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Lower Oral Microbial Alpha Diversity and Greater Community Heterogeneity Among Adults with Depression: A Cross-Sectional Analysis of NHANES 2009-2012.

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Lower Oral Microbial Alpha Diversity and Greater Community Heterogeneity Among Adults with Depression: A Cross-Sectional Analysis of NHANES 2009-2012.

Abstract

Background**:** Growing evidence links microbial communities to mental health, but studies examining oral microbial diversity in depression have produced inconsistent findings and have often included small samples. Using a large population-based sample, we examined whether oral microbial diversity, overall community composition, and between-person heterogeneity differed by depression status and whether associations with alpha diversity persisted after adjustment for sociodemographic, behavioral, and oral-health factors.

Methods: We analyzed oral microbiome data from the 2009–2012 National Health and Nutrition Examination Survey (NHANES) using the DADA2 dataset with the SV1032 sequence variant removed. Depression was defined using a PHQ-9–based DSM-IV algorithm requiring five or more symptoms, including depressed mood or anhedonia. Four measures of microbial diversity within each participant were compared by depression status using one-way analysis of variance and Cohen's d. Differences in overall microbial composition between groups were assessed using PERMANOVA across three beta-diversity measures. To evaluate between-person heterogeneity, we compared how far each participant's microbial profile was from the average profile of their group (the group centroid). Multivariable logistic regression models examined associations between each alpha-diversity measure and depression after adjustment for sociodemographic, behavioral, and oral-health factors.

Results: The final sample included 7,681 adults (49.3% female; 4.9% with depression; mean age, 42 years). Participants with depression had lower oral microbial diversity across all four alpha-diversity measures (all $p < 0.05$), although the differences were small (Cohen's $d < 0.21$). Overall microbial composition also differed by depression status, but these differences were small (PERMANOVA $R^2 \leq$

0.0021; all p = 0.001). Participants with depression showed greater variability in microbial composition from one individual to another on two of the three beta-diversity measures (Bray–Curtis, p = 0.010; unweighted UniFrac, p = 0.001; weighted UniFrac, p = 0.337). After adjustment for sociodemographic, behavioral, and oral-health factors, greater alpha diversity remained associated with lower odds of depression across all four measures (all p < 0.05).

Conclusions: Depression was associated with lower oral microbial diversity after adjustment for sociodemographic, behavioral, and oral-health factors. Participants with depression also showed greater between-person variation in microbial composition on two of the three beta-diversity measures, suggesting that depression may not be associated with a single, uniform microbial pattern. Although these differences were small, longitudinal studies are needed to determine their direction and underlying mechanisms. This study was supported by NIH/National Institute of Dental and Craniofacial Research.

Key words
oral microbiome; depression; NHANES; population; mental health; alpha diversity; beta diversity

Background

Major depressive disorder (MDD), commonly referred to as depression, is a mental disorder characterized by long-term feelings of sadness or hopelessness (1). Symptoms of depression can significantly impair quality of life by affecting motivation, interpersonal relationships, and physical health. According to the National Institute of Mental Health, approximately 21 million adults, or 8.3% of adults in the U.S., reported having experienced at least one major depressive episode in 2021 (1). Depression has widespread societal consequences, as depressive symptoms have been associated with reduced work productivity, impaired daily functioning, and loss of employment (2). In addition, it is considered one of the leading psychiatric risk factors for suicide, which remains a leading cause of preventable death worldwide (3). Considering the impact and prevalence of this mental disorder, improving methods for the diagnosis and treatment of depression is a major goal of current research.

A wide range of sociodemographic and behavioral factors have been associated with mental health outcomes (4). Core demographic characteristics, including age, sex, race/ethnicity, and education level, contribute to baseline differences in depression risk (5-8). In addition, lifestyle factors such as physical activity, smoking history, and body mass index (BMI) can affect physiological processes closely linked to mental well-being, including inflammation and metabolic function (9-11). Socioeconomic conditions, as measured by the income-to-poverty ratio, may further shape access to resources and exposure to stressors that affect mental health (12). These factors are commonly considered in depression research due to their potential confounding effects.

