinal microbiota in maintaining physiological processes within the gastrointestinal tract,[31,32] there is relatively little research on the predicted or actual functional alterations associated with the composition of intestinal microbiota in patients with psychosis. Multiple studies have documented an interaction between the gut microbiome and cognitive functioning and behavior in animal models. For example, findings from mechanistic studies in rodent models demonstrate that compositional alterations during early neurodevelopment or in adulthood can lead to direct CNS effects that manifest during adulthood.[33,34] Translational support from clinical populations that reflect endophenotypes characteristic of schizophrenia is more difficult to obtain.

We performed a systematic review and meta-analysis to identify, evaluate, and combine data on the compositional and functional alterations in intestinal microbiota in patients with psychosis or schizophrenia. Meta-analysis was performed to investigate microbial characteristics in humans. Data on the clinical and functional consequences of these alterations in humans and animals was systematically reviewed from a causal and mechanistic perspective. We evaluated the evidence for differences in relative abundance and diversity in microbial operational taxonomic units and their association with metabolic and neurotransmitter pathways, immunity, brain structure, and behaviors in both human and animal models.

Methods

This systematic review was based on the published protocol[35] which was also registered on PROSPERO, the international prospective register of systematic reviews (CRD42021260208). We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines for all procedures and reporting of this systematic review.[36]

Eligibility Criteria

The review included observational and experimental studies. Human and animal studies were deemed eligible: Studies included those that sampled a general adult population with a diagnosis of psychosis or schizophrenia and compared those to healthy controls. Healthy controls were defined as those without a diagnosis of psychosis, schizophrenia, or any other major mental illness. Preclinical studies included animal studies involving the fecal microbiota transplant of microbiota consortia from cases and controls. Studies were deemed eligible if (1) they performed gut microbiota analysis and reported diversity or relative abundance measures in the presence of a control group and (2) examined the clinical and functional consequences of these alterations in humans or animals.

Information Sources and Search Strategy

We conducted a systematic search using the electronic databases PsycINFO, EMBASE, Web of Science, PubMed/MEDLINE, and Cochrane. Peer-reviewed research articles from 1990 to July 2021 were considered so that current literature was reviewed. An updated search was conducted in March 2022 (Supplementary Appendix 1).

Selection of Studies

Primary searches were conducted by two reviewers (N.M. and K.O.) independently and studies that did not meet the eligibility criteria were excluded. Secondary screening, examining full texts, of potentially eligible studies was conducted by two independent reviewers (N.M. and S.A.) and disagreement was mediated through a third reviewer (G.C.). Reference lists of previous reviews were searched for further potentially relevant articles (N.M.).

Data Extraction and Management

Data from included studies were extracted using a pre-designed template in keeping with MECIR standards.[37] Compositional outcomes and functional consequences were of primary interest. Compositional outcomes include alpha diversity, beta diversity, differential abundance across taxonomic levels, and associations with demographic and clinical characteristics of

the population. Functional consequences include predicted (16s rRNA) or actual (metagenomic) differential abundance of microbial genes, metabolic pathways, hormones, brain function, and behavioral changes. In cases where required information was not directly available, study authors were contacted. Where no response was given and where possible numerical data were extracted from graphs using WebPlotDigitizer (v.4.42)[38] and Adobe Acrobat's inbuilt measuring tool (Adobe Systems). Medians and inter-quartile ranges were then transformed to means and standard deviations using web-based tool (https://www.calculator.net/mean-median-mode-range-calculator.html). A similar approach has been previously taken by others.[39,40] Where means and standard deviations were not provided and where it was not possible to extract data from graphs raw data was reanalyzed using Qiime 2.

Risk of Bias Assessment

We used the Newcastle-Ottawa Scale for observational studies[41] to assess internal validity, reliability, comparability, and risk of bias. We considered age, gender, severity/chronicity of symptoms, body mass index (BMI), diet, anti-depressant use, or similar psychotropic medication use as potential confounding variables (Supplementary Appendix 2).

Qualitative Synthesis

We included studies that used 16S rRNA gene sequencing and whole genome metagenomic sequencing to analyze alpha diversity, beta diversity, and taxonomy. Alpha diversity provides a summary of the microbial community in individual samples and can be compared across groups to evaluate the role that symptomatology or functional consequences may play in the number (richness) and distribution (evenness) of bacterial species within samples. Beta diversity is a measure of between group diversity and allows us to assess the similarity of communities between patient samples, eg, those with psychosis compared with those without.[42] Studies identified taxa which differed in those with and without psychosis at various levels of classification (order, family, and genus).[43] As a primary focus, the review included studies exploring associations of compositional alterations in gut microbiome with functional consequences, eg, in terms of metabolic and neurotransmitter pathways, immunity, brain structure, and behaviors in both human and animal models.

Quantitative Synthesis

Meta-analysis was performed on differences in alpha diversity when at least two studies used the same index of measures. Random-effects meta-analyses were used to calculate the standardized mean difference (SMD) and 95% confidence interval (CI) for alpha diversity indices between patients with psychosis and healthy controls. The results were displayed in a forest plot with 95% CIs. The Q and I^2 statistics were used to test heterogeneity between studies.[44] When statistical heterogeneity was measured using I^2 statistic, this was categorized as either low ($I^2 < 25\%$), medium ($I^2 = 25\%–50\%$) or high ($I^2 > 50\%$).[45] A sensitivity analysis was conducted, excluding each study one at a time, to assess if they had an influence on the results. Potential publication bias was assessed by visual inspection of funnel plots. We had planned to evaluate publication bias using Egger's test to statistically examine asymmetry of funnel plots; as we had fewer than 10 studies in each separate meta-analysis, we could not assess publication bias by this means. All analyses were performed using Review Manager, version 5.3 (Nordic Cochrane Centre) and $P < .05$ was considered statistically significant.

Results

Search Results

Our search yielded a total of 10 315 citations, with 7426 remaining once duplicate records were removed. Of these, 65 studies were assessed by full text review and 14 were deemed eligible for inclusion. Six studies were identified through citation searching and two were included. A total of 16 original studies met the inclusion criteria in this systematic review.[21–23,46–58] See PRISMA flow chart figure 1.

Characteristics of Included Studies

The 16 studies involved a total of 1376 participants: 748 cases and 628 controls, with sample sizes ranging from 10 to 129 for psychosis groups and from 16 to 81 for controls. They were published between 2015 and 2021, predominantly in China ($n = 12$, 75%). Two studies included subgroups,[48,50] so that there was a total of 36 comparison groups. Inclusion criteria for cases were heterogeneous across studies: All required a diagnosis of a psychotic disorder; four studies refer to first episode psychosis,[23,48,50,53] one refers to acutely relapsed/symptomatic cases,[53] and two refer to stable/remitted cases.[48,50] For study characteristics see Supplementary Appendices 2 and 3.

