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BASIC RESEARCH:

Secondary Analysis of Public Metagenomic Data Identifies Periodontal Pathogens in the Oral but Not Gut Microbiome

Un análisis secundario de datos metagenómicos públicos identifica patógenos periodontales en el microbioma oral, pero no en el intestinal

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ABSTRACT: The oral microbiome, particularly periodontopathogens, may influence the gut microbiome. The aim of this study was to assess the correspondence, diversity, and abundance of periodontopathogenic bacteria in oral and fecal samples from healthy adults. Secondary analyses of 12 public sequences from 6 healthy women, matched by anatomical site (gut and oral cavity), were performed using 16S rRNA-based metagenomics. The sequences were obtained from the BioProject PRJNA834584, published by the Chinese University of Hong Kong, with data generated via Illumina MiSeq. The Shaman application, which relies on Vsearch and DESeq2 for R, along with the Silva database, facilitated the determination of differential abundance and diversity at the species and genus levels between anatomical sites. After dereplication and removal of singletons and chimeras, 352 OTUs were identified. Taxonomic assignment resulted in 148 genera and 80 species, corresponding to 88.64% and 25.85% of annotations, respectively. The dendrogram displayed two distinct clusters separating oral and faecal samples, and principal coordinate analysis accounted for 53.7% of the variance by anatomical site (Permanova test, p=0.003). The Shannon diversity index was 2.14 (95% CI: 1.55-2.73) for fecal samples and 2.28 (2.03-2.53) for oral samples. The Simpson index was 0.70 (0.53-0.88) for faecal samples and 0.82 (0.76-0.88) for oral samples. Periodontopathogenic bacteria were found exclusively in oral samples, with variations in frequency. No periodontopathogenic species were detected in fecal samples. The human microbiome from two different niches in healthy adults shows distinct bacterial compositions between the oral cavity and the gut, with *Bacteroides* predominating in faecal samples and *Streptococcus* in oral

samples. Greater richness was observed in faecal samples. Both microbiomes exhibited high bacterial diversity, with no significant differences.

KEYWORDS: Human microbiome; 16s ribosomal RNA; Metagenomic.

RESUMEN: El microbioma oral, particularmente los periodontopatógenos, puede influir en el microbioma intestinal. El objetivo de este estudio fue evaluar la correspondencia, diversidad y abundancia de bacterias periodontopatógenas en muestras orales y fecales de adultos sanos. Este fue un análisis secundario de 12 secuencias públicas de un estudio previo, provenientes de 6 mujeres sanas, emparejadas por sitio anatómico (intestino y cavidad oral), utilizando metagenómica basada en 16S rRNA. Las secuencias se obtuvieron del BioProject PRJNA834584, publicado por la Universidad China de Hong Kong, y los datos fueron generados mediante Illumina MiSeq. La aplicación Shaman, basada en Vsearch y DESeq2 para R, junto con la base de datos Silva, permitió determinar la abundancia diferencial y diversidad a nivel de especies y géneros entre los sitios anatómicos. Tras la desreplicación y eliminación de singletons y quimeras, se identificaron 352 OTUs. La asignación taxonómica resultó en 148 géneros y 80 especies, correspondientes al 88.64% y 25.85% de las anotaciones, respectivamente. El dendrograma mostró dos grupos distintos que separaban las muestras orales y fecales, y el análisis de coordenadas principales explicó el 53.7% de la varianza por sitio anatómico (prueba Permanova, p=0.003). El índice de diversidad de Shannon fue de 2.14 (IC 95%: 1.55-2.73) en muestras fecales y de 2.28 (2.03-2.53) en muestras orales. El índice de Simpson fue de 0.70 (0.53-0.88) para muestras fecales y de 0.82 (0.76-0.88) para muestras orales. Las bacterias periodontopatógenas se encontraron únicamente en las muestras orales, con variaciones en frecuencia. No se detectaron especies periodontopatógenas en las muestras fecales. El microbioma humano de dos nichos diferentes, en adultos sanos, muestra composiciones bacterianas distintas entre la cavidad oral y el intestino, siendo *Bacteroides* predominante en muestras fecales y *Streptococcus* en orales, con mayor riqueza en las muestras fecales. Ambos microbiomas mostraron alta diversidad bacteriana, sin diferencias significativas.

