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Gut Microbiome Remodeling is Linearly Associated with Metabolic Syndrome Severity in Stable Schizophrenia: A Metagenomic Analysis

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Abstract

Background: Metabolic syndrome (MetS) is overrepresented in schizophrenia (SCZ), yet the gut microbial changes that accompany progressive metabolic decline remain poorly characterized. Here we set out to identify taxonomic and functional microbial features that correlate with MetS severity in clinically stable SCZ patients.

Methods: We performed shotgun metagenomic sequencing on fecal samples from SCZ patients with and without MetS. Instead of using a categorical diagnosis, we calculated a continuous MetS severity score (MetS-SS) to capture the gradient of metabolic burden.

Microbial community structure, diversity, and candidate biomarkers were examined using LEfSe and machine learning, followed by regression models to test linear associations with MetS-SS.

Results: Alpha diversity did not differ between groups, but beta diversity showed significant community restructuring in the MetS-comorbid cohort. We identified distinct dysbiotic signatures, including depletion of beneficial commensals (*Adlercreutzia equolifaciens*, *Evtepia gabavorous*) and expansion of opportunistic taxa. The abundances of these specific taxa showed robust linear relationships with MetS-SS. Functional profiling suggested that these shifts might compromise neuroactive metabolite synthesis and antioxidant defenses.

Conclusions: In stable SCZ, MetS comorbidity involves targeted microbial remodeling rather than a generalized loss of diversity. The linear tracking of key taxa with metabolic severity offers a potential mechanistic link between peripheral metabolic decline and central neurobiology, pointing toward microbiome-targeted strategies in psychiatric care.

Keywords: Stable schizophrenia; Metabolic syndrome; Metabolic syndrome severity score; Gut microbiota; Metagenomics

List of abbreviations

SCZ, schizophrenia; MetS, metabolic syndrome; PANSS, Positive and Negative Syndrome Scale; BMI, body mass index; F/B, Firmicutes/Bacteroidetes; SCFA, short-chain fatty acid; LEfSe, linear discriminant analysis effect size; LDA,

linear discriminant analysis; FDR, false discovery rate; PCoA, principal coordinate analysis; PERMANOVA, permutational multivariate analysis of variance; IQR, interquartile range.

Introduction

Schizophrenia (SCZ) continues to carry substantial cognitive and social burdens, and its physical comorbidities are often underappreciated[1]. Despite advancements in psychiatric treatment, individuals with SCZ exhibit a significantly reduced life expectancy, with excess mortality largely attributed to physical comorbidities, particularly cardiovascular diseases[2]. Within this population, the high prevalence of metabolic syndrome (MetS), which occurs at two to three times the rate observed in the general population, serves as a primary driver of these cardiovascular risks[3]. This metabolic burden often forms a deleterious feedback loop with psychiatric symptoms; metabolic dysfunction can exacerbate central nervous system inflammation and oxidative stress, which in turn hinders psychiatric symptom stability and impairs therapeutic efficacy[4, 5].

The clinical management of SCZ often suffers from a “physical health blind spot” once acute psychotic symptoms are stabilized[6, 7]. Previous studies of SCZ-related metabolic alterations have largely focused on first-episode or acute-phase patients[8]. Although this design helps reduce the cumulative effects of chronic illness and prolonged antipsychotic exposure, metabolic findings in these populations can still be confounded by acute psychopathology, lifestyle instability, and early treatment-related

changes, potentially obscuring the underlying pathophysiology of metabolic comorbidity[8-10]. Focusing on clinically stable SCZ patients allows for the isolation of metabolic-specific microbial signals from these acute stress-induced confounding noises, ensuring a clearer mapping of the pathophysiology underlying psychiatric-metabolic comorbidity.

Traditional binary clinical classifications of MetS often fail to capture the subtle, progressive nature of metabolic deterioration[11, 12]. Research has shown that individuals meeting only two diagnostic criteria for MetS exhibit significantly higher cardiovascular and mortality risks compared to those with fewer or no criteria[13, 14]. Treating metabolic dysfunction as a progressive process, rather than a static binary state, is essential for early detection[15]. If we treat metabolic dysfunction as a continuous spectrum rather than a binary diagnosis, we can uncover the progressive microbial alterations that precede the onset of full-blown clinical MetS[16]. This gradient-based approach provides a more sensitive, mechanism-based window for early clinical detection, addressing the inherent limitations of threshold-dependent diagnoses[13, 17].

The Microbiota-Gut-Brain Axis (MGBA) provides a useful model for understanding bidirectional communication between intestinal microbiota and host metabolic and neurological status[18]. Gut dysbiosis is recognized as a mediator in the development of MetS, often characterized by impaired intestinal barrier function and systemic low-grade inflammation[19]. While recent metagenomic studies have linked SCZ to altered gut microbiota composition, the specific microbial signatures associated

with the varying degrees of MetS severity in stable SCZ patients remain largely underexplored. We hypothesized that gut microbiota composition correlates with MetS severity in clinically stable SCZ patients. Using shotgun metagenomic sequencing and a continuous MetS severity score, we sought to characterize microbiome remodeling, identify core biomarkers, and test for linear associations between specific taxa and metabolic progression.

2.1 Materials and Methods

Study Design and Participants

This was a case-control study designed to investigate the association between gut microbiota composition and the presence and severity of MetS in patients with stable SCZ. The study protocol was approved by the Institutional Ethics Committee of Wuhan Mental Health Center (Approval No: KY2023.0104.01). All participants and their legal guardians provided written informed consent prior to enrollment.

A total of 104 clinically stable patients with SCZ were recruited from the inpatient wards of Wuhan Mental Health Center. Based on the Chinese diagnostic criteria for MetS, participants were stratified into two groups: a MetS comorbid group (study group, n=78) and a non-MetS control group (control group, n=26).

Inclusion Criteria:

Participants were required to meet all the following criteria:

(1) Met the diagnostic criteria for SCZ according to the *Diagnostic and Statistical*

Manual of Mental Disorders, 5th Edition (DSM-5).

(2) Clinically stable, defined as a Positive and Negative Syndrome Scale (PANSS) total score ≤ 60[20], and a score of ≤ 3 on all 8 key symptom items (P1-delusions, P2-conceptual disorganization, P3-hallucinatory behavior, N1-blunted affect, N4-passive/apathetic social withdrawal, N6-lack of spontaneity and flow of conversation, G5-mannerisms and posturing, G9-unusual thought content)[21].