Clinical and Lifestyle Characteristics of Study Populations

Most studies reported mean BMIs for cases and controls ($n = 14$, 88%); the overall mean and SD for those that reported BMI was 26.9 ± 4.09 for cases and 24.09 ± 3.16 for controls. Eight studies reported on the percentage of cases using antipsychotics.[21,22,47,48,50,52,54,55] Antipsychotics used varied throughout and included: Olanzapine, Risperidone, Quetiapine, Amisulpride, Aripiprazole, and Clozapine. Most studies reported validated measures

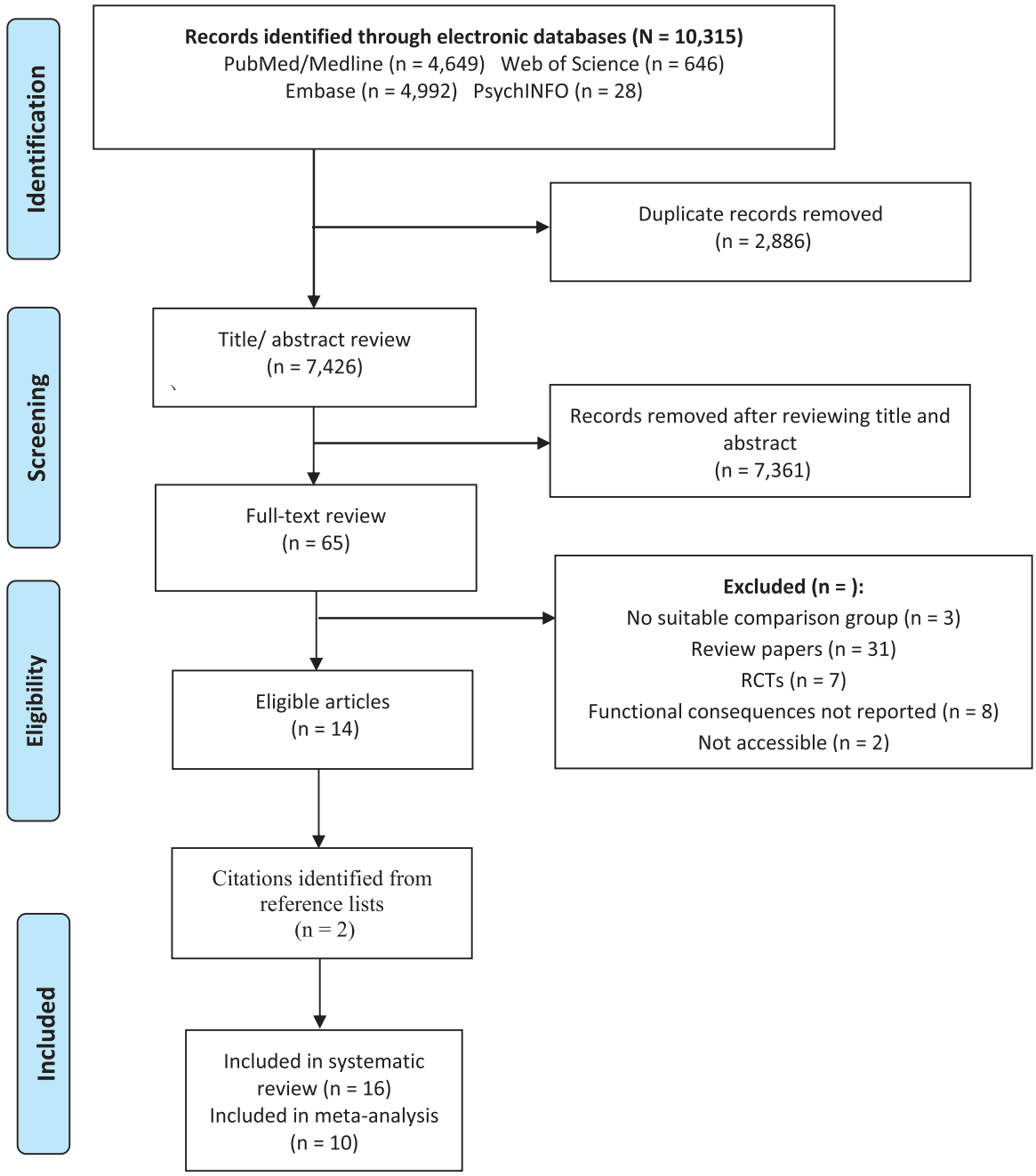

Fig. 1. PRISMA flow diagram for studies of oral and gut microbiome in psychosis or schizophrenia.

used for diagnosis (n = 15, 94%). Diagnostic measures included DSM-IV-TR, DSM V, ICD-10, and MINI 6.0.0. The majority also reported validated indices for severity of illness (n = 12, 75%). Indices included PANSS, SAPS, SANS, PHQ-9, BSI Anxiety Score, SF-36, and BPRS. Four studies included measures of physical health in cases and controls.[21,46,47,49] (Supplementary Appendix 4).

Bioinformatics: Methods and Analysis

Methods varied in some respects between studies. Thirteen studies used 16sRNA sequencing approach,[21–23,46–52,54,55,57] whilst two used Shotgun metagenomic sequencing.[53,58] Fifteen studies investigated gut microbiome, with six of those sequencing the v.4 regions[21,46,47,49,50,52] and five sequencing the v.3 and v.4 regions.[48,51,54,55,57] One study investigated oral microbiome, sampling Oropharyngeal microbiome.[58] Sequencing platforms also varied: Illumina MiSeq was used by eight studies;[23,46,47,49–51,54–56] Illumina HiSeq 2000 was used by three studies[21,22,57]; Illumina HiSeq 2500 was used by four studies,[48,52,53,57] and; Illumina HiSeq 4000 was used in conjunction with Illumina MiSeq by one study.[47] The most commonly used mapping data bases were Greengenes[46,49,50] and SILVA.[52,54,55] For analysis of

diversity four studies reported using permutational analysis of variance (PERMANOVA),[21,47,49,50] whilst eight studies reported using linear discriminant analysis effect size (LefSe).[22,23,48,51,54,55,57,58] (Supplementary Appendix 5).

Alpha Diversity

It was possible to ascertain means and standard deviations from 10 studies.[23,46,48–53,55,57] These were included in the meta-analysis (545 cases and 523 controls). Indices used to assess alpha diversity included: Indices of richness (Chao 1, Ace, Observed Species, Goods Coverage, and Number of Reads), indices of evenness (Shannon, Simpson, Evenness, and Inverse Shannon), and indices of biodiversity (Faith's Phylogenetic Diversity)—see Supplementary Appendix 4. The most commonly used were Shannon and Chao 1.

For Chao 1 index, seven studies were included (375 cases and 364 controls).[23,48,50–52,55,57] The pooled estimate showed a decrease in cases; SMD = −0.64; (95% CI, −1.32 to 0.03), however, this did not reach statistical significance (figure 2a). For the Ace index, four studies were included (218 cases and 195 controls).[48,50,51,57] The pooled estimate did not show a significant difference between cases and controls; SMD = −0.21; (95% CI, −0.51 to 0.09) (figure 2b) Shannon index did not show a significant difference between cases and controls; SMD = −0.06; (95% CI, −0.21 to 0.09). Nor did any other measure reported. Overall, there was low heterogeneity between the included studies in the meta-analysis, except for Chao 1, ACE and Simpson Indices (figure 2).

Alpha Diversity in First Episode Psychosis

Four studies investigated alpha diversity in gut microbiome of patients with first episode psychosis and compared that to both patients with chronic schizophrenia and healthy controls. We performed a meta-analysis comparing alpha diversity in gut microbiome of patients with first episode psychosis to healthy controls. Four indices were used to assess alpha diversity: Chao 1, Ace, Observed Species, Shannon and Simpson. No significant difference between cases and controls was found for any index. Heterogeneity level was low ($I^2 < 25\%$) in this meta-analysis (figure 3).

Beta Diversity

Beta diversity analysis was reported for 20 comparison groups across 12 studies,[21,23,46–51,53–55,57] most commonly using unweighted Unifrac ($n = 7$, 44%) and Brays Curtis dissimilarity ($n = 7$, 44%). PCoA analysis was conducted in 13 studies and Permanova analysis was conducted in four studies along with PCoA. Twelve studies reported a significant difference in beta diversity between schizophrenia groups and controls.[21–23,46–51,53–55,57] Other reported subgroup results include "acute vs remission" (significant difference),[48] "sex" (significant difference), and "current antipsychotic medication use"[21,47] (no significant difference) (Supplementary Appendix 6).

