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RESEARCH PAPER

Younger and older adults with major depressive disorder exhibit differential gut microbiome and gut-brain axis features

Robita Doley[1] · Kabyashree Bhuyan[1] · Quinat Tasneem Rafique[1] · Vijay Gogoi[2] · Pankaj Barah[1]

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Abstract
Depression is a common mood disorder that affects individuals across all age groups. Increasing evidence highlights the gut–brain axis as a critical contributor to its pathophysiology. Notably, depression differs in prevalence, clinical features, and underlying mechanisms across ages. To investigate whether gut microbiota contributes to these differences, comparative analyses across age groups are needed. In this study, we examined gut microbiota composition and functional alterations in younger adults (N = 43, aged 18–35) and older adults (N = 74, aged ≥ 60) with depression, using publicly available metagenomic datasets. Our findings highlight microbial shifts in dominant bacterial phyla such as Bacteroidota and Bacillota, which are strongly implicated in depression. Furthermore, alterations in metabolism and membrane transport pathways may affect oxidative stress, neurochemical balance, and hypothalamic–pituitary–adrenal (HPA) axis regulation, all of which play critical roles in the pathophysiology of depression. However, the absence of age-matched healthy controls and confounding factors such as diet, medication, lifestyle, and ethnicity limits the ability to predict these changes specifically to depression. Despite these limitations, our study underscores the importance of considering age when investigating gut–brain interactions in depression and highlights the need for multi-centric studies to validate age-dependent microbial and functional alterations and their clinical relevance.

Keywords Depression · Gut microbiome · Metagenomics · Age-groups · Microbiota-gut-brain axis · Differential psychology

Abbreviations

ABC	ATP-binding cassette
ASV	Amplicon sequence variants
BH	Benjamini–Hochberg
FDR	False discovery rate
FMT	Fecal microbiota transplantation
GABA	Gamma-aminobutyric acid
GMM	Gut metabolic modules
HMDAD	Human microbe-disease association database
HPA	Hypothalamic–pituitary–adrenal axis
KEGG	Kyoto encyclopedia of genes and genomes
KO	KEGG orthology
NCBI-SRA	National center for biotechnology information sequence read archive
PCoA	Principal coordinates analysis
PERMANOVA	Permutational multivariate analysis of variance
PICRUSt2	Phylogenetic investigation of communities by reconstruction of unobserved states
SCFA	Short-chain fatty acid

Robita Doley and Kabyashree Bhuyan have equal contribution to this work.

✉ Pankaj Barah
barah@tezu.ernet.in

[1] Department of Molecular Biology and Biotechnology, Tezpur University, Tezpur, Assam 784028, India

[2] Department of Psychiatry, Lokopriya Gopinath Bordoloi Regional Institute of Mental Health, Tezpur, Assam 784001, India

Introduction

Clinical depression is a complex neurological condition characterized by persistent and pervasive changes in mood, cognition, and physiological functions. Depression significantly impairs social and occupational functioning, severely affecting an individual's mental, emotional, and physical well-being (Otte et al. 2016). Its global impact is substantial, with more than 300 million people estimated to suffer from depression, equivalent to 4.4% of the world's population. Women experience depression approximately twice as often as men, and its prevalence increases with age, reaching 5.7% among those aged 60 and above (Pushap et al. 2025; Sagar et al. 2020).