(3) Han Chinese ethnicity, aged 18-45 years.

(4) Currently receiving monotherapy with one of the following four antipsychotics for ≥ 6 months: olanzapine, clozapine, risperidone, or quetiapine.

(5) No adjustment in the type or dose of antipsychotic medication within the 8 weeks prior to enrollment.

Exclusion Criteria:

Participants were excluded if they met any of the following criteria:

(1) A current DSM-5 diagnosis of any other psychiatric disorder, including depressive disorder, bipolar disorder, substance use disorder, and intellectual disability.

(2) Organic central nervous system diseases or a history of moderate-to-severe traumatic brain injury.

(3) Endocrine system diseases, including thyroid dysfunction, diabetes mellitus and other severe endocrine disorders.

(4) Severe somatic diseases, such as traumatic brain injury, epilepsy, tumors, and heart disease. Autoimmune diseases or use of immunomodulators within the past 3 months. Acute infection within 2 weeks prior to enrollment.

(5) Gastrointestinal-related factors: use of antibiotics or probiotics within the past month, chronic constipation, inflammatory bowel disease, or long-term adherence to a special diet such as a ketogenic diet or very low-carbohydrate diet.

Grouping Criteria:

The diagnosis of MetS was based on the 2024 guidelines of the Chinese Diabetes Society[22], requiring the presence of at least three of the following five components:

(1) Central obesity: waist circumference (WC) ≥ 90 cm for males or ≥ 85 cm for females.

(2) Hyperglycemia: fasting plasma glucose (FPG) ≥ 6.1 mmol/L and/or previously diagnosed type 2 diabetes.

(3) Hypertension: blood pressure ≥ 130/85 mmHg and/or previously diagnosed hypertension.

(4) Hypertriglyceridemia: fasting triglycerides (TG) ≥ 1.70 mmol/L.

(5) Low high-density lipoprotein cholesterol (HDL-C): fasting HDL-C < 1.04 mmol/L.

Based on these criteria, participants were divided into the control group (meeting 0 of the 5 criteria) and the study group (meeting ≥ 3 of the 5 criteria).

2.2 Clinical Assessments and Laboratory Measurements

Demographic and Clinical Data: Basic demographic information, including age, sex, education level, marital status, smoking and drinking history, age at onset, and total disease duration, was collected through a self-designed questionnaire and electronic medical records. Antipsychotic medication types and dosages were recorded.

Psychiatric Symptom Assessment: Psychiatric symptom severity was evaluated using the PANSS by two trained attending psychiatrists. The inter-rater correlation coefficient was > 0.80.

Anthropometric Measurements: All measurements were taken twice, and the average was used for analysis. Body weight and height were measured to calculate Body Mass Index (BMI, kg/m^2). Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest. Blood pressure was measured after a 10-minute rest using a calibrated electronic sphygmomanometer.

Laboratory Biochemical Panels: Fasting (10-12 hours) venous blood samples were collected the morning after enrollment. A complete metabolic panel was analyzed, including TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, and FPG. Complete blood counts (white blood cells [WBC], red blood cells [RBC], platelets [PLT]) were also measured.

MetS Severity Score: To quantify MetS severity as a continuous variable, we adopted a validated sex-specific MetS severity score formula developed for the Chinese adult population[16]:

Male: -2.9092 + 0.0262 × WC + 0.3098 × TG – 0.944 × HDL-C + 0.0097 × MAP + 0.0745 × FPG

Female: -2.4981 + 0.0199 × WC + 0.5218 × TG – 0.8616 × HDL-C + 0.0110 × MAP + 0.1074 × FPG

Where MAP (Mean Arterial Pressure) = 1/3 systolic blood pressure + 2/3 diastolic blood pressure. A higher score indicates greater MetS severity.

2.3 Fecal Sample Collection and Metagenomic Sequencing

Sample Collection: Morning midstream fecal samples were collected within 24 hours of enrollment using sterile collection tubes. Samples were immediately frozen and stored at -80°C until processing.

Shotgun Metagenomic Sequencing: Bacterial DNA was extracted from fecal samples using the Magbeads Fast DNA® kit (MP Biomedicals, Shanghai, China). DNA concentration and integrity were assessed using NanoDrop 2000 and 1% agarose gel electrophoresis. Qualified DNA was sheared to an average size of ~400 bp, and dual-index libraries were constructed using the KAPA HyperPlus PCR-free kit (Illumina, CA, USA). Libraries were quantified, pooled, and sequenced on the MGISEQ-T7 platform (Xi'an Shujun Biotechnology Co., Ltd.) using a paired-end 150 bp strategy. Raw sequencing reads were processed using fastp (v0.23.0) to remove low-quality data and adapters. Host DNA reads were removed by aligning to the GRCh38 human genome using Bowtie2 (v2.3.5.1).

2.4 Statistical and Bioinformatic Analysis

Clinical Data Analysis: Statistical analyses of clinical data were performed using SPSS 27.0. Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data were compared using the independent samples t-test and presented as mean ± standard deviation (SD). Non-normally distributed data were compared using the Mann-Whitney U test and presented as median [interquartile range, IQR]. Categorical data were compared using the chi-square test and presented as frequency (n, %). All tests were two-tailed, with significance set at $P < 0.05$.

Bioinformatic Analysis: All bioinformatic and downstream statistical analyses were performed using R software (v4.3.1).

(1) Taxonomic Profiling and Visualization: Clean metagenomic reads were taxonomically profiled using MetaPhlAn4 (v4.0). The relative abundance of each taxon was calculated as the percentage of mapped reads assigned to that taxon relative to the total assigned reads per sample. To compare the two dominant phyla, Firmicutes and Bacteroidetes, between the control and study groups, bar plots displaying mean relative abundance ± standard error (SE) were generated. The Firmicutes/Bacteroidetes (F/B) ratio was computed for each sample (excluding those with Bacteroidetes = 0) and visualized using violin plots overlaid with boxplots and jittered individual data points; the y-axis was logarithmically transformed ($\log_{10}$) to accommodate the wide range of ratio values. For order- and species-level analyses, the 30 most abundant taxa based on mean relative abundance across all samples were selected, and bar plots showing mean relative abundance ± SE were constructed. Group comparisons for all taxa (phyla, orders, and species) and the F/B ratio were performed using the two-sided Wilcoxon

rank-sum test. Significant differences were annotated on the plots with asterisks (v>*P* < *0.05, v>P* < 0.01, v>**P* < 0.001), while non-significant comparisons were left unannotated. All plots were generated using the R packages ggplot2, dplyr, tidyr, and ggpubr.