Differential Abundance of Microbial Taxa

Differential abundance of gut microbial taxa was reported for 17 comparison groups across 14 studies.[21–23,46–53,55–57] These were reported at order, family and genus levels. One study reported differential abundance of oral microbial taxa.[58] At genus level differential abundance was reported for 16 comparison groups across 13 studies.[21–23,46,48–53,55–57] The most frequently reported relative abundance increases in psychosis and schizophrenia groups compared to controls were in *Bifidobacterium*, *Lactobacillus*, *Megasphaera*, and *Veillonella*. Those most frequently reported relative abundance decreases were in *Coprococcus* and *Streptococcus*. Those with inconsistent patterns across studies were *Blautia*, *Clostridium*, *Colinsella*, *Fusobacterium*, *Prevotella*, *Ruminococcus*, and *Streptococcus* (figures 6–8). At order level, the most frequently reported relative abundance increases in psychosis and schizophrenia groups compared to controls were in *Actinomycetales* and *Fusobacteriales* (figure 4). At family level the most frequently reported relative abundance increases in psychosis and schizophrenia groups compared to controls were in *Actinomycetaceae, Bifidobacteriaceae, Christensenellaceae, Enterococcaceae, Lactobacillaceae, Prevotellaceae, Succinivibrionaceae*, *and Victivallacese.* The most consistently reported increase was in *Lactobacillaceae* (figure 5).

Functionality

Microbiome Associations with Metabolomic and Biosynthesis Alterations. Twelve studies reported associations with the gut/oral microbiome and metabolomic and biosynthesis alterations.[23,47,49–58] Alterations involved biosynthesis and metabolism of essential and non-essential amino acids, neurotransmitters, lipids and fatty acids, microbial enzymes, and hormones. Nguyen et al. reported that functional metabolic pathways Trimethylamine-*N*-oxide reductase and Kdo2-lipid A associated were altered in schizophrenia groups as compared with controls. These pathways were associated with proinflammatory cytokines, immune signaling and response and suggest potential mechanisms by which the microbiota may impact the pathophysiology of schizophrenia.[47] Li et al. investigated Polyketide sugar unit biosynthesis and C5-Branched dibasic acid metabolism and their association with gut microbiome. Polyketide sugar unit biosynthesis and CoA biosynthesis were enriched in control group, whereas Ascorbate and Aldarate metabolism, Nucleotide metabolism and Propanoate metabolism were enriched in the schizophrenia group.[49] Zhu

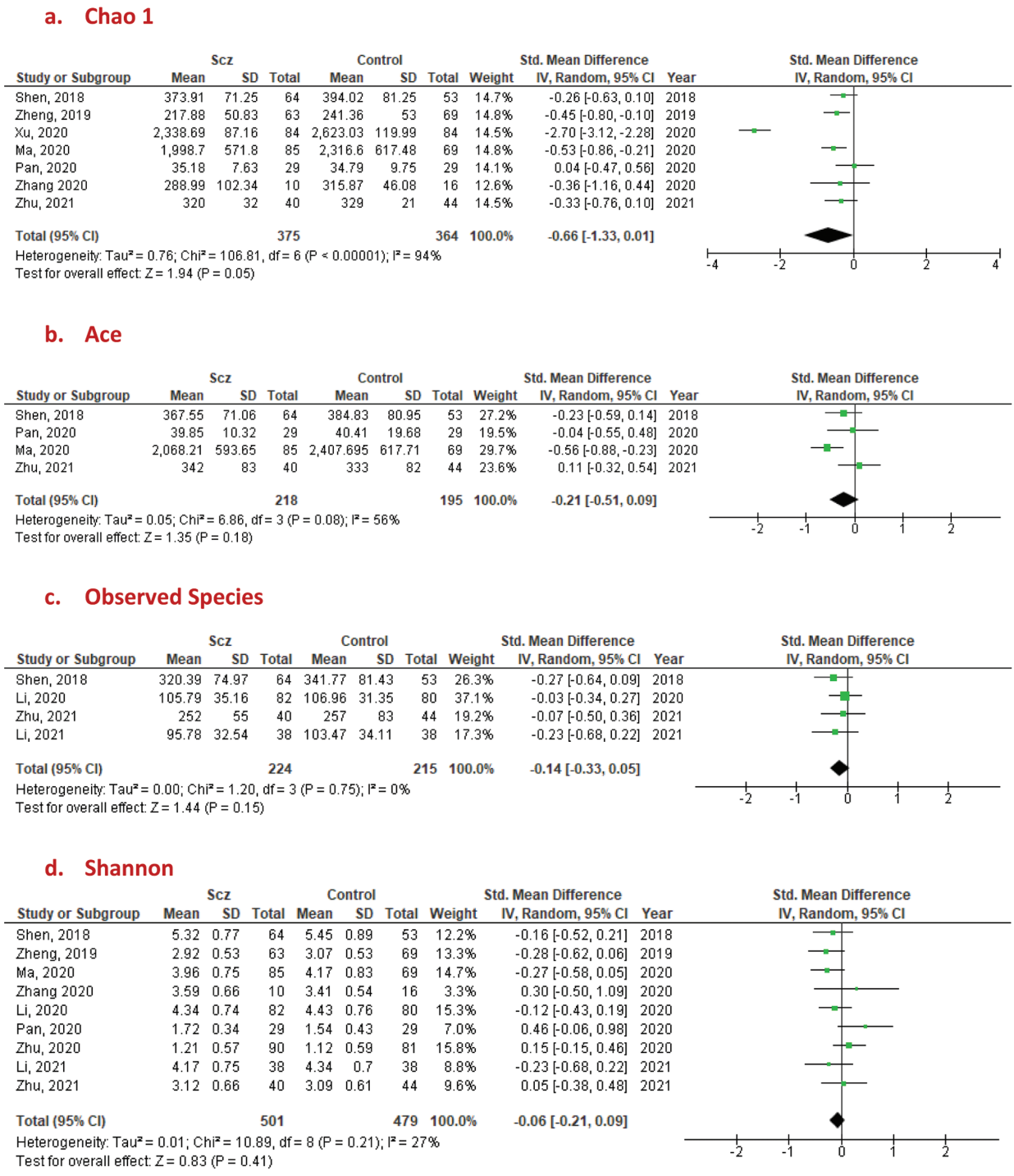

Fig. 2. Forest plots of Alpha Diversity in the gut microbiota of patients with schizophrenia compared with healthy controls. (a) Chao 1; (b) Ace; (c) Observed Species; (d) Shannon; (e) Simpson; (f) Evenness; (g) Faith's PD.

et al. reported that short-chain fatty acids synthesis, Tryptophan metabolism, and synthesis and degradation of neurotransmitters was found to be significantly increased in patients with schizophrenia.[53] (table 1 and Supplementary Appendix 7).

Microbiome Associations with Brain Structure and Function. Li et al. and Ma et al. investigated the association of brain structure with gut microbiome using compositional analysis and structural magnetic resonance imaging and resting-state functional.[46,50] Li et al. found that several brain regions showed significantly lower gray matter volume and regional homogeneity but significantly higher amplitude of low-frequency fluctuation in schizophrenia patients in comparison to controls.[46] Ma et al. found no group differences for total gray matter volume between the schizophrenia patients and controls. However patients with schizophrenia showed