KEYWORDS: Microbioma humano; ARN ribosómico 16s; Metagenómica.

INTRODUCTION

The digestive system serves as a critical entry point for microorganisms that have co-evolved with humans, establishing a symbiotic balance vital for bodily functions and processes (1). The gastrointestinal microbiome is an assembly of microbes, including commensal, symbiotic, and pathogenic organisms, which occupy the body's space and play a pivotal role in health and disease (2).

The oral and gastrointestinal microbiomes constitute the mouth-gut axis, sharing immunological tolerance mechanisms. These mucosal surfaces interact with antigens and external molecules through ingestion or inhalation (3).

The focus of this study is the gastrointestinal tract, which has specialized functions and contains distinct microbial communities. These communities are instrumental in food digestion, nutrient absorp-

tion, waste elimination, and are key to the development and maintenance of the immune response (4).

The gut microbiome boasts the highest diversity within the human body, with the oral microbiome ranking second. Despite their differences, they share genetic elements (5). The intestinal microbiome comprises approximately 100 trillion microorganisms, predominantly from the phyla *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*. Common genera include *Bacteroides* and *Bifidobacterium*, while *Lactobacilli* and *Streptococci* are found in smaller proportions (6).

In contrast, the oral microbiome consists of roughly 770 prokaryotic species, along with fungi, viruses, and protozoa. Its dynamism stems from the variety of niches within the oral cavity, such as teeth, tongue, and gums. Its primary phyla include *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Spirochaetes*, and *Fusobacteria*, existing in biofilms (7).

A prior study, utilizing a meta-analysis of 1,473 samples from the oral cavity and 2,182 intestinal metagenomes, demonstrated significant genetic diversity within the microbiome. It also found shared genomic sequences between these two anatomical sites. The research revealed that half of the genes in a metagenomic sample are unique to an individual, suggesting that personal microbiomes can be distinguished by certain rare microbial species exclusive to each person (5).

Despite the connection between oral and gut microbiomes, the extent of the influence of oral bacteria on systemic health remains complex. Further investigation is necessary to elucidate the implications of periodontal disease on overall health. This study aims to assess the correspondence, diversity, and bacterial abundance in oral and faecal samples from healthy adults, employing metagenomic analysis based on 16S rRNA.

While the oral and gut microbiomes are interlinked, the precise influence of oral bacteria on systemic health is intricate and warrants additional research to grasp the full impact of periodontal disease on general well-being. Variations in the array of bacteria associated with gum disease in oral and faecal samples from healthy individuals could indicate notable differences in microbial composition related to oral health status. Consequently, the aim of this study was to estimate the correspondence, diversity, and bacterial abundance in oral and faecal samples from healthy adult subjects, through a metagenomic analysis based on 16S rRNA.

METHODS

This is a study based on a secondary analysis of previously published sequences.

SEQUENCES SEARCH

To locate sequences for analysis, a systematic search was performed in the MGNIFY database of the European Molecular Biology Laboratory (EMBL) and the National Library of Medicine's (NLM) BioProject using the terms "human gut," "oral," and "metagenome." The search specifically targeted amplicon samples that had FASTQ files readily accessible for download. Out of three studies identified, the study conducted in China featured the most extensive collection of samples available for download. Table 1 provides a summary of the identified studies, including their country of origin, as well as the type and quantity of samples available in each.

The study titled "Human Oral-Gut Microbiota Axis in Health" utilized amplicon-based assays, adopted the Illumina MiSeq sequencing approach, and incorporated associated metadata to identify participants who fit the criteria for the present investigation. Details of the original study from which the sequences were derived are accessible at [NCBI BioProject PRJNA834584] (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA834584). Table 1 outlines the principal attributes of this foundational research. Table 2 presents the characteristics of the study from which the sequences were sourced.