Depression manifests differently across age groups, with distinct symptom patterns and prevalence rates. Younger individuals often experience guilt and reduced sexual function, while older adults tend to have more somatic symptoms like agitation, hypochondriasis, and gastrointestinal issues. Late-life depression is typically chronic, with higher relapse rates, poorer long-term outcomes, and increased medical comorbidities such as cognitive impairment and cardiovascular disease. It also carries a higher mortality risk (Hegeman et al. 2012; Sikström et al. 2023; Wagner et al. 2020). Epidemiological data indicate a U-shaped relationship between age and depression prevalence, with younger and older age groups having higher rates of depression and lower rates in the middle age groups (Wagner et al. 2020; Grover et al. 2019). This age-related pattern highlights the need for targeted interventions across different age categories. The gut–brain axis has emerged as a key contributor to depressive disorders. Alterations in gut microbiota composition can lead to immune activation through the bidirectional communication between the gut and the brain, potentially contributing to the development of various psychiatric symptoms (Wang and Kasper 2014). Animal studies have demonstrated that disruption of the gut microbiota can induce depression-like behaviors (Barandouzi et al. 2020). Specific bacterial taxa, including Flavonifractor and Faecalibacterium, have been found to be altered in individuals with depression. Recent findings highlight that gut microbiota composition undergoes significant age-related changes, suggesting that its role in depression may vary with age. For instance, younger depression patients often exhibit elevated levels of Bacteroidota and reduced levels of Bacillota when compared to age-matched healthy controls, while middle-aged individuals with depression tend to display the opposite pattern. Chen et al. (2020) reported that older adults with depression have significantly higher levels of Bacteroidota compared to younger individuals, whereas middle-aged patients show a reduction in Bacteroidota and an increase in Actinomycetota relative to controls. These patterns suggest that age may influence the trajectory and persistence of depressive symptoms by shaping microbial composition. Although increasing evidence supports the involvement of gut microbiota in the pathogenesis of depression, the specific role of microbial dysbiosis remains unclear, particularly whether the dysbiosis is causal or a consequence of depression-related physiological changes. Most studies exploring age-related differences in depression have categorized participants into just two broad groups: those aged 65 and younger, and those older than 65 (Veltman et al. 2017; Wagner et al. 2020). Recent studies have begun to investigate the gut microbiome in young-aged, middle-aged, and old-aged patients; however, direct comparisons between these groups, particularly between younger and older individuals where prevalence rates are highest, remain limited. By investigating age-related variations in microbial composition, diversity, and function, the present study aims to understand how gut microbiota may differentially influence depression across distinct age groups.

Materials and methods

Data acquisition

Publicly available gut microbiome datasets were retrieved from the National Center for Biotechnology Information Sequence Read Archive (NCBI-SRA). A comprehensive search was conducted using a combination of relevant keywords, including: “depression”, “young adults”, “old adults”, “late life”, “early life”, “metagenomics”, “human gut microbiome”, “DNA”, “paired”, and “fastq.” We selected two datasets that aligned with our target age groups: younger adults (18–35 years) and older adults (≥60 years), all diagnosed with depression. PRJNA591924 (Liu et al. 2020) represents the younger adult group, and PRJNA991320 (Magzal et al. 2023) corresponds to the older adult group (Table 1). We excluded other datasets that did not match these specific age ranges or lacked accessible raw metagenomic sequencing data from the study. We acknowledge that restricting our analysis to only two datasets may introduce potential biases. Additionally, the absence of age-matched healthy controls represents a significant limitation.

Analysis of metagenomic data

The raw amplicon sequencing data were processed using the DADA2 (version 1.34.0) (Callahan et al. 2016) to generate amplicon sequence variants (ASVs), and SILVA reference database (version 138) was used for taxonomic classification (Quast et al. 2013). Metabolic functional profiling was predicted using Phylogenetic Investigation of Communities

Table 1 Metagenomic dataset characteristics for younger and older adults with depression

	Young adults	Old adults
Bio Project ID	PRJNA591924	PRJNA991320
SRA Study title	Gut microbiome of young adults with MDD	Depression in older adults
File type	FASTQ	FASTQ
Sample number	43	74
Age	18–35	≥ 60 years
Assay type	Amplicon	Amplicon
Sequencing platform	Illumin MiSeq	Illumin MiSeq
Layout	Paired	Paired
Hypervariable region	V4	V3-V4
Sample medium	Stool sample	Stool sample

by Reconstruction of Unobserved States (PICRUSt2) software (Douglas et al. 2020), and their comparative visualization was carried out using ggpicrust2 (version 2.0.1) (Yang et al. 2023). KEGG (Kyoto Encyclopedia of Genes and Genomes) Orthology (KOs) were mapped to Gut Metabolic Modules (GMMs) (Valles-Colomer et al. 2019) using the OmixerR package (Darzi et al. 2016). The Human Microbe–Disease Association Database (HMDAD) (Ma et al. 2017) was used to annotate the identified taxa.

Statistical analysis

All statistical analyses were performed in R (version 4.4.2). Alpha-diversity, including the Shannon and Simpson indices, was calculated using the phyloseq package (McMurdie and Holmes 2013). Beta diversity was assessed using Principal Coordinates Analysis (PCoA) based on the Bray–Curtis index with the vegan package (version 2.5–1). The results were visualized using ggplot2. Permutational multivariate analysis of variance (PERMANOVA) was conducted to test for differences between groups. The nonparametric Wilcoxon test was used to assess statistical significance, and *p*-values were adjusted for false discovery rate (FDR) using the Benjamini–Hochberg (BH) method.