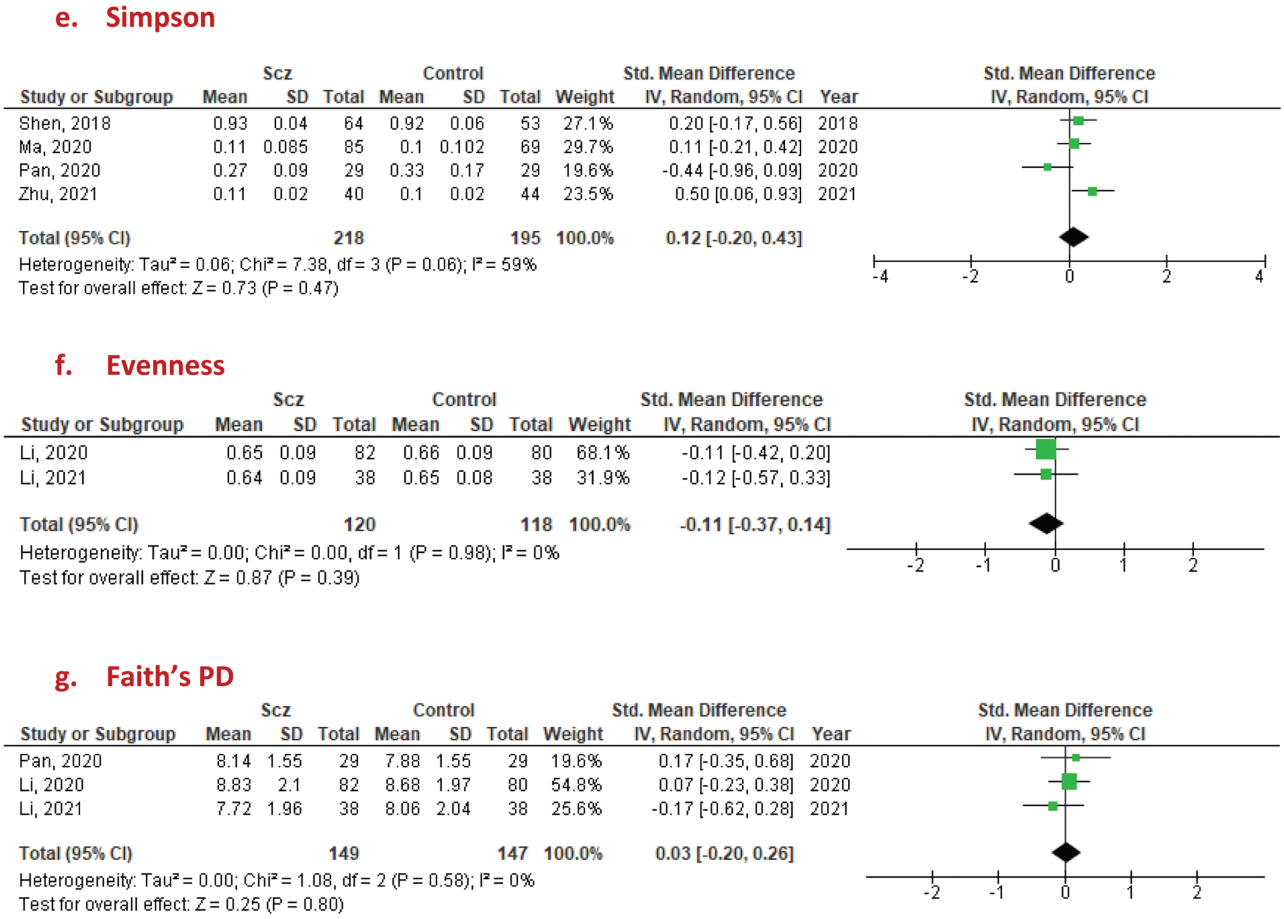

Fig. 2. Continued

significantly increased in the volume of right middle frontal gyrus compared to controls.[50]

Microbiome Association with Behavioral, Cognitive and Clinical Outcomes. Thirteen studies (81%) investigated functionality through the association of the gut microbiome with behavioral, cognitive, and clinical outcomes.[21–23,46–54,56] Four investigated the association of the gut microbiome and illness symptoms (positive and negative) and their severity.[21,22,48,49] These reported associations between negative symptoms and *Bacteroides*[21] and *Haemophilus*,[48] and associations between severity of total symptoms and *Lactobacillus*[22] and *Succinibrivio*.[49] Schwarz et al. and Zhu et al. explored remission rates and treatment response, reporting that patients with highest increases in the above microbiota showed lowest remission rates.[22,48]

Animal Studies. Four animal studies investigated causality using FMT and implicated the schizophrenia associated microbiota with deficits in social behaviors and neurotransmitter levels in the peripheral tissues and brain regions.[53–56] Behaviors investigated included locomotor activity, sociability, sensorimotor response, depressive-like behaviors and spatial learning, and memory. Zhu et al. found that transplantation of a schizophrenia-enriched bacterium, *Streptococcus vestibularis* induced deficits in social behaviors and altered neurotransmitter levels in the peripheral tissues of recipient mice.[53] Another study conducted by Zhu et al. found that transplantation of fecal microbiota from drug-free patients with schizophrenia into antibiotic-treated mice could cause schizophrenia-like behavioral abnormalities such as psychomotor hyperactivity, impaired learning, and memory in the recipient animals. These recipient mice also showed elevation of the kynurenine–kynurenic acid pathway of tryptophan degradation in the brain compared with their counterparts receiving feces from healthy controls. The Kyn–Kyna pathway was increased, whilst the serotonin pathway of tryptophan catabolism was reduced.[56]

Discussion

Significant differences in beta diversity between psychosis and schizophrenia groups and controls were consistently reported across the identified studies. Patterns in differential abundance of microbial taxa were also noted across the identified studies. Our meta-analysis did not, however,