SELECTION CRITERIA

Samples were selected from participants who fulfilled the following inclusion criteria: age range of 23-65 years, body mass index (BMI) between 18.5-24.9 kg/m², a Bristol stool scale score of 4, absence of antibiotic usage, abstention from alcohol consumption, non-smoking status, systolic blood pressure below 120 mm Hg, diastolic blood pressure under 80 mm Hg, and waist circumference less than 87 cm for males and under 80 cm for females. A total of six women conformed to these specifications, yielding 12 samples comprising one faecal sample and one oral rinse sample per participant. These are detailed in Table 3.

DATA ANALYSIS

Upon acquisition of the sequences in. fastq format, the SHAMAN application (https://shaman.pasteur.fr/), an open-access resource for differential metagenomic data analysis, was employed. This platform facilitates both statistical evaluation and graphical representation of the findings. SHAMAN's bioinformatic workflow utilizes Vsearch for sequence processing and the DESeq2 R package for statistical analysis, which employs a Generalized Linear Model to detect features with differential abundance across comparative groups.

The analytical procedure within SHAMAN encompasses several critical steps: 1) Operational Taxonomic Unit (OTU) selection, which includes dereplication, noise reduction, chimera elimination, and clustering. 2) Quantification of OTUs present in each sample. 3) Annotation of OTUs using a curated taxonomic reference database (9).

Subsequent to these steps, comprehensive tables and visualizations were generated for the differential analysis of the metagenomic data, focusing on 16S ribosomal RNA. The Silva database was utilized for the annotation process.

Table 1. Studies with available sequences, type of information and country of origin.

Country	Study Title	Accession number	Sample Type	Number of Samples
Italy	Lifestyles and gut microbiome composition	SRP291976	human gut metagenome	40
USA	Dysbiosis and alterations in predicted functions of the subgingival microbiome in chronic periodontitis	PRJNA269205	human oral metagenome	50
China	Human oral-gut microbiota axis in health	PRJNA834584	human oral metagenome	940

Table 2. Characteristics of the Source Study for the Obtained Sequences.*

BioProject	PRJNA834584
Consent	Public
Assay Type	Amplicon
BioSampleModel	MIGS/MIMS/MIMARKS.human-associated, MIMARKS.survey
Center Name	The Chinese University Of Hong Kong
Collection_Date	missing
DATASTORE filetype	FASTQ, SRA
DATASTORE provider	GS, S3
DATASTORE region	gs.US, s3.us-east-1
Ethnicity	chinese
geo_loc_name_country	Hong Kong
geo_loc_name_country_continent	Asia
geo_loc_name	Hong Kong
Host	Homo sapiens
Instrument	Illumina MiSeq
Lat_Lon	22.18 N 114.10 E
LibraryLayout	Paired
LibrarySelection	PCR
LibrarySource	Metagenomic
Platform	Illumina
ReleaseDate	2022-10-19
SRA (Sequence Read Archive) Study	SRO373282

*Download link of sequences:
https://www.ncbi.nlm.nih.gov/Traces/study/?uids=21597576%2C21597354%2C21597218%2C21597152%2C21597140%2C21597130%2C21597112%2C21596996%2C21596892%2C21596645%2C21596552%2C21596500%2C21596392%2C21596378%2C21596339%2C21596338%2C21596301%2C21596281%2C21596270%2C21596156%2C21596150%2C21596148%2C21596088%2C21596046%2C21596043%2C21596036&o=acc_s%3Aa#

Table 3. Sample associated characteristics.

Run	Sample ID	Subject ID	Age	Sample type
SRR19047639	HM0005_stool	HM0005	57	Faecal
SRR19047214	HM0005_oral	HM0005	57	Oral
SRR19047254	HM0109_stool	HM0109	23	Faecal
SRR19047092	HM0109_oral	HM0109	23	Oral
SRR19046934	HM0233_stool	HM0233	24	Faecal
SRR19047038	HM0233_oral	HM0233	24	Oral
SRR19046926	HM0248_stool	HM0248	54	Faecal
SRR19047311	HM0248_oral	HM0248	54	Oral
SRR19047200	HM0259_stool	HM0259	48	Faecal
SRR19047291	HM0259_oral	HM0259	48	Oral
SRR19047458	HM0388_stool	HM0388	65	Faecal
SRR19047551	HM0388_oral	HM0388	65	Oral

RESULTS

The annotation success rate at the genus level reached 88.64%, resulting in the taxonomic assignment of 148 genera within the samples.