Results

The taxonomic composition of gut microbes varies between younger and older adults with depression

Microbial diversity was analyzed (Supplementary File S1), revealing differences in gut microbial composition at the phylum level between younger and older adults with depression (Fig. 1). Bacteroidota and Bacillota were among the most abundant phyla in both age groups. Among older

Fig. 1 Relative abundance of gut microbiota at Phylum levels in younger and older adults with depression

adults, Bacillota and Bacteroidota were the predominant phyla, whereas in younger adults, these phyla remained dominant with smaller contributions from Pseudomonadota, Actinomycetota, and Thermodesulfobacteriota. At the class level (Supplementary File S2), Clostridia, Bacteroidia, Bacilli, Gammaproteobacteria, Coriobacteriia, and Desulfovibrionia were observed in younger individuals. Clostridia and Bacteroidia were found to be significant in both groups. Order-level comparisons (Supplementary File S2) revealed a greater representation of Lachnospirales, Oscillospirales, and Bacteroidales in the younger group. At the family level (Supplementary File S2), Ruminococcaceae and Bacteroidaceae were present in both groups; however, Lachnospiraceae and Oscillospiraceae were more abundant in younger individuals.

Microbial diversity

No significant difference in Shannon diversity (Fig. 2a) was observed between the two age groups (Wilcoxon rank-sum test, $p = 0.926$). In contrast, the Simpson diversity index (Fig. 2b) revealed a significant difference between the two groups ($p < 0.001$). PCoA based on the Bray–Curtis distance (Fig. 2c) showed distinct clustering patterns between older and younger adults. The PERMANOVA test further confirmed significant differences in the overall microbial composition between the groups (PERMANOVA, $p = 0.001$, permutations = 999).

Functional alterations in the gut microbiome of younger and older adults with depression

PICRUSt2 was used to predict the functional profiles of the microbial communities based on the KEGG and KO database. The predicted pathways were categorized, with