Several treatments have proven to be effective in alleviating symptoms, such as behavioral therapy and antidepressant medications (13, 14). The earlier depressive symptoms are detected, the sooner these interventions can be implemented, which can help prevent the disorder from escalating further (15). Accordingly, a major focus of current depression research is to explore reliable methods for early diagnosis. Clinical depression is currently diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5), which requires the presence of at least one of two core symptoms, depressed mood or anhedonia, along with at least five total symptoms and clinically significant distress or functional impairment (16) In research and clinical settings, depressive symptoms are commonly assessed using the Patient Health Questionnaire 9 (PHQ 9), a standardized self-report questionnaire developed from the DSM symptom criteria for major depressive disorder (17). The summed score of its nine items provides a standardized measure of depressive symptom severity and is commonly used as a screening tool for depression.

In recent decades, the microbiome-brain axis has become a major area of research, with most studies focusing on the gut microbiome. This growth has been driven by initiatives such as the Human Microbiome Project (HMP) and advances in metagenomic sequencing technologies, which have enabled more detailed characterization of microbial composition and function (18). Simpson et al. (2021) noted that the body of literature investigating the gut microbiota in depressive disorders nearly doubled between

2019 and 2021 (19). Findings comparing alpha and beta diversity between depressed and non-depressed groups have been inconsistent, with some studies reporting reduced microbial diversity in depression and others finding no significant differences (20-22). Despite inconsistencies, studies consistently reported increased abundance of pro-inflammatory species in individuals with depression (19, 22). In addition, experimental evidence suggests that the microbiome may play a causal role in depressive symptoms. In one study, Kelly et al. (2016) performed fecal microbiota transplantation from patients with depression into microbiota-depleted rats and observed increased depression-like and anxiety-like behaviors in the recipients (23). Therefore, although alpha and beta diversity metrics may not reliably distinguish individuals with depression, other evidence supports the presence of depression-associated differences in the gut microbiome.

Based on current research, the oral microbiome may influence brain health through two main pathways (24). First, microbial signals and components may reach the brain through the trigeminal and olfactory pathways, potentially contributing to neuroinflammatory processes that affect mental function (25). Alternatively, dysbiosis of the oral microbiome can disrupt gut microbial communities after oral bacteria are swallowed, leading to downstream effects such as systemic inflammation, altered immune responses, and increased oxidative stress (26). Animal studies provide some direct support for a causal role of the oral microbiome in behavioral outcomes. For example, one study found that healthy control mice transplanted with saliva from mice exposed to chronic restraint stress (CRS) exhibited increased depressive-like behaviors (27). This study offers preliminary evidence that oral microbial dysbiosis can affect behavior. Together, these findings suggest that the oral microbiome may influence brain health through both direct and indirect mechanisms.

To investigate this relationship, we focused on oral microbial diversity because high diversity indicates a more stable and resilient community. Low-diversity communities are often more vulnerable to dysbiosis and the proliferation of harmful bacteria. To evaluate microbial diversity, studies commonly assess both alpha and beta diversity metrics. Alpha diversity describes the diversity within a single

microbial sample and includes two main factors: richness and evenness (28). Richness simply refers to the number of taxa present, whereas evenness reflects how evenly their abundances are distributed. In contrast, beta diversity measures differences in composition between microbial samples using distance or dissimilarity metrics (29).

Given the growing interest in the oral microbiome-brain axis, the present study aims to evaluate whether oral microbiome alpha and beta diversity differ by depression status and to determine which diversity metrics most effectively capture these associations. We additionally compare the magnitude of these associations with those of established depression risk factors in multivariable models.

Methods

Study Population and Data Source

We used data from the 2009–2010 and 2011–2012 cycles of the National Health and Nutrition Examination Survey (NHANES), the only cycles with available oral microbiome data. NHANES is a nationally representative survey conducted by the National Center for Health Statistics (NCHS). We included adults aged ≥18 years with available oral microbiome diversity data and sufficient Patient Health Questionnaire-9 (PHQ-9) responses to classify depression status. Participants with missing covariate data were retained using imputation as described below.