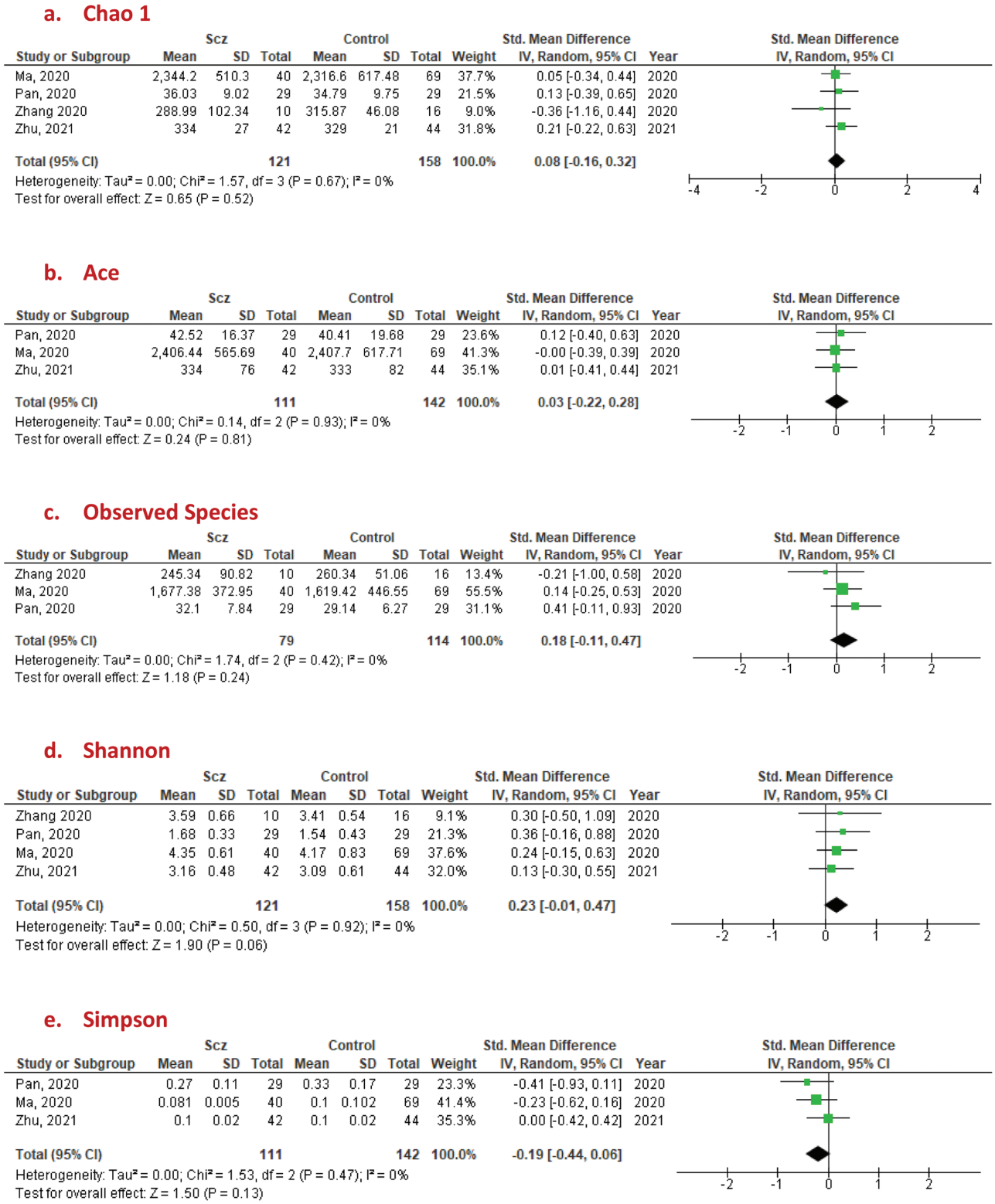

Fig. 3. Forest plots of Alpha Diversity in the gut microbiota of patients with first episode psychosis compared with healthy controls. (a) Chao 1; (b) Ace; (c) Observed Species; (d) Shannon; (e) Simpson.

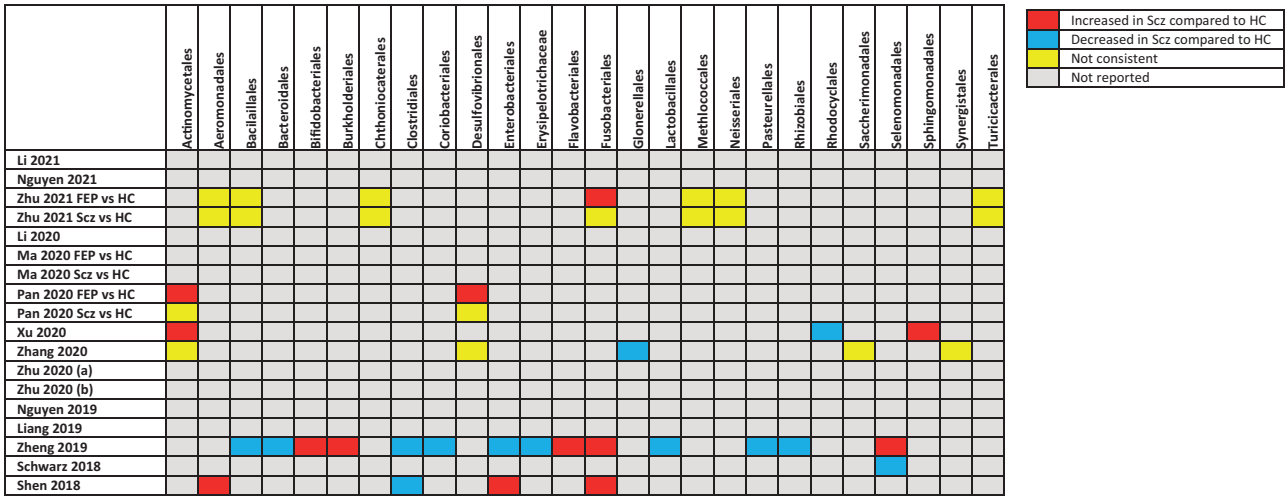

Fig. 4. Differential abundance of microbial taxa at order level.

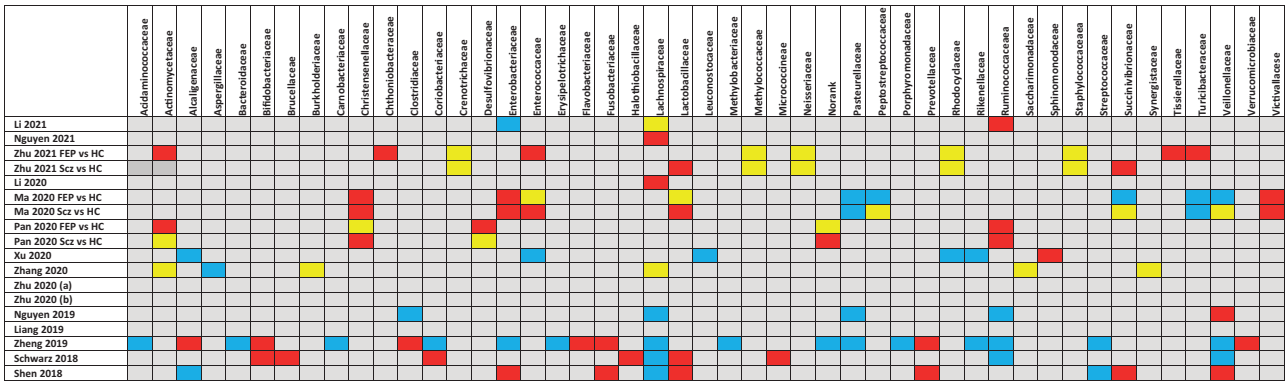

Fig. 5. Differential abundance of microbial taxa at family level.

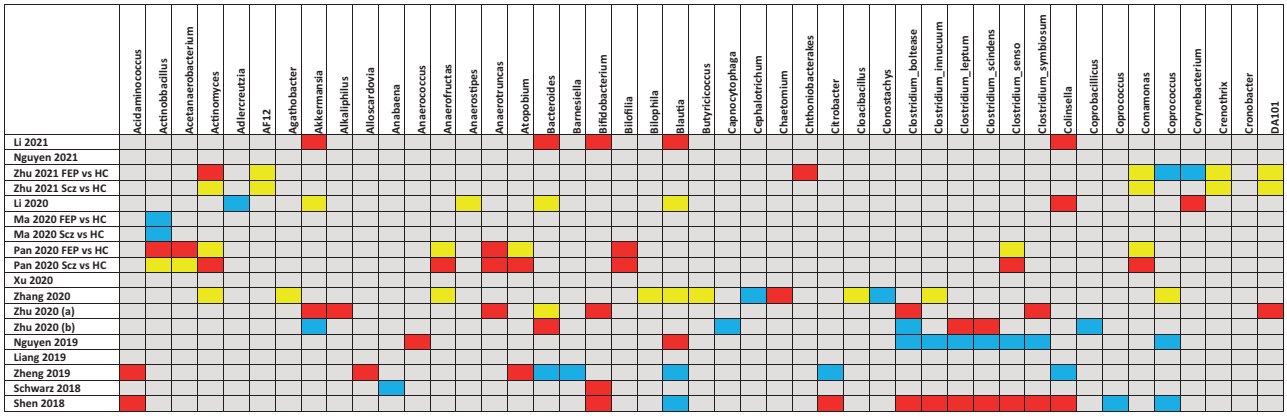

Fig. 6. Differential abundance of microbial taxa at genus level (i).

find evidence of variations in the alpha diversity of gut microbiota between patients with psychosis or schizophrenia and controls. Potential functional consequences were reported in all of the studies included in this review. Predicted functional pathways mainly involved biosynthesis and metabolism. To our knowledge, this is the first review to move beyond an assessment of the compositional alterations in intestinal microbiota, and towards the potential functional consequences of these microbiota alterations in patients with schizophrenia compared with controls.