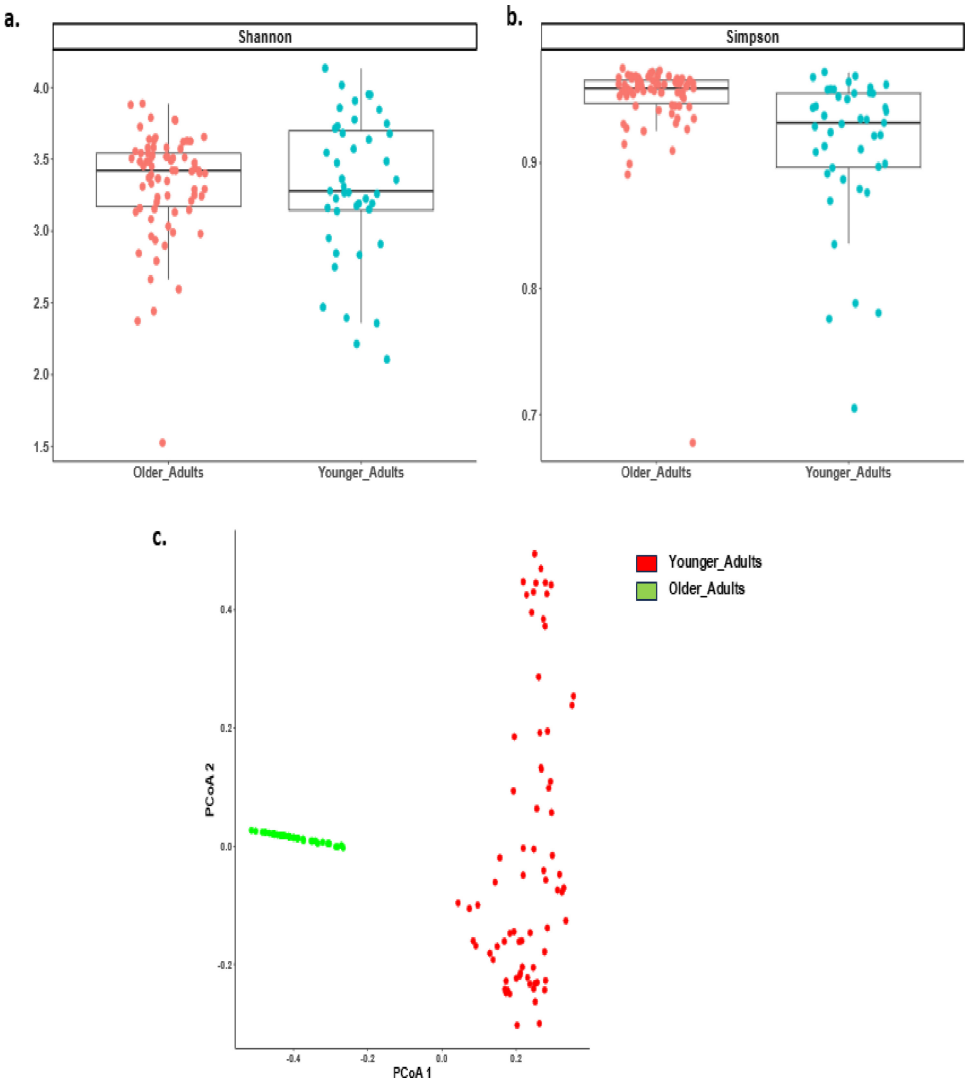

Fig. 2 Alterations of gut microbiota in younger and older adults with depression. (**a**, **b**) Comparison of alpha-diversity between younger and older adults with depression. The x-axis represents the older adults (red) and younger adults (blue), the y-axis represents the value of Shannon index **(a)**, Simpson index **(b)**. **(c)** Beta-diversity as a PCoA plot based on Bray–Curtis dissimilarity

metabolism identified as the most prevalent functional group, followed by environmental information processing and cellular processes. Differentially abundant predicted pathways ($p<0.05$) were identified between the two age groups (Fig. 3). The BH correction was applied to control for FDR. ATP-binding cassette (ABC) transporters were highly abundant in both age groups, with higher levels observed in younger individuals. Similarly, energy metabolism was higher in the younger adults, whereas carbohydrate metabolism, glycan biosynthesis and metabolism, and cellular processes, were more enriched in older adults. Predicted KOs were mapped to GMMs (minimum coverage set to 0.5). Beta diversity (Fig. 4a), based on Bray–Curtis dissimilarity, showed partial overlap in functional profiles between the two age groups. PERMANOVA analysis indicated that the functional modules were not significantly different ($p=0.254$) between the groups. Key pathways detected in both groups (Fig. 4b and 4c) include cysteine degradation I, methionine degradation I, glutamine degradation II, and serine degradation. Alterations in these pathways may contribute to the neurobiological mechanisms underlying depression.

Discussion

Depression exhibits notable age-related variation in its prevalence and clinical presentation. While numerous studies have examined the influence of gut microbiota on brain function, few have directly compared microbial profiles across distinct age groups in individuals with depression. Our findings address this gap by demonstrating that age-related differences in gut microbiota composition and function may contribute to depression in younger and older adults.

The present investigation contributes to the growing body of evidence on the gut-brain axis, highlighting the impact of age-related differences in microbiota on depression. The findings align with previous reports on compositional shifts in several dominant bacterial phyla in depression. In both the age groups, Bacteroidota and Bacillota were among the most abundant phyla. Reductions in Bacillota have been associated with depressive phenotypes in both human and animal models. Fecal microbiota transplantation (FMT) from depressed patients into germ-free mice has been shown to induce depression-like behaviors (Zheng et al. 2016). Exposure to social defeat stress in mice results in a marked decrease in Bacillota, linking stress exposure to microbial imbalance (Liu et al. 2024). Despite these observations, inconsistencies remain across studies. The age-associated variability in the Bacillota/Bacteroidota ratio highlights the need to account for age groups when