Depression Classification

Although some studies define depression using a summed PHQ 9 score of 10 or higher as a screening threshold (30), we used the PHQ 9 diagnostic algorithm, which is based on the DSM symptom criteria for major depressive disorder and has been shown to provide greater specificity than a summed PHQ 9 score threshold (31). Specifically, individuals were classified as depressed if they endorsed at least one core symptom, either anhedonia or depressed mood (score of 2 or higher), along with five or more total symptoms rated 2 or higher, including suicidal ideation (score of 1 or higher) (31). This stricter definition ensured that all participants classified as depressed also had PHQ 9 scores of 10 or higher; however, not

all individuals with PHQ 9 scores of 10 or higher met the PHQ 9 diagnostic algorithm and were therefore not included in our depressed group.

The DSM criterion of clinically significant distress or functional impairment (DPQ100) was not incorporated into our depression classification because responses were unavailable for a substantial proportion of NHANES participants. This approach aligns with depression classification used in previous NHANES based studies and literature (31, 32).

Covariates

Sociodemographic and behavioral data

Sociodemographic, behavioral, and health-related covariates were selected a priori based on established associations with depression and/or the oral microbiome. These included age, sex, race/ethnicity, education level, family income-to-poverty ratio, body mass index (BMI), smoking history (≥100 lifetime cigarettes), vigorous work-related physical activity, active transportation, vigorous recreational activity, and self-rated oral health.

Race/ethnicity was categorized as Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, or Other/multiracial. Education was categorized as less than 9th grade, 9th–11th grade, high school graduate/GED, some college/associate degree, or college graduate or above. Self-rated oral health was categorized as excellent, very good, good, fair, or poor.

Microbiome Data

Oral microbiome profiles were generated by the National Center for Health Statistics (NCHS) using 16S rRNA gene sequencing of oral rinse samples collected during NHANES 2009–2012. We used the “Remove SV1032” version of the microbiome dataset, which filters out potentially misclassified sequence variants to improve taxonomic accuracy. All microbial diversity metrics, including alpha and beta diversity measures, were precomputed and provided by NCHS.

For alpha diversity, NHANES provides multiple rarefaction depths ranging from 1,000 to 10,000 sequencing reads, with several subsampled estimates at each depth to account for variability in sequencing depth. We selected a rarefaction depth of 6,000 reads, as it represented the highest sequencing depth while retaining a large proportion of participants, thereby balancing sequencing depth with sample size. The average value across subsamples at this depth was calculated to represent each individual's alpha diversity for the four metrics analyzed.

Statistical Analysis

Alpha Diversity

We analyzed four NHANES-provided alpha diversity metrics: Observed Operational Taxonomic Units (OTUs), Faith's Phylogenetic Diversity, Shannon diversity, and Inverse Simpson diversity. Unadjusted differences in alpha diversity between participants with and without depression were evaluated using one-way analysis of variance (ANOVA). Cohen's d was calculated using the pooled standard deviation to quantify effect sizes, with negative values indicating lower alpha diversity among participants with depression. Boxplots were generated to visualize the distributions of alpha diversity by depression status.

Beta Diversity

Microbial community composition was assessed using three beta diversity metrics: dissimilarity, Unweighted UniFrac, and Weighted UniFrac. Group differences in microbial composition by depression status were tested using permutational multivariate analysis of variance (PERMANOVA). To assess within-group microbial heterogeneity (beta-dispersion), we calculated the distance of each sample to the centroid of its respective group using the betadisper function in the vegan package, following the approach of Pereira et al (33). Differences in beta-dispersion between groups were evaluated using a permutation test with 999 permutations. Greater distance to the group centroid indicates greater within-group microbial heterogeneity (lower similarity among individuals within the group).

Multivariable Regression

We assessed the association between oral microbiome diversity and depression using separate multivariable logistic regression models for each alpha diversity metric. Each model included one diversity metric as the primary exposure and adjusted for all covariates described previously, including demographic, behavioral, and oral health factors. Results are reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and p-values.