Measures of Alpha and Beta Diversity

We did not find evidence of variations in richness or evenness of gut microbiota between patients with schizophrenia,

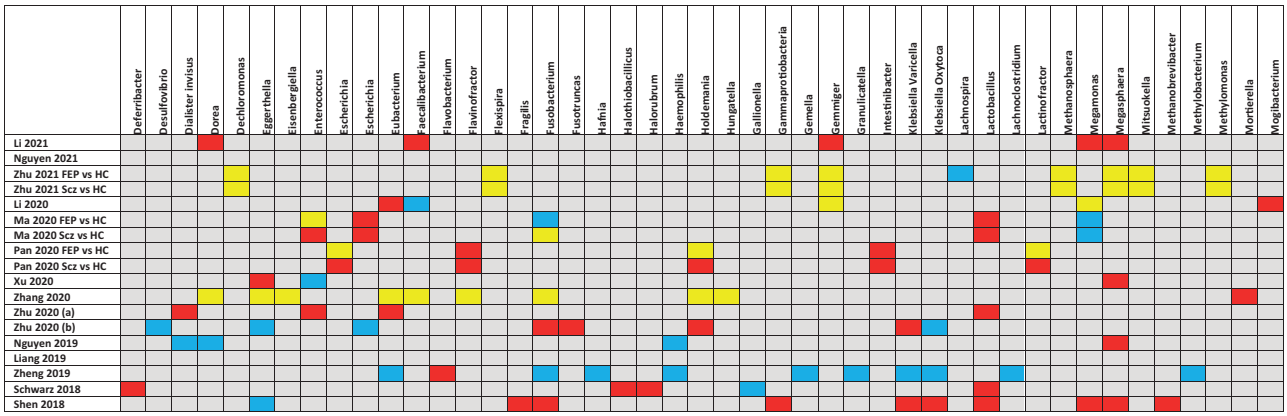

Fig. 7. Differential abundance of microbial taxa at genus level (ii).

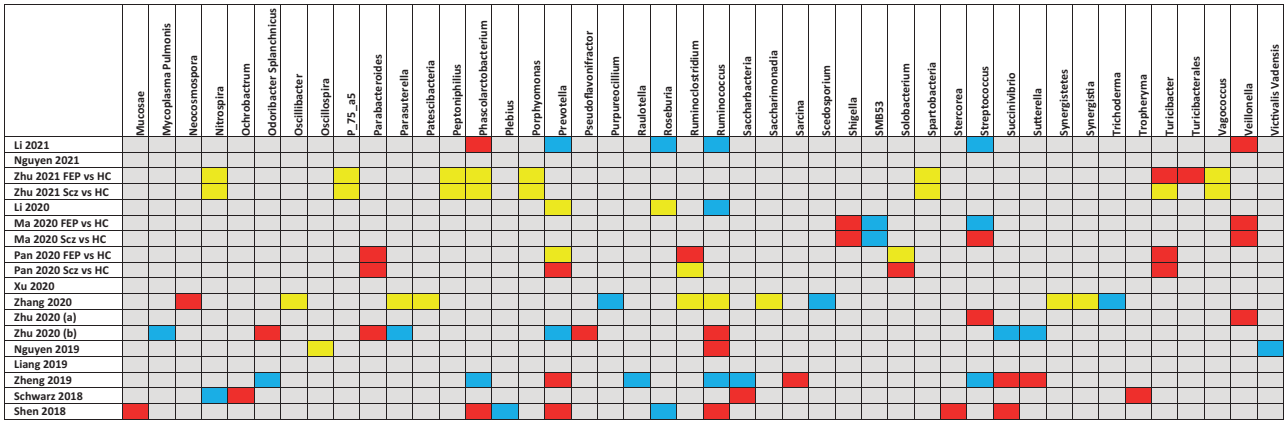

Fig. 8. Differential abundance of microbial taxa at genus level (iii).

first episode or acute psychosis, and controls, in contrast to what might be expected for disease states. Until recently it had been thought that greater alpha diversity, both richness and evenness, reflected better gut health as greater number of species would increase the quality and resilience of the gut ecosystems.[59,60] However, more recent evidence suggests that alpha diversity has limited use as a biomarker for central nervous system disorders such as Parkinson's disease,[61] and global developmental disorders such as autistic spectrum disorder[62] and attention deficit hyperactivity disorder.[63] Studies on central nervous system and developmental disorders and those included in this review have reported heterogeneity in terms of alpha diversity. Alpha diversity is a within sample measure of richness and evenness, whilst beta diversity is a between sample measure. Neither differentiates between microbial type, abundance of taxa and the potential functional implications that these taxa may have for the host. A move beyond compositional analysis towards functional analysis may provide more accurate indicators for disease state.

Heterogeneity in terms of methodology may have a role to play here. Of the five studies that reported increases in alpha diversity in schizophrenia groups, three used SILVA or other mapping data bases. Whilst databases are generally updated and curated on an iterative basis, Greengenes has not been updated since 2013. It is extensively used in microbiota research and was used for one quarter of the studies in this review. This may impact the accurate detection and identification of relative abundance alterations in the gut microbiota.[42,64] Our findings on alpha diversity are in line with recent reviews conducted on gut microbiota composition across a spectrum of psychiatric disorders, including schizophrenia, depression, and bipolar affective disorder.[40,65] Beta diversity analysis was reported for 20 comparison groups across 12 studies, and a significant difference between schizophrenia groups and controls was reported by all 12 studies. These results suggest that individuals with psychosis or schizophrenia harbor more similar gut microbiota to each other than to controls.

Subgroups included those which compared differences in sex, BMI, smoking status, and current antipsychotic medication use. Significant differences were also reported across all subgroups between schizophrenia groups and controls. Again, whilst beta diversity indicate that difference exist between groups, they do not indicate what the differences are, or what the clinical or functional meaning of these differences might entail.