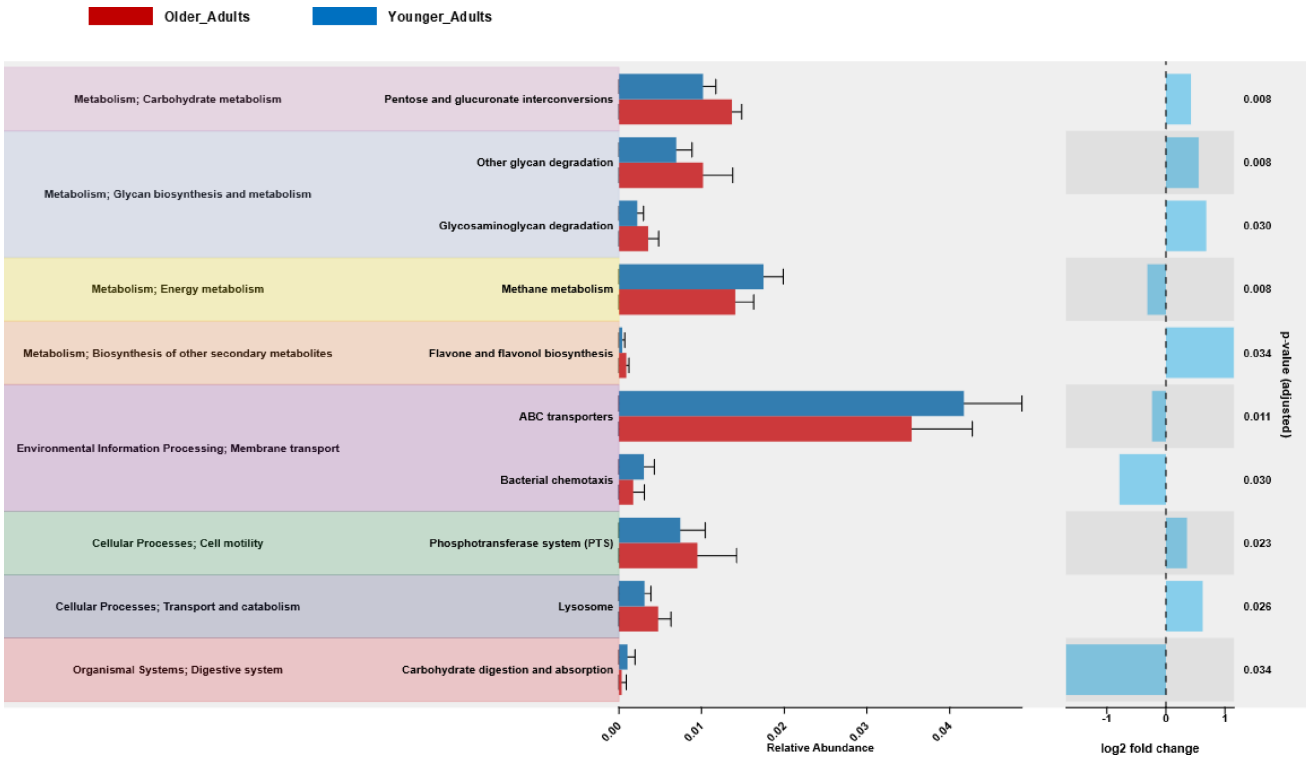

Fig. 3 Differentially abundant KEGG pathways ($p<0.05$) of younger and older adults with depression