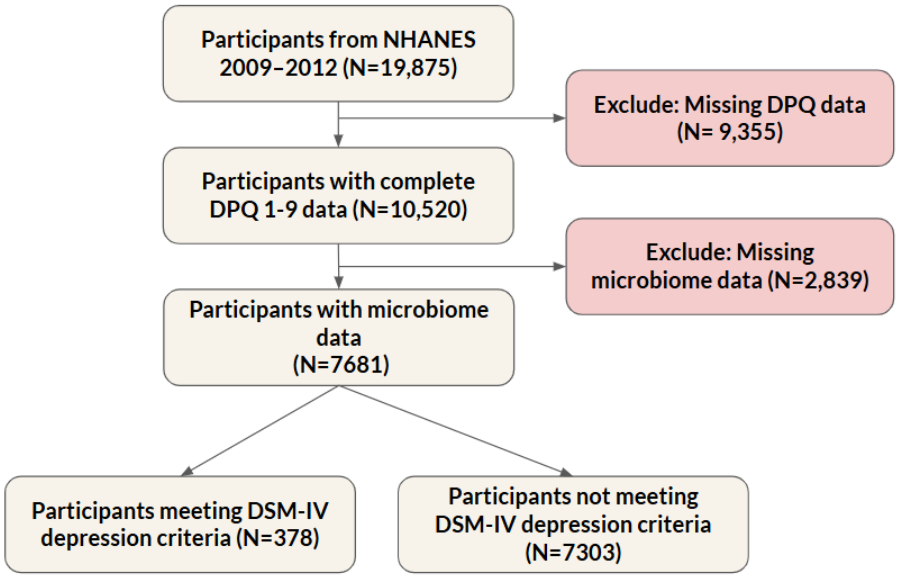
Continuous covariates were analyzed on their original scale without centering or standardization. To handle missing data, NHANES-specific codes for missing or unreliable responses (e.g., 7, 9, 77, 999) were first recoded as missing (NA). Continuous variables were imputed using mean imputation, while categorical variables were imputed using the most frequently occurring value (mode). All categorical variables were subsequently converted to factors for inclusion in the regression models.

Results

Descriptive Statistics

The final sample included 7,681 participants aged 18 to 69 years from the 2009–2012 NHANES cycles. A total of 378 individuals (4.9%) met criteria for depression according to DSM diagnostic criteria. Participant characteristics are summarized in Table 1 and Table 2. Missingness was generally low, with the highest proportions observed for self-rated oral health (14.9%), family income-to-poverty ratio (7.8%), and education (6.3%).

Figure 1 Participant selection flow diagram.



Flow diagram illustrating participant inclusion and exclusion for the final analytic sample. Participant counts were derived from the NHANES 2009–2012 documentation (34, 35).

Table 1 Categorical Variable Descriptions and Summary Statistics

Characteristic	Category	n (%)	Missing (%)
Education	Less than 9th grade	631 (8.8)	6.3
	9th–11th grade	1,063 (14.8)	
	High school/GED	1,569 (21.8)	
	Some college/Associate degree	2,190 (30.4)	
	College graduate or higher	1,738 (24.1)	
Self-rated oral health	Excellent	649 (9.9)	14.9
	Very good	1,249 (19.1)	
	Good	2,415 (36.9)	
	Fair	1,470 (22.5)	
	Poor	747 (11.4)	
Sex	Male	3,894 (50.7)	0
	Female	3,787 (49.3)	
Race/ethnicity	Mexican American	1,277 (16.6)	0
	Other Hispanic	792 (10.3)	
	Non-Hispanic White	2,934 (38.2)	
	Non-Hispanic Black	1,827 (23.8)	
	Other race/multiracial	851 (11.1)	
Ever smoked ≥100 cigarettes	Yes	3,161 (43.9)	6.3

Characteristic	Category	n (%)	Missing (%)
	No	4,036 (56.1)	
Vigorous work activity	Yes	1,469 (19.1)	0
	No	6,210 (80.8)	
Walks/bicycles for transportation	Yes	2,441 (31.8)	0
	No	5,239 (68.2)	
Vigorous recreational activity	Yes	1,943 (25.3)	0
	No	5,737 (74.7)	
Depression status (DSM-IV)	No	7,303 (95.1)	0
	Yes	378 (4.9)	