(2) Diversity Analysis: Alpha diversity (within-sample richness and evenness) was assessed using the Shannon and Simpson indices. Differences between groups were tested using the Wilcoxon rank-sum test. Beta diversity (between-sample community dissimilarity) was calculated based on the Bray-Curtis distance matrix and visualized using Principal Coordinate Analysis (PCoA). Statistical significance of the separation between groups was assessed using permutational multivariate analysis of variance (PERMANOVA).

(3) Differential Abundance Analysis: Linear discriminant analysis Effect Size (LEfSe) was employed to identify taxa with significant differences in relative abundance between the study and control groups. The analysis used a Kruskal-Wallis test (α=0.05) followed by pairwise Wilcoxon tests, with an LDA score threshold of > 2.0. Additionally, a Random Forest machine learning algorithm was used to identify key taxa contributing to the classification of MetS status, ranked by the Mean Decrease Gini value.

(4) Association with MetS Severity: Within the study group, linear regression models were constructed to assess the association between the relative abundance of microbial taxa (dependent variable) and the MetS severity score (independent continuous variable). The regression coefficient (Beta), model explanatory power (R^2),

and nominal *P*-value were reported. To control multiple testing, *P*-values were adjusted using the Benjamini-Hochberg false discovery rate (FDR) correction, with significance set at *P*-adj < 0.05.

3. Results

3.1 Demographic and Clinical Profiles of the Study Cohort

Clinically stable SCZ patients were enrolled and assigned to the study group (n = 78) and the control group (n = 26). Age, age at onset, disease duration, and family history were comparable (all $P > 0.05$). The study group had a higher proportion of males (64.10% *vs.* 38.50%, $P = 0.022$) and significantly higher PANSS total scores ($P = 0.011$) and WBC ($P = 0.003$). All MetS components and the MetS severity score differed significantly between groups (all $P < 0.001$). Additionally, non-diagnostic lipid markers, including TC ($P = 0.024$) and LDL-C ($P < 0.001$), were significantly elevated in the study group (**Table 1**).

Table 1:

Index	Control Group	Study Group	$\chi^2/Z/t$	*P*
Gender			5.253	0.022*
Male	10 (38.50%)	50 (64.10%)		
Female	16 (61.50%)	28 (35.90%)		
Family history			0.150	0.698
Negative	20 (76.90%)	57 (73.10%)		
Positive	6 (23.10%)	21 (26.90%)		
Age (years)	29.50±7.54	32.19±6.07	-1.840	0.069
Age at onset (years)	24.92±7.45	25.51±6.99	-0.367	0.715
Disease duration (months)	40.00 (15.50, 72.00)	70.00 (25.50, 122.50)	-1.923	0.054
PANSS	47.50 (36.00,	51.00 (46.50, 56.00)	-2.528	0.011*

	55.00)			
BMI (kg/m^2)	21.67 (19.86, 22.85)	28.25 (25.10, 32.16)	-6.362	< .001*
WBC (×10^9/L)	5.90 (4.87, 7.25)	7.09 (5.78, 8.35)	-3.007	0.003*
RBC (×10^{12}/L)	4.41 (4.05, 5.37)	4.64 (4.29, 4.98)	-1.295	0.195
PLT (×10^9/L)	237.00±50.21	234.23±51.37	0.239	0.811
TC (mmol/L)	3.92 (3.40, 4.69)	4.50 (3.94, 5.18)	-2.252	0.024*
LDL-C (mmol/L)	2.33±0.7	3.03±0.7	-4.441	< .001*
MetS Components				
WC (cm)	76.22±7.25	100.58±12.92	-11.941	< .001*
SBP (mmHg)	107.31±11.38	121.65±10.58	-5.877	< .001*
DBP (mmHg)	69.77±8.77	81.78±8.3	-6.302	< .001*
FPG (mmol/L)	4.80 (4.30, 5.03)	5.20 (4.88, 6.03)	-3.868	< .001*
TG (mmol/L)	0.82 (0.69, 1.13)	2.36 (1.95, 3.37)	-7.361	< .001*
HDL-C (mmol/L)	1.27 (1.12, 1.46)	0.94 (0.85, 1.01)	-6.402	< .001*
MetS Scores	-0.36 (-0.63, -0.16)	1.20 (0.89, 1.53)	-7.605	< .001*

Note: PANSS, Positive and Negative Syndrome Scale; BMI, body mass index; WBC, white blood cell; RBC, red blood cell; PLT, platelet; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol. *$P < 0.05$

3.2 Taxonomic Profiling and Core Microbiome Alterations

Both groups were dominated by *Firmicutes* and *Bacteroidetes* (**Figure 1A** and **Additional file 1: Figure S1A)**. The study group exhibited an elevated F/B ratio (**Figure 1B**), driven by expansion of *Clostridia*/*Eubacteriales* and contraction of *Bacteroidia*/*Bacteroidales* (**Figure 1C** and **Additional file 1: Figure S1B, S1C**). Among beneficial commensals, *Bifidobacterium* longum was significantly reduced and *Faecalibacterium prausnitzii* showed a non-significant decreasing trend in the study

group, whereas *Blautia wexlerae* and *Eubacterium* rectale were enriched (**Figure 1D** and **Additional file 1: Figure S1F**).