In the group analysis, the dendrogram depicted in Figure 1 demonstrates distinct clustering of oral and faecal samples. The oral samples distinctly aggregate within the left cluster, whereas the faecal samples are clearly grouped on the right, indicating a separation based on sample origin.

In the principal component analysis (PCA), it was determined that 68.81% of the variance within the model is attributable to the anatomical site from which the sample was obtained. Correspondingly, the principal coordinates analysis (PCoA) revealed analogous clustering of samples by anatomical site, accounting for 53.7% of the model's variance ascribed to this factor (Permanova test, p=0.003). This pattern is visually represented in Figure 2.

Among the genera annotated during the analysis, 74 displayed differential features when contrasting oral sites with faecal samples. Notably, a greater number of distinct genera were present in the faecal samples (indicated in green), as illustrated in Figure 3.

The analysis of the most abundant genera in both sample types reveals a clear dominance of the genus *Bacteroides* in faecal samples, accounting for 72.5% of the total. This is followed by smaller proportions of the genera *_Prevotella*_9, *Faecalibacterium*, *Streptomyces*, *Alistipes*, *Fusobacterium*, *Haemophilus*, and *Streptococcus*. Conversely, oral samples are predominantly composed of *Streptococcus*, representing 46.3%, and *Neisseria*, at 16.9%. Other notable genera include *Gemella*, *Fusobacterium*, *Haemophilus*, *Porphyromonas*, *Prevotella*_7, and *Streptomyces*, as depicted in Figure 4.

Bacteroides predominates in faecal samples, accounting for 72.5% of the total abundance. It is followed by the genera *Prevotella*_9, *Faecalibacterium*, *Streptomyces*, *Alistipes*, *Fusobacterium*, *Haemophilus*, and *Streptococcus*, albeit in smaller proportions. Conversely, oral samples exhibit a predominance of *Streptococcus* at 46.3% and *Neisseria* at 16.9%. Additional genera present in oral samples include *Gemella*, *Fusobacterium*, *Haemophilus*, *Porphyromonas*, *Prevotella*_7, and *Streptomyces* (Table 4).

With respect to the diversity within oral and faecal niches, it was found that both anatomical sites possess considerable microbiome diversity. In terms of Alpha diversity, indicative of species richness or the mean species count within a specific habitat, faecal samples demonstrated higher diversity (62.83 CI: 51.54-74.13) in comparison to oral samples (52.33 CI: 46.79-57.87); however, this difference did not reach statistical significance. Beta diversity, denoting the variation between distinct habitats, was more pronounced in faecal samples (0.67) relative to oral samples (0.43). Similarly, Gamma diversity, which represents the overall species richness across each anatomical site, was greater for faecal samples (105) than for oral samples (75).

The Shannon diversity index, which measures species abundance and evenness, presented comparable values for the two anatomical sites: 2.14 for faecal samples and 2.28 for oral samples. Simpson's diversity index, reflecting the probability that two individuals randomly selected from a

sample will belong to the same species, also indicated similar trends, with faecal samples scoring 0.70 and oral samples scoring 0.82. Regarding beta diversity, which assesses the diversity between different communities, faecal samples displayed greater diversity in comparison to oral samples. These findings are summarized in Table 5.

At the species level, certain periodontopathogenic bacteria were identified in oral samples with varying frequencies, yet were absent in faecal samples. These included *Porphyromonas gingivalis* in 1 out of 6 samples, *Filifactor alocis* in 2 out of 6 samples, *Prevotella nigrescens* in all 6 samples, and T*reponema denticola* in 3 out of 6 samples.