Table 1. Predicted and Inferred Functional Consequences

Author Year	Predicted Functional Pathways	Altered Functional Pathways Metagenomic and Metabolomic Findings	Clinical Implications
Li 2021	Role of alterations in gut microbiome in SZ and association with alterations in brain structure and function.	Relative abundance of Ruminococcus and Roseburia was significantly lower, whereas the abundance of Veillonella was significantly higher in SZ patients than in NCs.	In terms of brain structure, the alpha diversity of the gut microbiota showed a strong linear relationship with the values of both GMV and ReHo. In SZ patients, the ReHo indexes in the right STC ($r = -0.35$, $P = .031$, FDR corrected $P = .039$), the left cuneus ($r = -0.33$, $P = .044$, FDR corrected $P = .053$), and the right MTC ($r = -0.34$, $P = .03$, FDR corrected $P = .052$) were negatively correlated with the abundance of the genus Roseburia.
Nguyen 2021	Trimethylamine-*N*-oxide reductase and Kdo2-lipid A biosynthesis.	Functional pathways related to trimethylamine-*N*-oxide reductase and Kdo2-lipid A biosynthesis were altered in schizophrenia. Pro inflammatory biomarkers: (high-sensitivity C-reactive protein [hs-CRP], tumor necrosis factor [TNF]α, and interleukin [IL]-6) and explored relationships with an anti-inflammatory cytokine (IL-10).	A significantly greater proportion of patients with schizophrenia exhibited hs-CRP levels ≥ 2 mg/l, a level above which is associated with increased risk of major cardiovascular events.
Zhu 2021	Symptom severity of schizophrenia and remission.	The structure of the fecal microbiota and the predominant bacteria in the acute, remission, and healthy control groups, revealing that the most significant shifts in the composition of the microbiota were primarily related to Fusobacteria, Nitrospira, Succinivibronaceae, and Methylococcaceae.	The abundance of Haemophilus was positively correlated with negative psychiatric symptoms ($r = 0.303$, $P = .021$). Abundance of Coprococcus was negatively correlated with negative psychiatric symptoms ($r = -0.285$, $P = .025$). Abundance of Haemophilus was positively correlated with cognition ($r = 0.428$, $P = .009$), excitement ($r = 0.266$, $P = .037$), and depression ($r = 0.295$, $P = .020$).
Li 2020	Varieties of biosynthesis and metabolism pathways: Polyketide sugar unit biosynthesis, Valine, Leucine, and Isoleucine biosynthesis, Pantothenate and CoA biosynthesis, C5-Branched dibasic acid metabolism and Phenylpropanoid biosynthesis.	Polyketide sugar unit biosynthesis, Valine, Leucine, and Isoleucine biosynthesis, Pantothenate and CoA biosynthesis, C5-Branched dibasic acid metabolism and Phenylpropanoid biosynthesis were enriched in HC group Ascorbate and aldarate metabolism, Nucleotide metabolism, and Propanoate metabolism pathways were enriched in the SZ group.	Among the SZ group, the abundance of Succinivibrio was positively correlated with the total Positive and Negative Syndrome Scale (PANSS) scores ($r = 0.24$, $P < .05$, uncorrected) as well as the general PANSS scores ($r = 0.22$, $P < .05$, uncorrected); Corynebacterium was negatively related to the negative scores of PANSS ($r = 0.22$, $P < .05$, uncorrected).
Ma 2020	Role of alterations in gut microbiome in SZ and association with alterations in brain structure and function.	Low microbiome alpha-diversity indexes in TSCZ patients but not in FSCZ patients as compared to HCs Both FSCZ and TSCZ patients had distinct changes in gut microbial composition, including Escherichia at genus level as compared to HCs.	Specific SCZ associated microbiota to be correlated with the right middle frontal gyrus volume which was aberrant in SCZ patients.
Pan 2020	Lipoic acid metabolism, proximal tubule bicarbonate reclamation, steroid hormone biosynthesis, alpha-Linolenic acid metabolism, bacterial invasion of epithelial cells, toluene degradation.	Bacteria anaerofustis, atopobium, bilophila, candidatus_soleaferrea, clostridium sensu stricto 1, flavonifractor, and intestinimons. are positively related to functional pathways, While intestinimonas, desulfovibrio, and paraprevotella were negative with KEGG functional pathways.	As a status marker of the disease, the AUC of 0.7 (95% CI [0.56, 0.84]) was achieved between 29 rSCZ and 29 HCs. There were differences between SCZ patients and HCs, acute and remission patients as well, suggesting that the potential of the gut microbiota as a non-invasive diagnostic tool.
Xu 2020	Pyruvate formate lyase activating enzyme [EC:1.97.1.4], Phosphate transport system permease protein, Ribonuclease G [EC:3.1.26.-], etc.	Thirty-four significantly differentially abundant functional pathways were found, of which, 15 were significantly increased in patients with schizophrenia, and 19 were significantly decreased in patients with schizophrenia compared with healthy controls. Most differential pathways were significantly associated with differential taxonomies.	IgA levels in patients with schizophrenia were higher than those of healthy controls and IgA levels were positively correlated with the MD index indicating that the alteration in gut microbiota-associated mucosal immunity was associated with altered gut microbiota compositions. GOGAT activity was significantly higher in the guts of patients with schizophrenia than in those of the healthy controls.

Table 1. Continued

Author Year	Predicted Functional Pathways	Altered Functional Pathways Metagenomic and Metabolomic Findings	Clinical Implications
Zhang 2020	Short-chain fatty acids production.	The microbiota of the SC patients were characterized by increased abundance of harmful bacterial (Proteobacteria) and decreased short-chain fatty acid-producing bacteria, such as the Faecalibacterium and Lachnospiraceae genera.	Both the bacterial gut microbiota as well as the gut mycobiota contributed to gut dysbiosis in patients with SC.
Zhu 2020(a)	Short-chain fatty acids synthesis, tryptophan metabolism, and synthesis/degradation of neurotransmitters.	Schizophrenia depleted microbial functional modules included pectin degradation, lipopolysaccharide biosynthesis, autoinducer-2 (AI-2) transport system, glutamate/aspartate transport system, beta-carotene biosynthesis, whereas schizophrenia-enriched functional modules included methanogenesis, the gamma-aminobutyrate (GABA) shunt, and transport system of manganese, zinc, and iron.	Transplantation of a schizophrenia-enriched bacterium, Streptococcus vestibularis, appear to induce deficits in social behaviors, and alters neurotransmitter levels in peripheral tissues in recipient mice.
Zhu 2020(b)	Kyn pathway and 5-hydroxytryptamine (5-HT) pathway.	FMT into antibiotic-treated mice caused elevation of the kynurenine–kynurenic acid pathway of tryptophan degradation in both periphery and brain, as well as increased basal extracellular dopamine in prefrontal cortex and 5-hydroxytryptamine in hippocampus, compared with FMT from HCs	Transplantation of fecal microbiota from schizophrenic patients into antibiotic-treated mice caused behavioral abnormalities such as psychomotor hyperactivity, impaired learning and memory in the recipient animals. Tryptophan biosynthesis function was significantly enriched in the fecal microbiome of HC mice, which is in line with the decreased tryptophan levels noted in SCZ mice, highlighting regulatory effects of gut bacteria on tryptophan metabolism and neurochemicals in the brain.
Nguyen 2019	Role of alterations in gut microbiota and symptom severity in Scz.	Significant differences in microbiome composition between Sczs and HCs. At the phylum level, Proteobacteria were found to be relatively decreased in schizophrenia subjects compared to NCs. At the genus level, Anaerococcus was relatively increased in schizophrenia while Haemophilus, Sutterella, and Clostridium were decreased.	Within individuals with schizophrenia, abundance of Ruminococcaceae was correlated with lower severity of negative symptoms; Bacteroides was associated with worse depressive symptoms; and Coprococcus was related to greater risk for developing coronary heart disease.
Liang 2019	Glycerophospholipid and fatty acyl metabolism.	263 of the 499 metabolites were up-regulated, and the remaining down-regulated in the schizophrenia microbiota recipient mice relative to the healthy microbiota recipient mice. The differential metabolites are involved in lipid, amino acid, and carbohydrate metabolism, especially glycerophospholipid and fatty acyl metabolism.	Scz recipient mice displayed schizophrenia-relevant behaviors vs HCs recipient mice: including hyperactivity, increased startle responses, decreased anxiety, and depressive-like behaviors.
Zheng 2019	Glutamate-glutamine-GABA cycle.	Functional clustering analysis showed that differentially expressed fecal, serum, and hippocampal metabolites were consistently involved in amino acid metabolism, eg, in the glutamate-glutamine-GABA cycle, transport of several amino acids, and lipid metabolism.	Animal experiments resulted in SCZ-relevant behavioral changes similar to those observed in glutamatergic mouse models of Scz. Altered lipids were mainly glycerophospholipids including phosphatidylethanolamines, phosphoserines, phosphatidylcholines, or phosphatidylinositol and were generally decreased in the serum and hippocampus of SCZ recipient.
Schwarz 2019	Role of alterations in gut microbiota and symptom severity and treatment response in Scz.	N/r	Numbers of Lactobacillus group bacteria were elevated in FEP-patients an correlated with severity along different symptom domains.

Table 1. Continued

Author Year	Predicted Functional Pathways	Altered Functional Pathways Metagenomic and Metabolomic Findings	Clinical Implications
Shen 2018	Alterations to metabolic pathways: Vitamin B6, fatty acid, starch and sucrose, tryptophan, cysteine, methionine, and linoleic acid metabolism and degradation of some xenobiotics.	Blautia, Coprococcus, Roseburia were negatively associated with Vitamin B6, Taurine, and Hypotaurine metabolic pathway, and positively associated with Methane metabolic pathway in both Scz and HCs.	Several metabolic pathways differed significantly between HCs and Scz patients, including vitamin B6 and fatty acid.
Castro-Nallar 2015	Alterations to metabolic pathways: Siderophores, glutamate, and vitamin B12, carbohydrate and lipid pathways and energy metabolism.	An increased number of metabolic pathways related to metabolite transport systems including siderophores, glutamate, and vitamin B12. In contrast, carbohydrate and lipid pathways and energy metabolism were abundant in controls.	Functionally, the microbiome of schizophrenia patients was characterized by an increased number of metabolic pathways related to metabolite transport systems.