Table 2 Continuous Variable Descriptions and Summary Statistics

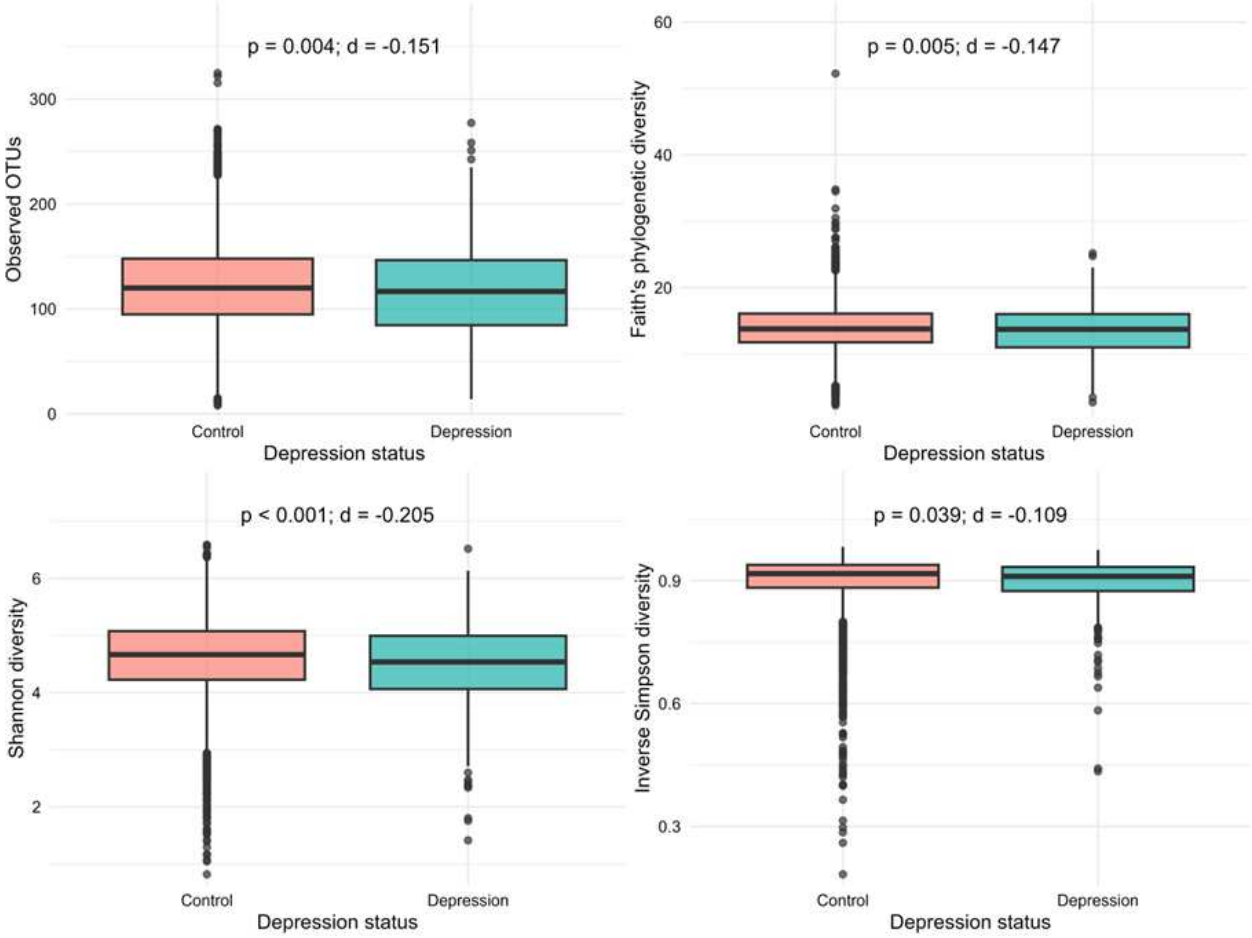
Characteristic	N	Missing (%)	Mean ± SD	Range
Age (years)	7,681	0.0	42.25 ± 15.25	18–69
Body mass index (kg/m²)	7,628	0.7	29.04 ± 7.05	13.6–82.1
Family income-to-poverty ratio	7,080	7.8	2.42 ± 1.68	0–5
Observed OTUs (richness)	7,681	0.0	122.68 ± 41.12	8.0–324.7
Faith's phylogenetic diversity	7,681	0.0	13.97 ± 3.38	2.24–52.25
Shannon diversity (richness + evenness)	7,681	0.0	4.61 ± 0.70	0.82–6.59
Inverse Simpson diversity (diversity + dominance)	7,681	0.0	0.90 ± 0.06	0.18–0.98

Microbiome Diversity by Depression Status

Alpha Diversity

All four oral microbiome alpha diversity indices were significantly lower among individuals with depression compared with those without (Figure 2). While statistically significant, these differences were characterized by small effect sizes (Cohen’s d ranging from −0.109 to −0.205), suggesting modest differences in oral microbial richness and diversity between groups.