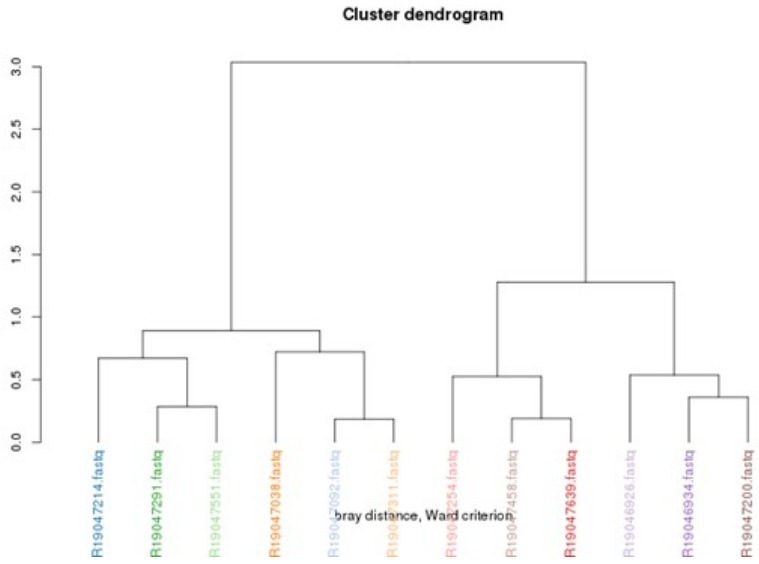

Figure 1. Cluster dendrogram with Bray distance, Ward criterion.

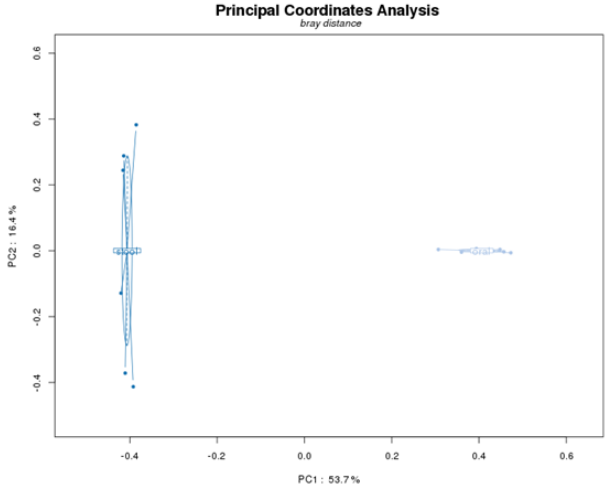

Figure 2. Principal Coordinates Analysis.