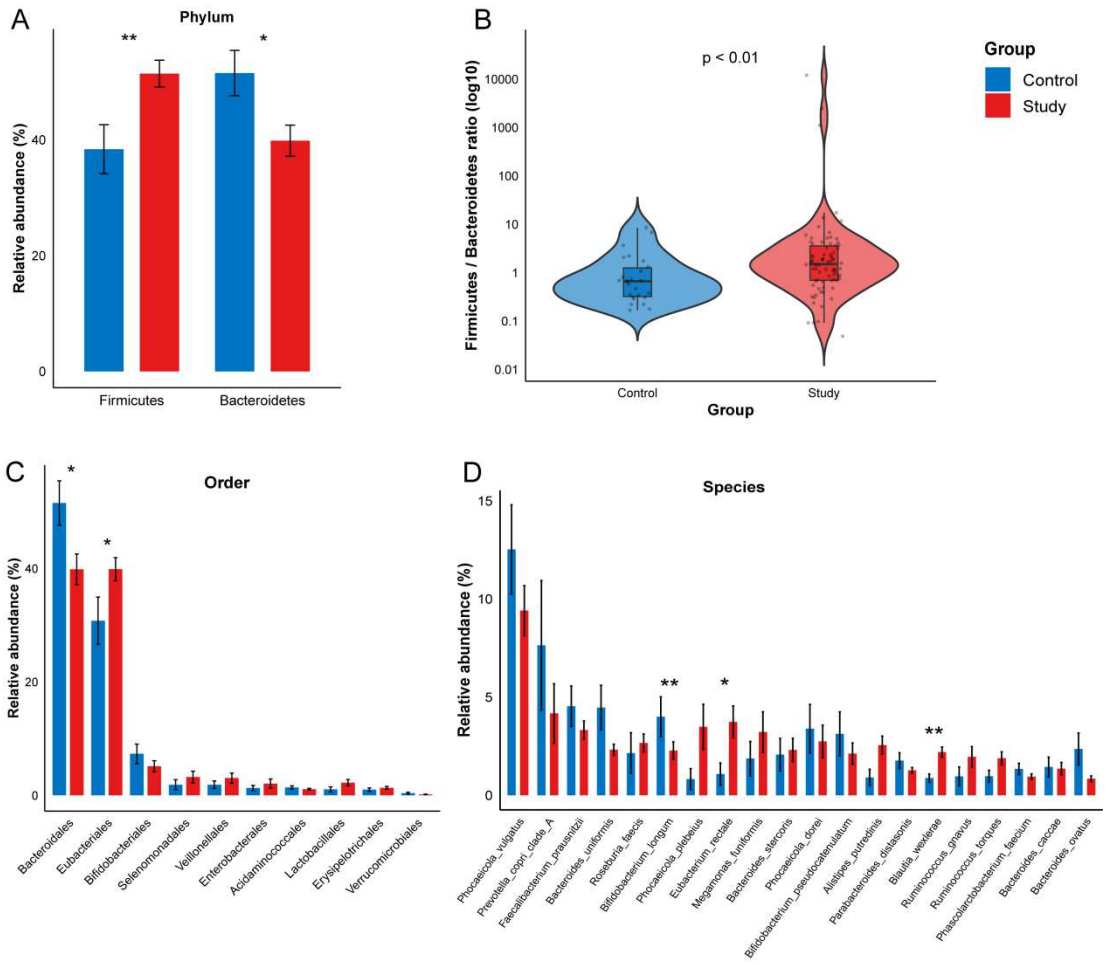
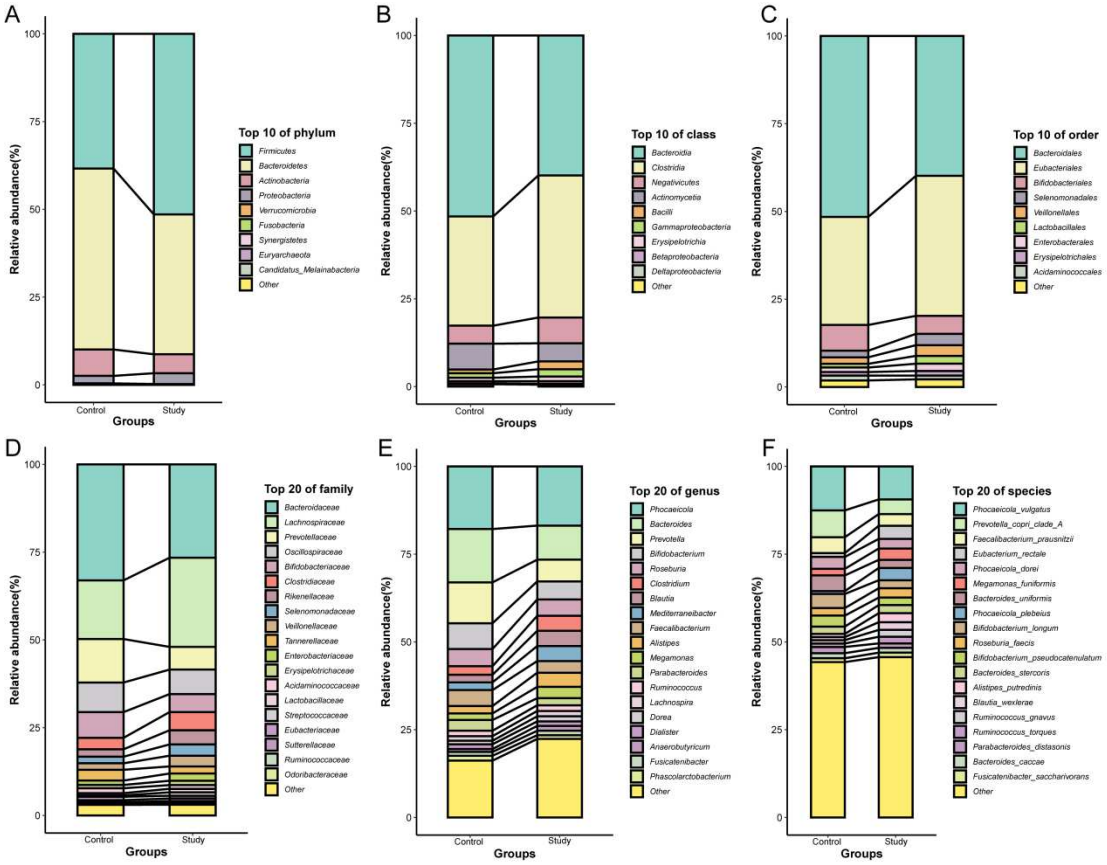


Figure 1. Taxonomic composition of gut microbiota at phylum, order, and species levels

(A) Bar plot showing mean relative abundance ± SE of the two dominant phyla (Firmicutes and Bacteroidetes) in the control (non-MetS) and study (MetS-comorbid) groups. (B) Violin plot of the Firmicutes/Bacteroidetes (F/B) ratio (log_{10}-transformed) between groups; boxes indicate median and interquartile range, with jittered individual data points. (C) Mean relative abundance ± SE of the top 30 most abundant orders. (D) Mean relative abundance ± SE of the top

30 most abundant species. Group comparisons were performed using two-sided Wilcoxon rank-sum tests; significance levels: *P < 0.05, **P < 0.01, ***P < 0.001. ns, not significant.