Figure 2 *Alpha diversity metrics of the oral microbiome by depression status.*



Boxplots show (A) Observed OTUs, (B) Faith's phylogenetic diversity, (C) Shannon diversity, and (D) Inverse Simpson diversity among participants with and without depression. P-values represent unadjusted between-group comparisons using one-way analysis of variance (ANOVA). Cohen's d represents the standardized mean difference between participants with and without depression; negative values indicate lower alpha diversity among participants with depression.

Beta Diversity

Beta diversity analyses demonstrated statistically significant but small differences in overall oral microbial community composition by depression status across all three distance metrics (PERMANOVA, all $p = 0.001$; $R^2 = 0.00099–0.00205$; Table 3). Tests of multivariate dispersion were significant for Bray–Curtis and unweighted UniFrac, indicating greater within-group heterogeneity in oral microbial community composition among participants with depression (Figure 3). These differences in dispersion

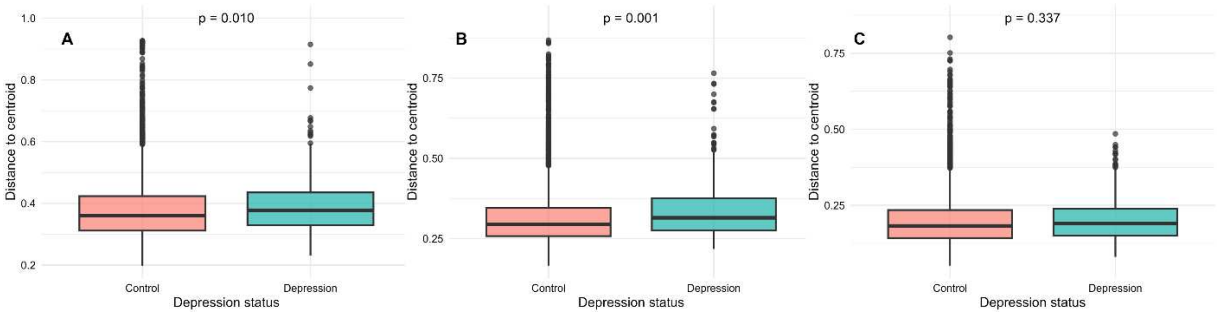
may partially contribute to the observed PERMANOVA results. In contrast, weighted UniFrac showed no significant difference in dispersion (Table 3).

Table 3 *Beta diversity analyses comparing oral microbiome composition by depression status.*

Beta diversity metric	PERMANOVA R^2	PERMANOVA p	Betadisper p
Bray–Curtis dissimilarity	0.00121	0.001	0.010
Unweighted UniFrac	0.00099	0.001	0.001
Weighted UniFrac	0.00205	0.001	0.337

PERMANOVA R^2 represents the proportion of variation in oral microbial community composition explained by depression status. PERMANOVA p-values test for differences in overall microbial community composition between groups, whereas betadisper p-values test for differences in within-group dispersion (heterogeneity).

Figure 3 *Beta diversity dispersion by depression status.*



*Panels show **(A)** Bray–Curtis dissimilarity, **(B)** Unweighted UniFrac distance, and **(C)** Weighted UniFrac distance. Greater distances to the group centroid indicate greater within-group heterogeneity in oral microbial community composition. P-values indicate differences in dispersion between participants with and without depression.*

Adjusted Associations Between Oral Alpha Diversity and Depression

All four alpha diversity metrics were significantly associated with reduced odds of depression in the multivariate logistic regression models (Table 4). The strongest association was observed for Shannon diversity, whereas the inverse Simpson index demonstrated a wider confidence interval, indicating greater uncertainty in the estimated effect. These associations remained consistent across models adjusted for sex, age, race/ethnicity, education, income, BMI, smoking, physical activity, and oral health status. Across all

four multivariable models, lower income, female sex, higher BMI, smoking, poor self-rated oral health, and lack of vigorous recreational physical activity were consistently associated with increased odds of depression (Supplemental Table 1).