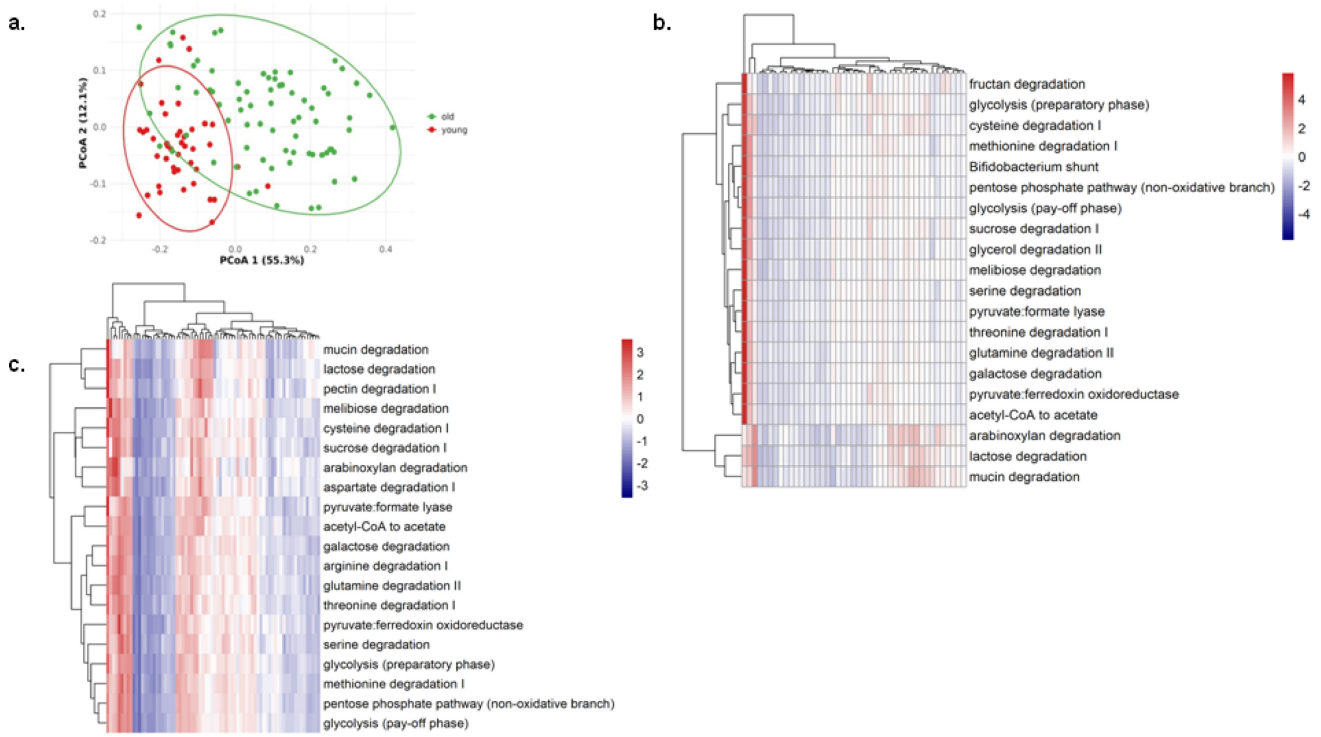

Fig. 4 Functional alterations of gut microbiota in younger and older adults with depression. **(a)** PCoA plot based on Bray–Curtis dissimilarity in the GMMs. Heatmap showing top 20 most abundant pathways in younger **(b)** and older adults **(c)** with depression

investigating microbiome associations in psychiatric conditions. Gut microbial diversity is known to be influenced by multiple factors, including age, health status, diet, and antibiotic use (Jiang et al. 2015). Previous reports suggest diversity increases with age due to cumulative environmental exposures, dietary patterns, and immune system maturation (Mariat et al. 2009; Odamaki et al. 2016; O'Toole and Jeffery 2015; Kelly et al. 2016). Therefore, observed differences in bacterial diversity may also reflect age or lifestyle variations between study populations. This study's dependence on two distinct populations with varying geographic locations and ethnicity likely introduced variability that influenced the findings. Variations in dietary habits may have contributed to the observed differences in bacterial diversity. The Mediterranean diet has been associated with reduced risk and improved management of depression and anxiety (Slyepchenko et al. 2016; Sánchez-Villegas et al. 2013). The personalized diet intervention in older age groups might have further impacted the results. As microbial abundance alters, functional redundancy allows distinct microbiomes to perform similar biological roles. Thus, functional changes can provide more clinically significant understanding of gut–brain interactions. Functional predictions on membrane transport and carbohydrate metabolism may affect depression. Adequate carbohydrate intake supports regulation of the hypothalamic–pituitary–adrenal (HPA) axis, thereby modulating cortisol levels and mitigating stress-induced neuroendocrine disruptions linked to depression (Ghosn et al. 2025). Similarly, ABC transporters may play a role in depressive pathology by regulating oxidative stress levels (Jin et al. 2025). However, further research is needed to fully understand their therapeutic potential. Metabolic dysregulation has been closely linked to depression (Bharti et al. 2021). The GMM identification showed no overall difference in function between groups. However, alterations in amino acid pathways, such as cysteine, methionine, and arginine, may contribute to the pathophysiology of depression. These pathways may regulate oxidative stress and neurochemical regulation. Increased cysteine degradation may exacerbate oxidative stress and impair cellular signaling, while reduced arginine metabolism has been implicated in the progression of depressive disorders (Fan et al. 2021; Maurya et al. 2016; Maes et al. 2019). Metabolites such as short-chain fatty acids (SCFAs) play a key role in host mood regulation. Alterations in SCFA profiles, including reduced butyrate, have been reported in depressed patients (Den Besten et al. 2013; Skonieczna-Żydecka et al. 2018). Butyrate exerts antidepressant-like effects by promoting neurotrophic signaling (O'Riordan et al. 2022; Silva et al. 2020; Stilling et al. 2016). Bacillota, major butyrate producers, are involved in the synthesis of gamma-aminobutyric acid (GABA), a neurotransmitter dysregulated in depression (Dinan and Cryan 2017; Louis and Flint 2017). These findings highlight the complex and potentially bidirectional