Additional file 1: Figure S1. Detailed taxonomic bar plots of the gut microbiota composition at additional levels

Mean relative abundance ± SE of the top 30 taxa at (A) phylum, (B) class, (C) order, (D) family, (E) genus, and (F) species levels. Only taxa with mean relative abundance > 0.1% are shown. Group comparisons were performed using two-sided Wilcoxon rank-sum tests, with significance indicated as *P < 0.05, **P < 0.01, ***P < 0.001. This figure supplements the core taxonomic findings presented in Figure 1.

3.3 Microbial Diversity and Community Restructuring

As shown in Figure 2, Alpha diversity (Shannon and Simpson indices) showed no significant difference between groups at any taxonomic level (all $P > 0.05$). Beta diversity (PCoA) demonstrated significant separation at all levels (PERMANOVA: phylum $P = 0.008$, class $P = 0.010$, order $P = 0.008$, family $P = 0.013$, genus $P = 0.037$, species $P = 0.034$), indicating substantial community restructuring without overall loss of overall richness (**Figure 3**).

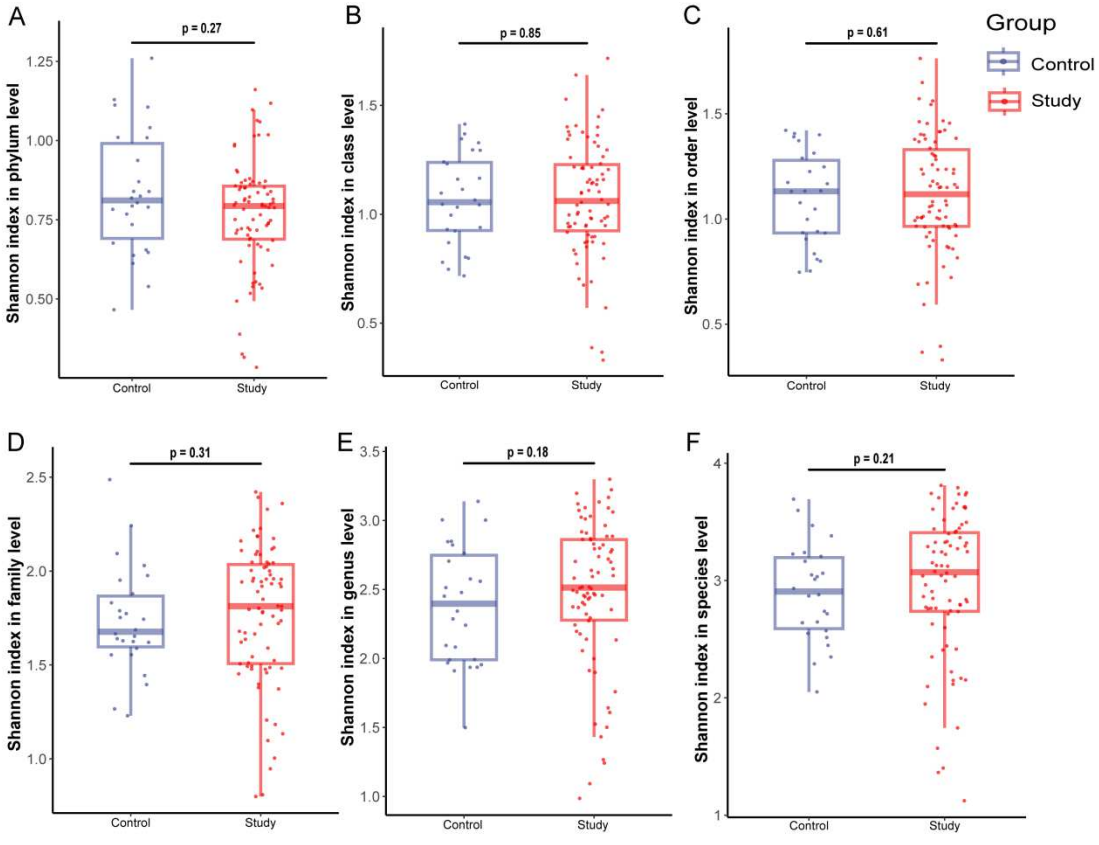


Figure 2. Alpha diversity comparisons between groups at different taxonomic levels

Shannon diversity index distributions for the control and study groups at (A) phylum, (B) class, (C) order, (D) family, (E) genus, and (F) species levels. Boxes

represent median and interquartile ranges; whiskers extend to 1.5× IQR. P-values were calculated using two-sided Wilcoxon rank-sum tests, with no significant differences observed at any level (all P > 0.05).

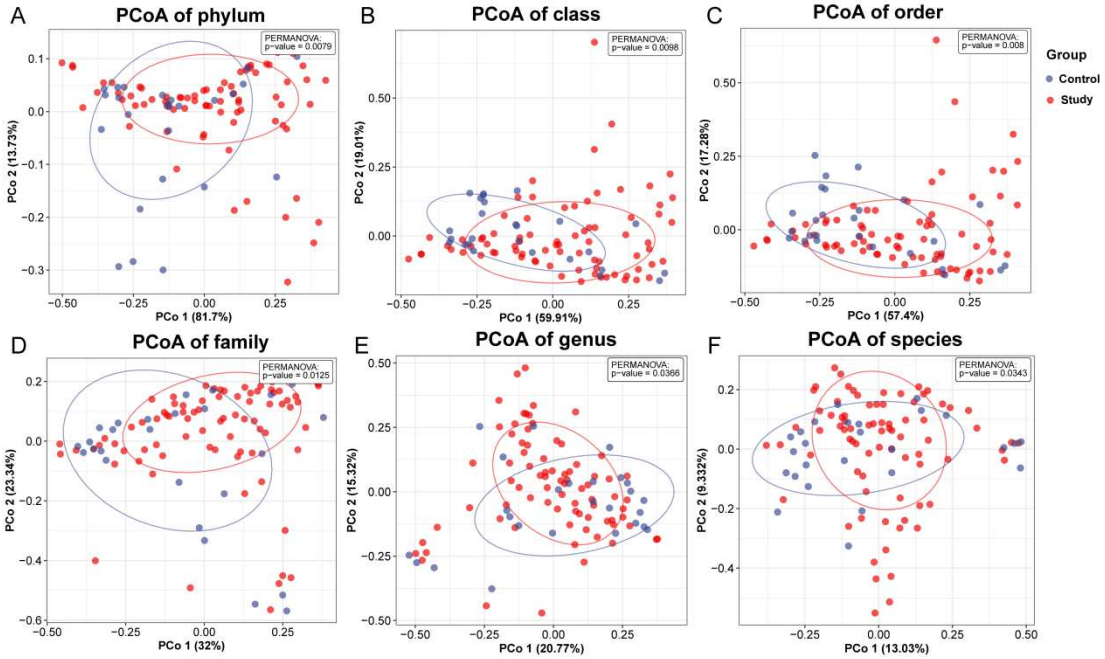


Figure 3. Beta diversity analysis based on Bray-Curtis dissimilarity at multiple taxonomic levels