Taxa Most Frequently Reported as Increased in Psychosis and Schizophrenia Groups

Consistent patterns in differential relative abundance of microbial taxa were noted across studies. Those most frequently reported relative abundance increases of genera for first episode psychosis and schizophrenia groups (ie, reported in at least four studies) were in *Bifidobacterium*, *Lactobacillus, Megaspheara*, and *Veillonella*. *Megaspheara* and *Veillonella* are recognized as potentially pathogenic.[66] *Veillonellaceae* has the ability to produce succinate, which has been implicated in tissue inflammation and found to be increased with rheumatoid arthritis[67] and cardiovascular risk.[68] *Megaspheara* has been shown to have increased abundance in Parkinson's disease and has been associated with cognitive decline.[69,70] Interestingly, *Bifidobacterium* and *Lactobacillus* have traditionally been associated with better gut health. They play a role in maintaining microecological balance and have been associated with anti-inflammatory and immune-modulatory properties.[71] Both *Bifidobacterium* and *Lactobacillus* have been used as probiotic supplementation in an effort to ameliorate symptoms of mental health disorders. Trials to date have not demonstrated a significant impact of these probiotics on symptoms of depression and psychosis.[72,73] Previous in vitro and preclinical studies have demonstrated an impact of antipsychotic use on gut microbiome composition.[74–76] It is worth noting that of the five subgroups reporting an increase in *Lactobacillus*, two reported antipsychotic use.[22,50] Ma et al. compared a drug naive first episode psychosis group and a schizophrenia group to controls; Both showed a significant increase in *Lactobacillus. Lactobacillus* was associated with an increase in positive symptoms and decrease in global functioning in patients with first episode psychosis.[22,50]

Predicted and Inferred Functional Consequences

Most studies used predictive analysis, based on taxonomic alterations and on observed compositional alterations. Over 500 predicted functional pathways were identified across seven studies using PICRUSt analysis. Heterogeneity in pathways was identified and it is difficult to identify clear consistent patterns. However, tyrosine and tryptophan biosynthesis were identified as a predicted functional pathway by four studies[52,53,57,58] and were found differ significantly between schizophrenia and control groups on further analysis of metabolomics (with metabolism increased in schizophrenia groups).

Metagenomic wide association analysis was conducted in several studies.[52,53,58] Most differential pathways were significantly associated with differential taxonomies, including *Veillonella* and *Streptococcus*, which was expected based on 16sRNA analysis. Using this analysis most frequently reported altered functional pathways included Tyrosine and Tryptophan metabolism[52,53] and Glutamate metabolism.[52,53,58] Tryptophan is an essential amino acid that is a precursor for the production of serotonin, melatonin, and niacin and nicotinamide. The products produced from tryptophan have been implicated in the regulation of mood, sleep, and neurocognition. Interestingly Zhu et al. found that the Kyn–Kyna pathway of tryptophan metabolism was markedly increased, whilst the serotonin pathway was decreased in FMT recipient mice from schizophrenia patient donors.[53]

Emerging evidence suggests that tryptophan and the kynurenine pathway play a role in affective disorders and neurodegenerative diseases,[77,78] including microbiota induced depressive-like behaviors.[79] Increasing evidence suggests that these pathways may play a role in the development of schizophrenia. Animal models exploring the role of tryptophan in schizophrenia, have linked the etiology of schizophrenia with tryptophan catabolism and kynurenine pathways.[80] Human models have found similar results using diffusion tensor imaging and magnetic resonance spectroscopy to assess white brain matter[81] and randomized control trials have reported beneficial effects of L-Tryptophan supplementation in patients with schizophrenia.[82] As schizophrenia is associated with impaired cognitive abilities and alterations in mood it is plausible that reduction in this essential amino acid may play a role in disease progression (table 1).

Fecal Microbiota Transplantation: Composition, Behavioral Phenotypes, and Causality

All animal studies employed compositional analysis the gut microbiota of human donors, followed by fecal microbiota transplantation (FMT) to recipient mice.[53–56] Differential metabolites identified using predicative analysis included lipid, amino acid and carbohydrate metabolism. All reported "schizophrenia-relevant" behaviors in the recipient mice of schizophrenia patient donors. Most consistently reported behavioral phenotypes in these mice were decreased anxiety-like behaviors,[53–55] hypermobility,[53,55] increased sensorimotor response[54,55], and increased depressive-like behaviors.[54,55] These behaviors were associated with altered metabolic pathways such as short-chain fatty acid and tryptophan metabolism; transcriptional alterations affecting Kynurenine and serotonin pathways; and alterations in brain structure resulting in reduced neurotransmitters in peripheral brain tissues. Whilst these studies have shown somewhat consistent transfer of relevant behavioral phenotypes there are limitations here in terms of establishing causality. Animal models of complex psychiatric disorders are valuable for studying the neurobiological bases of these disorders in terms of brain function and for identifying new drug targets. However, neuropsychiatric disorders, including schizophrenia, include symptoms such as paranoid delusions and auditory hallucinations that are uniquely human and this can make interpretation of results obtained from animal models more difficult.[83] It remains to be seen how these preclinical findings will translate into the clinical population and whether FMT may in time offer a therapeutic opportunity for people with psychosis and schizophrenia.

Limitations

There are several methodologic factors that should be considered when interpreting results. We identified heterogeneity in the analysis and reporting of data between studies; there was variations in sequencing, gene data bases, analysis pipelines, and statistical analysis. There was also heterogeneity in terms of design, with variations in inclusion and exclusion criteria for study populations and in controls for confounding factors and covariates. Factors such as diet, use of prebiotics, probiotics, antibiotics, and antipsychotics are known to influence gut microbiota and may impact on study results.[84–86] Using populations that are drug-naïve is now more common and may shed further light on the open questions in this field. In terms of geographical distribution of studies, there is a clear overrepresentation of studies conducted in China. Geographical differences in diet and genetics may lead to variation in gut microbiome within given populations.

Studies were on the whole small in size. It is possible that the inability to detect differences is due to the lack of the true effect or because these studies have insufficient statistical power to detect differences in alpha diversity. Reporting the results of human microbiome research has long since been a challenge due to the interdisciplinary nature of the field and lack of a standardized protocol and consistent guidelines for analysis and reporting.[87] Due to the potential impact of design, methodology, and reporting on reproducibility and results it is important that consistent protocols on methodologies and reporting guidelines be further developed and employed.[88] Key differences in methodologies and confounding factors may influence results here. Despite these limitations the data provided here in terms of composition, diversity, and functional alterations in microbial taxonomic units provide an important foundation for our understanding of intestinal microbiome in psychosis and schizophrenia.

Conclusions

Our meta-analysis did not find evidence of variations in richness or evenness of intestinal microbiota between patients with psychosis or schizophrenia and controls. However, significant differences in beta diversity between psychosis and schizophrenia groups and controls were reported across studies. In addition, consistent patterns in differential abundance of microbial taxa were noted across studies. Functional consequences were reported in the form of potential biomarkers for disease and clinical implications. Alterations in the relative abundance of specific taxa were associated with metabolic and neurotransmitter pathways, immunity, brain structure, and behaviors in both human and animal models. The existing evidence suggests that the microbiome may play a role in the etiology, pathology, and symptomatology in schizophrenia. Understanding how predicted or functional alterations in microbial genes or metabolic pathways influence symptomatic expression and downstream clinical outcomes may contribute to the development of microbiome targeted interventions for psychosis.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

Acknowledgments

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