GUT MICROBIOME DYSBIOSIS IN FIRST EPISODE PSYCHOSIS: A REVIEW OF RECENT LITERATURE

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BACKGROUND

- The microbiome is altered in schizophrenia and related psychotic illness, but the relationship is complex, as gut microbiome is influenced by diet, exercise, sedentary lifestyle, and antipsychotic (AP) use.[1] Also, gut microbes can produce metabolites that can reach the brain and cause neuroinflammation, a possible precursor to psychosis.[2]
- Despite previous studies indicating the microbiome-altering properties of antipsychotics, previous research in SCZ and gut microbiome has been conducted in patients stabilized APs, leading to warranted criticism that studies exploring SCZ-related changes in gut microbiome are largely due to the confounding influence of APs.
- In light of this, we present a review of recent literature regarding the relationship of gut microbiota in first episode psychosis (FEP) in schizophrenia-spectrum disorders compared to healthy controls. We aim to understand if psychotic illness is associated with gut microbiome changes independent of AP use so that the gut microbiome may be explored as a target for future intervention in psychotic illness.
- Terms: alpha-diversity: within-group diversity; beta-diversity: between-group diversity

METHODS

- We conducted a literature review using specific key words including schizophrenia, first episode psychosis, microbiome, and dysbiosis to identify controlled studies published on PubMed between 2018-Januarary 2022. We focused on human studies investigating the relationship of the gut microbiota in first episode psychosis in schizophrenia-spectrum disorders compared to healthy controls. Titles and abstracts were screened from PubMed search, relevant full-text articles were assessed for eligibility, and 4 articles met the full criteria.

RESULTS

4 studies met criteria, shown in Table 1. All studies used 16S rRNA sequencing to analyze the bacteria in fecal samples, as a representation of gut microbiome.

Table 1: Results of Search

Study Design, N	Diversity Findings	Main Findings for Gut Microbiome in FEP	Reference
Case-control with 1 year prospective cohort -FEP, average AP usage 20 days (N=28) -HC (N=16)	None reported	FEP: increased *Lactobacillus* Abnormal gut microbiome cluster correlated to decreased remission rates at 12 mo follow-up, controlling for variables like symptom severity, antipsychotic usage.	Schwarz et al, 2018[3]
Case-control with FEP pts receiving 24 week risperidone treatment and follow-up. -FEP, AP-naive (N=41) -HC (N=41)	None reported	FEP: decreased *Bifidobacterium, Escherichia coli, Lactobacillus*. Increased *Clostridium coccoides*. FEP before v. after 24-week risperidone treatment: increase in the numbers of fecal *Bifidobacterium* spp. and *E. coli*. Decrease in *Clostridium coccoides* and *Lactobacillus*. Changes correlated to increases in weight.	Yuan et al, 2018[4]
Cross-sectional case-control -FEP, AP-naïve (N=40) -Chronic SCZ, AP-treated (N=85) -HC (N=69)	**Alpha**: lower in chronic, AP-treated SCZ v. HC; no difference found between FEP v. HC. **Beta:** no difference with weighted UniFrac; unweighted showed difference between 3 groups.	-Both SCZ groups (v. HC): Increased *Christensenellacceae, Enterobacteriaceae,* *Decreased Pasteurellaceae, Turicibacteraceae.* -Chronic SCZ (v. both HC and FEP): increased *Enterococcus, Lactobacillus, Shigella, Streptococcus, Veillonella* (increased compared to HC, decreased compared to FEP), *Enterococcaceae, Lactobacillaceae.* -FEP SCZ (v. both HC and chronic SCZ): Decreased *Fusobacterium, Megasphaera, Peptostreptococcaceae, Veillonellaceae.* -Right Middle Frontal Gyrus (rMFG) volume associated with increased *Actinobacillus, Veillonellaceae* in FEP SCZ. No association found between microbes and rMFG volume in chronic SCZ.	Ma et al, 2020[5]
Cross-sectional FEP, AP-naive (N=42) Remission, AP-treated (N=40) HC (N=44)	**Alpha**: not different between groups **Beta**: FEP group distinct from HC and chronic groups.	-FEP (v. HC and/or remission): increased *Fusobacteriales, Actinomyces, Turicibacter, Turicibacterales*, and *Chthoniobacterales* -HC (v. FEP and/or remission): increased *Lachnospira* and *Coprococcus.* -Remission (v. FEP and/or HC): increased *Succinivibrionaceae* and *Lactobacillaceae, Desulfovibrio, Mitsuokella, Lactobacillus*, and *Succinivibrio.* -Among SCZ: Numerous clinical correlations to microbiome found.	Zhu et al, 2021[5]

DISCUSSION

- We conducted a review of the gut microbiome in FEP v. HC in 4 studies, 3 studies included groups that were antipsychotic naïve.
- In our review, diversity results varied between two studies that reported these results, varying from previous studies in chronic SCZ v. HC report no difference in alpha diversity but report changes in beta diversity in chronic/AP-treated SCZ.[7]
- There is no obvious confounding to account for this discrepancy.
- All studies, including the 3 studies with AP-naïve groups, reported changes in gut microbiome bacteria in FEP compared to HC, indicating changes present in the gut microbiome of SCZ are independent of AP use. Specific bacterial changes vary across studies.
- Further changes are seen between AP-treated and AP-naïve (FEP) groups, indicating gut microbiome changes are likely associated with AP use (consistent with previous studies)[1] and SCZ-related pathology, independently.
- A main limitation of many of these studies includes small sample size and lack of temporal relationship between gut microbiome and onset of psychotic symptoms.

CONCLUSIONS

Our review shows that psychotic illness is likely associated with altered gut microbiome independent of AP use, but that AP use also influences gut microbiome. This provides preliminary evidence that the gut microbiome may be a useful target for intervention in SCZ. Further studies, especially with temporal components and larger sample sizes, are required.

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