Principal Coordinate Analysis (PCoA) plots showing community separation between control and study groups at (A) phylum, (B) class, (C) order, (D) family, (E) genus, and (F) species levels. Each point represents an individual sample; ellipses indicate 95% confidence intervals. The proportion of variance explained by each principal coordinate is shown on the axes. Statistical significance of group separation was assessed by PERMANOVA with P-values displayed on each panel (phylum P = 0.0079, class P = 0.0098, order P = 0.008, family P = 0.0125, genus P = 0.0366, species P = 0.0343).

3.4 Identification of MetS-Associated Microbial Biomarkers

LEfSe analysis revealed distinct enrichment patterns: the control group was characterized by Bacteroidetes lineage members including *Bifidobacterium longum*, *Prevotella hominis*, *Paraprevotella clara*, and *Flavonifractor plautii* (LDA > 2.0); the study group was enriched in *Firmicutes* lineages, particularly *Lachnospiraceae* and *Clostridiaceae*, with *Blautia wexlerae*, *Eubacterium rectale*, and *Streptococcus parasanguinis* showing the highest LDA scores (**Figure 4A**). Random Forest analysis identified *Bifidobacterium longum*as the top classifier for the control group (highest Mean Decrease Gini), while *Blautia wexlerae*was the top classifier for the study group (**Figure 4B**). Other important contributors included *Flavonifractor plautii*, *Paraprevotella clara*, and low-abundance species such as *Actinomyces sp. ICM47* and *Eubacterium sulci* (**Figure 5**).

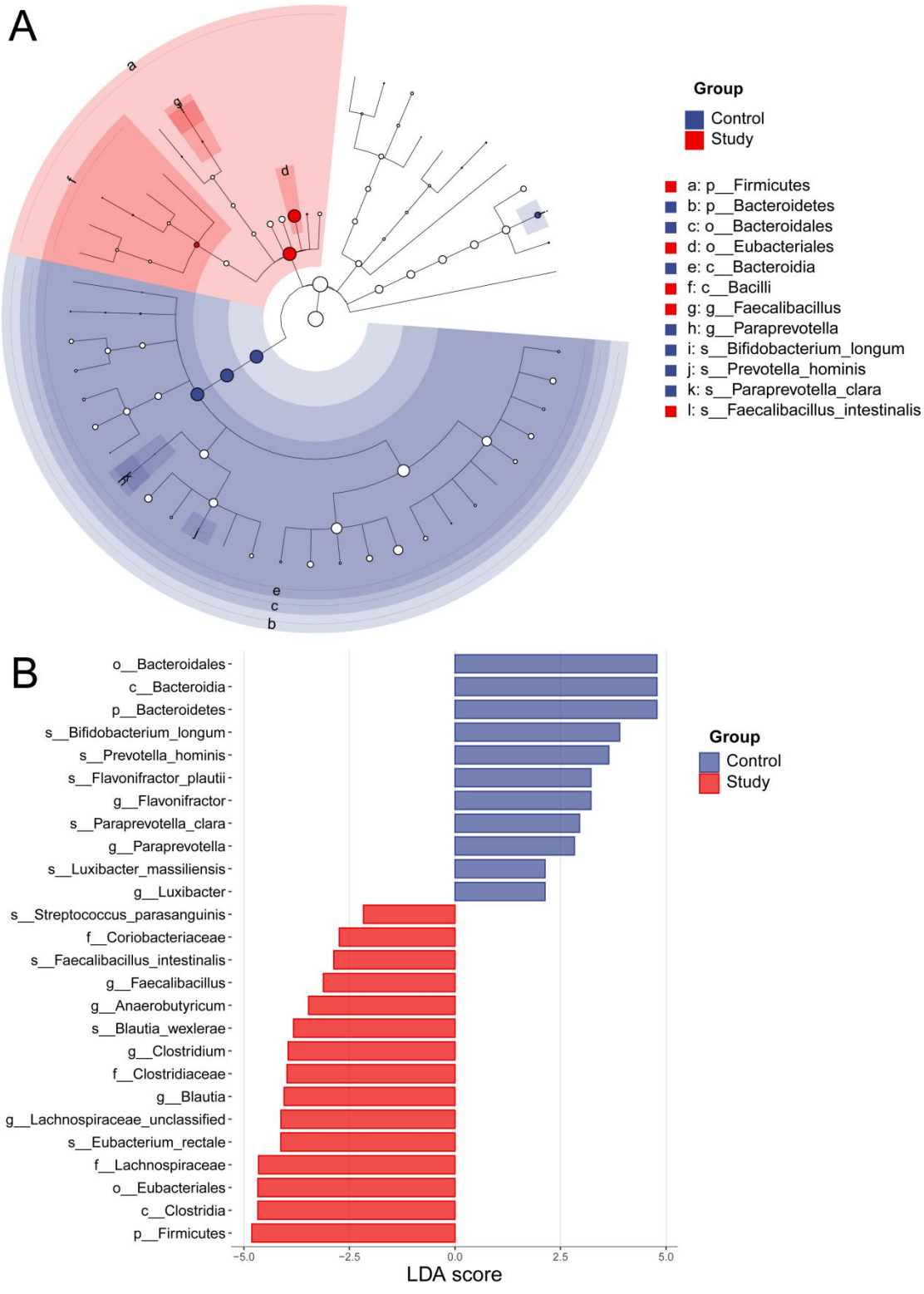


Figure 4. Identification of differentially abundant taxa between groups using LEfSe and Random Forest

(A) LEfSe histogram showing taxa with significant differential abundance

between control and study groups (LDA score > 2.0, Kruskal-Wallis test α=0.05 followed by pairwise Wilcoxon tests). Red bars indicate taxa enriches in the study group; green bars indicate taxa enriched in the control group. Taxonomic levels are denoted by prefixes: p__, c__, o__, f__, g__, s__ for phylum, class, order, family, genus, and species, respectively. (B) Random Forest variable importance ranking (Mean Decrease Gini) for the top 20 species contributing to classification of MetS status. Relative abundance of these species in each group is shown in the accompanying dot plot.