interplay between microbial metabolism and neurochemical balance in depression, emphasizing the need for deeper mechanistic investigation. Depression is a multifactorial and complex disorder. Emerging evidence links metabolic disturbances, chronic inflammation, oxidative stress, and gut dysbiosis with depression (Chang et al. 2022; Chen et al. 2020; Yao et al. 2023; Zhong et al. 2022). While these systemic mechanisms are recognized as key contributing factors, knowledge of their combined effect remains limited. Our study has highlighted the role of age-related differences in depression. However, the absence of age-matched healthy controls limits our understanding. The observed microbial alterations across age groups cannot be attributed solely to aging. Although aging naturally influences microbial composition, diversity, and function, such as shifts in Bacillota/Bacteroidota ratios and reductions in metabolic pathways, these changes are significantly shaped by various factors. Moreover, certain taxa associated with aging are also implicated in depression, underscoring that microbial changes reflect complex interactions between aging, health, and environment rather than aging alone. The directionality of the observed associations between gut microbiota and depression remains unclear. Depression itself may influence gut microbial composition through factors such as stress responses, dietary changes, or medication use. In addition, age-related and lifestyle differences between younger and older adults could also contribute to the observed variations in microbial composition and function. The absence of data on antidepressant use in our study groups is another confounding factor that may have affected microbial and functional outcomes. Therefore, future multi-centric, well-controlled studies that integrate demographic, dietary, and clinical variables are needed to validate these age-dependent microbial and functional alterations in depression. This approach opens the possibility of identifying age-specific microbial signatures that could serve as potential biomarkers for early diagnosis or prognosis of depression. Moreover, understanding these distinct microbial patterns may enable the development of personalized therapeutic strategies tailored to the unique needs of different age groups.

Conclusion

This study highlights potential age-related differences in gut microbiota composition and predicted functional capacity between younger and older adults with depression. Our findings suggest that alterations in microbial profiles, diversity, and functional capacity may be associated with early-life and late-life depression, underscoring the importance of age as a critical variable in depression. With more extensive research in this area, there is potential for developing age-specific microbial biomarkers for diagnosis and prognosis. Additionally, targeted probiotic or dietary interventions tailored to different age groups could modulate these microbiota-related pathways and potentially alleviate depressive symptoms. It is crucial to acknowledge the study's significant limitations. The analysis relied on two separate public datasets, with possible confounding factors such as the participants' ethnicity, geography, diet, and genetics that may have influenced the results. The lack of age-matched control groups for comparison also makes it difficult to distinguish between microbial changes related to depression and those associated with normal aging. The absence of data on antidepressant use in our study groups is another confounding factor that may have affected microbial and functional outcomes. Moreover, differences in sample collection, storage, or analysis techniques across age groups may have affected the results. To better understand these complex interactions, future research should conduct longitudinal studies with more demographically balanced cohorts, including age-matched controls without depression. These studies should adjust for confounding factors and track changes across the lifespan in individuals with and without depression. Such studies will be essential for identifying age-specific microbial signatures. This may help in the development of more personalized, microbiome-based interventions, potentially enhancing treatment outcomes for individuals across different stages of life.

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Author contributions Robita Doley: Writing—original draft, Methodology, Formal analysis, Visualization. Kabyashree Bhuyan: Writing—original draft, Visualization, Methodology, Formal analysis, Conceptualization, Data curation. Quinat Tasneem Rafique: Writing—original draft, Methodology, Conceptualization, Data curation. Vijay Gogoi: Writing—review & editing, Clinical insight. Pankaj Barah: Writing, review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

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Data availability All datasets used in this study are publicly accessible from NCBI-SRA under accession PRJNA591924 and PRJNA991320.

Declarations

Conflict of interest The authors declare no conflict of interest.

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