Table 4 *Association between alpha diversity and depression across multivariate logistic regression models*

Alpha Metric	OR	95% CI	p-value
Observed OTUs	0.995	0.993 – 0.998	<0.001
Faith's Phylo. Diversity	0.945	0.915 – 0.976	<0.001
Shannon Index	0.751	0.653 – 0.867	<0.001
Inverse Simpson Index	0.200	0.048 – 0.937	0.033

ORs represent the association between each alpha diversity metric and odds of depression. Models were adjusted for sex, age, race/ethnicity, education, family income-to-poverty ratio, body mass index, smoking, physical activity, and self-rated oral health. OR, odds ratio; CI, confidence interval.

Discussion

In this study, we examined the relationship between oral microbiome diversity and depression in 7,681 adults from the 2009–2012 NHANES cycles. In unadjusted alpha and beta diversity analyses, individuals with depression demonstrated significantly lower oral microbial diversity across all four alpha diversity metrics (Observed OTUs, Faith's Phylogenetic Diversity, Shannon Index, and Inverse Simpson Index), although effect sizes were small (Cohen's $d < 0.205$). Beta diversity analyses also revealed statistically significant but small differences in microbial community composition, with depressed individuals exhibiting greater within-group dispersion, particularly for Bray-Curtis and Unweighted UniFrac metrics. This pattern suggests that while depressed individuals tended to have lower overall diversity, their microbial communities were also more variable. This greater variability may reflect the biological and behavioral heterogeneity of depression, which is influenced by factors such as age, sex,

physical activity, smoking, and socioeconomic status, each of which may differentially shape the oral microbiome across individuals (5, 6, 9, 10, 12).

In multivariable logistic regression models adjusting for demographic, behavioral, and oral health covariates, all four alpha diversity metrics remained independently associated with depression, with Shannon diversity showing the strongest. Because the Shannon index incorporates both microbial richness and evenness, this finding may reflect broader disruption in microbial community balance rather than loss of taxa alone (28). Based on distance from the null odds ratio of 1.0, the association between Shannon diversity and depression was broadly comparable in magnitude to established socioeconomic and behavioral factors such as income and smoking status, stronger than the association observed for BMI, but weaker than those observed for female sex, physical inactivity, and poor self-rated oral health. These consistent findings across multiple diversity metrics support a potential relationship between oral microbiome dysbiosis and depression.

Our findings are consistent with and extend those of prior NHANES-based studies examining the relationship between oral microbiome diversity and depression. Similar to Qiu et al. (2025) and Zheng et al. (2025), we observed significant associations between reduced oral microbial diversity and depression using 16S rRNA sequencing data from the 2009–2012 NHANES cycles (30, 36). However, our analysis expands upon these studies in several important ways. We evaluated a broader range of alpha diversity metrics, including measures incorporating microbial evenness that were not examined in prior NHANES studies. This included the Shannon index, which demonstrated the strongest association with depression. We also utilized stricter DSM diagnostic criteria for depression classification and included additional covariates such as physical activity and self-rated oral health measures. Additionally, we contextualized the magnitude of microbiome associations relative to established depression risk factors such as income, smoking, BMI, and physical inactivity.

While NHANES studies consistently identified depression-related differences in alpha and beta diversity, the oral microbiome literature showed a pattern of mixed findings similar to that previously

reported for the gut microbiome (19, 21, 22). In our review of oral microbiome studies with fewer than 100 participants, some reported significant differences in both alpha and beta diversity measures, whereas others reported differences in only one measure or neither (20, 24, 37-39). One possible explanation for these inconsistencies is the greater interpersonal heterogeneity in microbial community composition among individuals with depression observed in our beta diversity analyses. This heterogeneity may leave smaller studies underpowered to detect differences in alpha and beta diversity. This pattern highlights the value of large population-based cohorts for detecting microbiome associations.

This study has several limitations. Its cross-sectional design prevents determining whether oral microbiome differences precede depression, result from depression, or reflect shared underlying factors. Depression was identified using self-reported PHQ-9 symptoms rather than a clinical diagnostic interview, creating the possibility of misclassification. Additionally, the relatively small proportion of participants with depression (4.9%) resulted in unequal group sizes and may have limited the reliability of comparisons between groups. Residual confounding remains possible, particularly from factors such as antibiotic use and detailed dietary patterns, and mean and mode imputation may have introduced bias if covariate data were not missing at random. Finally, 16S rRNA sequencing provides limited species-level and functional information, and we did not examine associations with specific microbial taxa (40). Furthermore, we did not investigate associations between depression and specific microbial taxa.