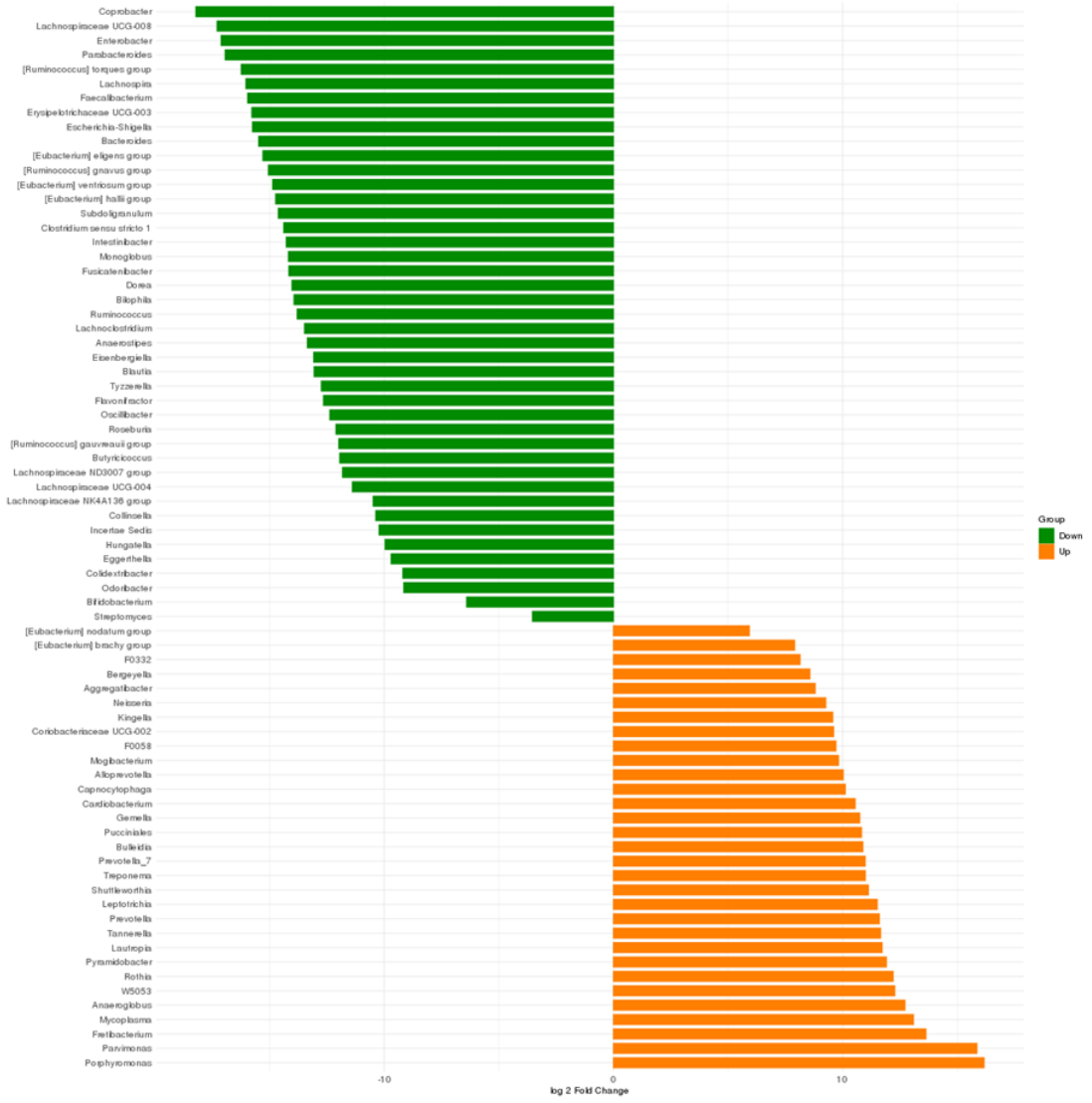

Figure 3. Barchart of differential genders. Oral vs stool contrast.