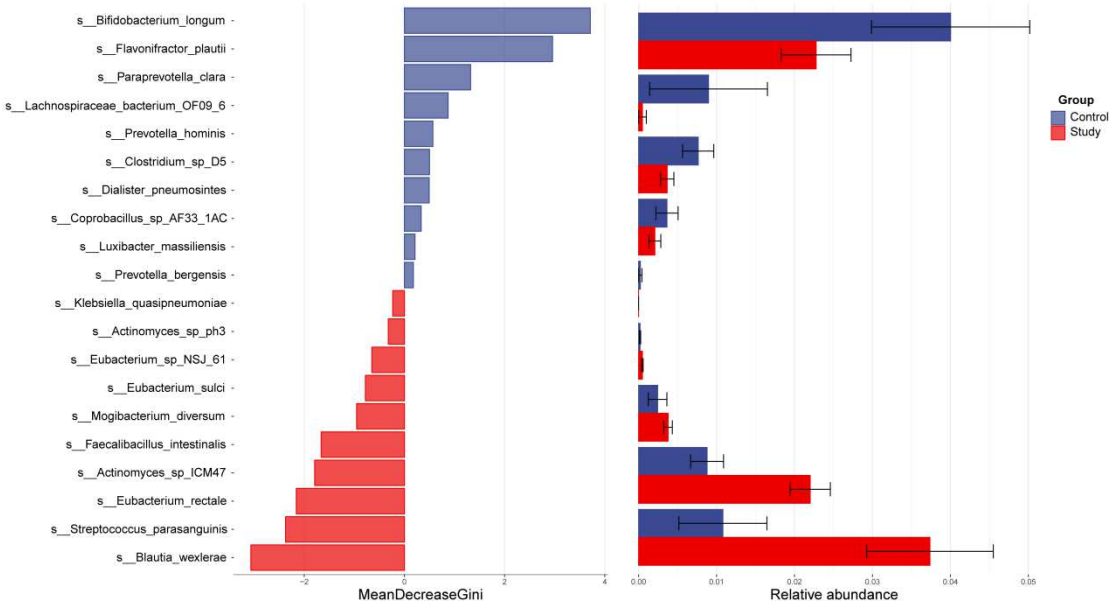


Figure 5. Random Forest-based features of species-level biomarkers. The main panel displays a dot plot of the top 20 species ranked by Mean Decrease Gini value. Each dot corresponds to a species, with its x-coordinate representing the importance score, and its color indicating the group showing higher relative abundance (green: control; red: study). The upper panel shows the mean relative abundance of these species within each group for direct visual comparison. Species with higher discriminatory importance for the

MetS-comorbid group include Blautia wexlerae, Streptococcus parasanguinis, and Eubacterium rectale, whereas Bifidobacterium longum, Flavonifractor plautii, and Paraprevotella clara were more important for the control group.

3.5 Linear Associations Between Specific Taxa and MetS Severity

Within the study group, linear regression identified taxa whose abundance significantly correlated with MetS severity score (**Table 2**). After FDR correction, two genera and their corresponding species-maintained significance: *Evtepia genus* (Beta = −1.377, $R^2 = 0.188$, $P < 0.001$, P-adj = 0.014) and *Evtepia gabavorous* (Beta = −1.377, $R^2 = 0.188$, $P < 0.001$, P-adj = 0.039) showed strong negative associations. *Adlercreutzia genus* (Beta = −3.195, $R^2 = 0.179$, $P < 0.001$, P-adj = 0.014) and *Adlercreutzia equolifaciens* (Beta = −3.195, $R^2 = 0.179$, $P < 0.001$, P-adj = 0.039) also exhibited robust negative correlations.

Table 2: Linear Regression Analysis of Gut Microbiota and MetS Scores in the Study Group

Taxon	*Beta*	R^2	*P*	*P*-adj
genus				
Evtepia	-1.377	0.188	0.000	0.014*
Adlercreutzia	-3.195	0.179	0.000	0.014*
species				
Evtepia_gabavorous	-1.377	0.188	0.000	0.039*
Adlercreutzia_equolifaciens	-3.195	0.179	0.000	0.039*

Note: $*P < 0.05$

At nominal significance ($P < 0.05$, P-adj > 0.05), several other taxa showed notable associations. Among positively associated taxa, *Dorea phocaeensis* (Beta =

431.26) and *Anaerotignum lactatifermentans* (Beta = 404.97) exhibited exceptionally large effect sizes, while negatively associated taxa included the phylum *Euryarchaeota* and the family *Comamonadaceae*. Complete regression results, including all nominally significant taxa, are detailed in Additional file 2: Table S1.

4. Discussion

This study identifies a gut microbial signature in clinically stable SCZ patients that tracks linearly with metabolic severity. Previous studies often conflated metabolic dysfunction with acute illness, by focusing on a stable cohort screened for symptom remission, we were able to isolate metabolic-specific signals from confounding effects of psychiatric crises or rapid medication changes.

The distinct compositional divergence observed between the MetS-comorbid and non-MetS stable SCZ subgroups further validates the presence of a MetS-specific microbial dysbiosis that persists independently of psychiatric medication effects[23]. The data show that while the core microbial skeleton remains conserved without a significant reduction in Alpha diversity, the comorbid group shows marked structural reshuffling. Unlike some previous studies reporting a generalized collapse of species richness in metabolic or psychiatric cohorts[24-26], our findings indicate a specific ecological niche replacement. This is highlighted by a shift in the F/B ratio, a hallmark of metabolic pathology[19]. The significant community-level restructuring, as evidenced by the distinct Beta diversity separation in our cohort, indicates that MetS-comorbid SCZ patients occupy a fundamentally altered ecological niche compared to

their metabolically healthy counterparts [27, 28]. This compositional divergence is driven primarily by the contraction of *Bacteroidetes* and the expansion of *Clostridia*, a shift that likely mirrors a transition toward a more efficient energy-harvesting microbiota profile[29]. Such evidence suggests that the presence of MetS imposes a unique environmental pressure on the gut ecosystem, overriding the stabilizing influence of maintaining psychiatric symptom remission and potentially fueling a sustained state of metabolic instability[30].