As a next step, future research should further investigate the causal and mechanistic bases of the observed relationship between oral microbiome diversity and depression. Currently proposed mechanisms include systemic inflammation, immune dysregulation, and bidirectional signaling through the oral-gut-brain axis. Recent reviews have highlighted the ability of oral pathogens and byproducts, including lipopolysaccharides and gingipains, to influence neuroinflammatory pathways through immune and endocrine signaling mechanisms (41). Longitudinal and mechanistic studies are therefore needed to determine whether differences in the oral microbiome contribute directly to depression or are consequences of depression-related behaviors or inflammation. In addition to studying the oral microbiome, future studies may benefit from integrating complementary salivary biomarkers of

neuroendocrine function, stress, and immune activity (e.g., cortisol, melatonin, α-amylase, chromogranin A, and secretory immunoglobulin A) (42, 43). These approaches together may provide a more comprehensive understanding of the biological pathways linking oral health and depression. Clarifying the directionality of the relationship may help identify whether interventions targeting the oral microbiome could have preventive or therapeutic use in mental health.

If validated in longitudinal and mechanistic studies, oral microbiome profiling may eventually have clinical utility not only as a noninvasive biomarker for depression risk monitoring, but also as a potential therapeutic target. Saliva-based diagnostics have gained increasing attention because saliva is easily accessible, inexpensive to collect and noninvasive compared with many traditional diagnostic methods (44). Salivary biomarkers are already being investigated for several neurologic disorders, including Parkinson's disease, highlighting growing interest in saliva as a clinically practical diagnostic medium (45). In parallel, emerging microbiome intervention research has suggested that probiotics, prebiotics, and synbiotics may modestly improve depressive symptoms through effects on inflammatory, immune, and neuroendocrine pathways (21). Although the present findings are insufficient for clinical application or causal inference, they support continued investigation into the oral microbiome as both a potential biomarker and biologically relevant contributor to depression, further reinforcing the broader connection between oral and systemic health.

Conclusions

Reduced oral microbiome diversity was significantly associated with depression across multiple alpha and beta diversity frameworks in a nationally representative NHANES cohort. Depressed individuals demonstrated not only lower overall microbial diversity, but also greater interpersonal heterogeneity in microbial community composition, suggesting that oral microbiome alterations in depression may reflect a biologically heterogeneous process. Although causality cannot be inferred from this cross-sectional analysis, these findings support continued investigation into the oral microbiome as a potential

contributor to depression pathophysiology and a future target for biomarker development and microbiome-based interventions.

List of Abbreviations

ANOVA: analysis of variance; BMI: body mass index; CI: confidence interval; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HMP: Human Microbiome Project; MDD: major depressive disorder; NCHS: National Center for Health Statistics; NHANES: National Health and Nutrition Examination Survey; OR: odds ratio; OTU: operational taxonomic unit; PERMANOVA: permutational multivariate analysis of variance; PHQ-9: Patient Health Questionnaire-9; rRNA: ribosomal ribonucleic acid; SD: standard deviation.

Declarations

Ethics approval and consent to participate

The National Health and Nutrition Examination Survey (NHANES) protocols were approved by the National Center for Health Statistics Research Ethics Review Board, and written informed consent was obtained from all participants prior to participation. The present study is a secondary analysis of publicly available, de-identified NHANES data and was therefore exempt from additional institutional review board approval.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are publicly available from the National Health and Nutrition Examination Survey (NHANES) website (https://www.cdc.gov/nchs/nhanes/). The analysis code used in this study is available and will be shared upon article acceptance. It is not provided here to remain anonymous during the peer review process.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
Initials are not listed to remain anonymous, and placeholders ("XX") are inserted. XX contributed to study design, performed the statistical analyses, interpreted the data, and drafted the manuscript. XX drafted the manuscript, performed literature review, and reviewed the methodology. XX contributed to study design. XX contributed to study design, supervised the project, and critically revised the manuscript. All authors read and approved the final manuscript.

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