The observation that *Adlercreutzia equolifaciens* abundance displays a consistent inverse correlation with the MetS-SS suggests that the loss of this key equol-producing commensal may be a pathological indicator of metabolic vulnerability. Recent studies have highlighted *Adlercreutzia equolifaciens* as a critical anti-inflammatory commensal bacterium, and its depletion in our SCZ cohort parallels the decline in intestinal barrier function and systemic metabolic homeostasis observed in non-psychiatric metabolic disorders[31, 32]. This specific association suggests that metabolic deterioration in SCZ is associated with gut microbiota changes linked to a reduced capacity for equol production, a daidzein-derived microbial metabolite with antioxidant and favorable cardiometabolic associations[33-36]. We interpret this as evidence that the metabolic-psychiatric cycle is partially governed by the progressive dismantling of the host's endogenous antioxidant defense, directly exacerbating insulin resistance and lipid dysregulation.

Furthermore, our finding that *Evtepia gabavorous* diminishes as the MetS-SS rises provides a plausible link between the central neurological symptoms of SCZ and

peripheral metabolic decline. The GABAergic system is pivotal in both psychiatric symptom regulation and peripheral metabolic control such as insulin sensitivity[37]. The depletion of *Evtepia gabavorous* in patients with higher MetS-SS suggests that metabolic deterioration may actively disrupt the gut-to-brain neurochemical signaling pathway[23, 38].

In addition to taxa tracking with metabolic severity, our models identified a marked loss of SCFA-producing commensals, particularly *Bifidobacterium longum* and *Faecalibacterium prausnitzii*, in patients with MetS. As a primary butyrate producer, *F. prausnitzii* is well known for maintaining epithelial integrity and limiting inflammation, whereas *B. longum* contributes broadly to barrier function and immune regulation[39, 40]. The concurrent loss of these core commensals points to a reduced capacity for SCFA synthesis as metabolic burden increases[41-43]. Such a deficit may compromise the intestinal barrier and promote the systemic low-grade inflammation seen in our MetS cohort, which is consistent with the elevated WBC observed.

Blautia wexlerae emerged as a primary classifier for the MetS-comorbid group, though this finding requires careful interpretation. While some evidence links *Blautia* species to health in general populations, their enrichment here mirrors compensatory patterns seen in chronic metabolic disease[44]. Specific taxa may proliferate in response to a pro-inflammatory microenvironment. The co-occurrence of this enrichment with elevated WBC counts suggests a dysbiotic state driven by chronic inflammation and potential bacterial translocation, consistent with recent reports of gut-immune dysfunction in SCZ[23, 45].

Using a continuous severity score rather than binary MetS categorization allowed us to identify microbial signatures that evolve along a clinical continuum, addressing a methodological limitation in prior psychiatric research[13, 16]. This gradient-based perspective suggests microbial shifts occur before standard diagnostic thresholds are met, manifesting as dose-dependent degradation alongside worsening metabolic components. Severe metabolic deterioration in stable SCZ appears to coincide with progressive gut microbial and metabolic dysfunction, supporting a microbiota-gut-brain-metabolic axis linking psychiatric and metabolic burden, although direct evidence for a causal role of equol- and GABA-related taxa loss, vagal feedback, and neuroinflammatory amplification remains limited[46, 47]. We consider these markers promising early, preemptive metabolic risk stratification in psychiatric practice.

We acknowledge several limitations. The cross-sectional design precludes causal inference between gut microbial alterations and MetS, longitudinal and interventional studies are required to validate these findings. Furthermore, our sample size was relatively small, necessitating replication in larger, diverse cohorts. Key gaps also include unmeasured variables such as detailed dietary intake, physical activity, and specific metabolic medications, all of which significantly impact the gut microbiome[48]. Finally, despite strict criteria for clinical stability, the MetS group exhibited slightly higher symptom scores and a greater male proportion, introducing potential residual confounding that cannot be entirely excluded.

5. Conclusions

In clinically stable SCZ, MetS comorbidity is characterized by specific gut microbial remodeling, not a generalized loss of diversity. Importantly, the progressive depletion of key functional taxa, particularly *Adlercreutzia equolifaciens* and *Evtepia gabavorous*, tracks linearly with continuous metabolic severity. This provides a potential mechanistic bridge linking peripheral metabolic decline to central neurobiology via the gut-brain axis. These gradient-based microbial signatures suggest that microbiome-targeted precision interventions could help mitigate metabolic risk and improve long-term outcomes in psychiatric care.

Abbreviations

BMI: Body mass index

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

FDR: False discovery rate

FPG: Fasting plasma glucose

HDL-C: High-density lipoprotein cholesterol

LDA: Linear discriminant analysis

LDL-C: Low-density lipoprotein cholesterol

LEfSe: Linear discriminant analysis Effect Size

MAP: Mean arterial pressure

MetS: Metabolic syndrome

MetS-SS: Metabolic syndrome severity score

MGBA: Microbiota-Gut-Brain Axis

PANSS: Positive and Negative Syndrome Scale

PCoA: Principal Coordinate Analysis

PERMANOVA: Permutational multivariate analysis of variance

SCFA: Short-chain fatty acid

SCZ: Schizophrenia

TC: Total cholesterol

TG: Triglyceride

WC: Waist circumference

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Authors' contributions

JM and XL made substantial contributions to the conception and design of the study. JM and YW drafted the manuscript. YW and YC polished the language and logic of the article. XL and YZ were responsible for supplementing and modifying the content of the manuscript. JM gave final approval for the version to be published. All authors read and approved of the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are available in the NCBI repository, BioProject accession number PRJNA1551129 (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1551129).

Ethics approval and consent to participate.

The ethics committees of the Wuhan mental health center reviewed and approved this study. All subject guardians knew about this study and signed informed consent. All procedures carried out in studies conformed to the 1964 Helsinki Declaration and its subsequent amendments or similar ethical standards.

Consent for publication

Not applicable.

Competing interests

None.

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