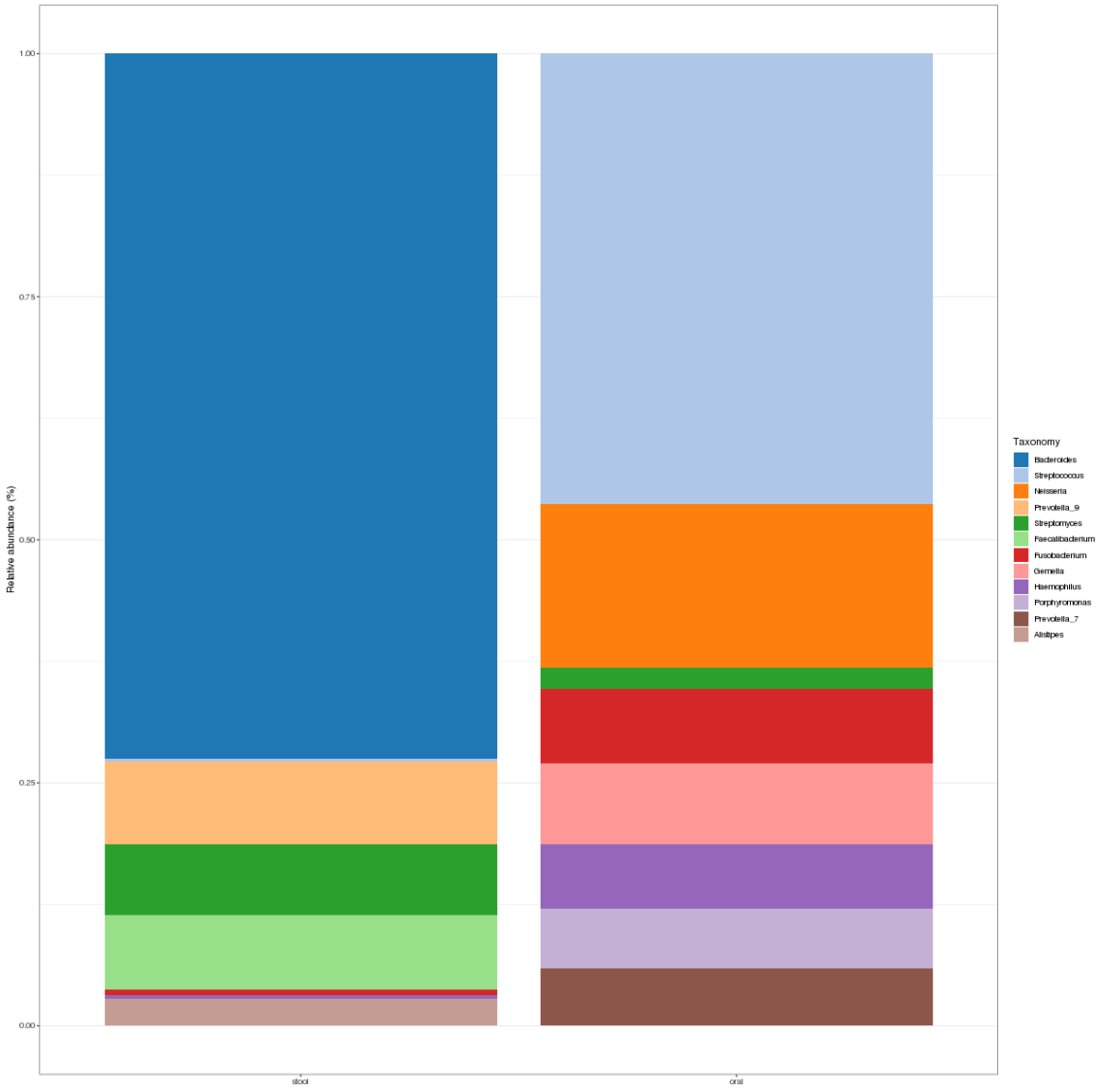

Figure 4. Barplot of most abundant genera in faecal and oral samples.

Table 4. Most abundant genera from faecal and oral samples.

Genus	Faecal Samples	Oral Samples
Bacteroides	72.5%	
Prevotella_9	8.5%	
Faecalibacterium	7.7%	
Streptomyces	7.3%	2.1%
Alistipes	2.8%	
Fusobacterium	0.5%	7.7%
Haemophilus	0.4%	6.6%
Streptococcus	0.3%	46.3%
Neisseria		16.9%
Gemella		8.3%
Porphyromonas		6.2%
Prevotella_7		5.9%

Table 5. Indexes of diversity between anatomic sites.

Diversity Index	Site	value	ci. down	ci. up
Shannon	Stool	2.14	1.55	2.73
Shannon	Oral	2.28	2.03	2.53
Simpson	Stool	0.70	0.53	0.88
Simpson	Oral	0.82	0.76	0.88
Beta	Stool	0.67		
Beta	Oral	0.43		

DISCUSSION

In this study, the absence of periodontopathogenic bacteria in faecal samples from healthy adult women was noted. This finding contrasts with other research that suggests a possible translocation of such bacteria between anatomical sites, especially given their location within the same gastrointestinal tract. However, it is important to consider that the small sample size in this study may limit the generalizability of these results. Therefore, it would be prudent to investigate this hypothesis further in a larger cohort to determine if the observed pattern holds true across a broader population.

Consistent with the findings of this investigation, other researchers have reported that periodontopathic bacteria are typically scarce or absent in the faecal samples of healthy individuals, indicating a limited transfer of bacteria from the oral cavity to the gut. Notably, some studies have detected minor infiltration of oral bacteria, predominantly streptococci, into the intestinal environment. This occurrence appears to be independent of the participants' periodontal health status, suggesting that while certain oral microbes may migrate to the gut, the existence of periodontal disease does not appear to significantly influence this migration (10). The implications of these observations are multifaceted and underscore the complexity of microbial interactions within the human body, as well as the potential barriers to bacterial movement between distinct biomes. Further research is warranted to elucidate the mechanisms governing microbial translocation and its impact on systemic health.

The relationship between periodontal bacteria and inflammatory bowel diseases, such as Crohn's disease, is an area of growing interest within the medical community. Notably, the prevalence of *Porphyromonas gingivalis* has been observed to be significantly higher in faecal samples from patients with Crohn's disease. This observation was made through a detailed analysis of taxonomic assignment files derived from the Crohn's Disease Viral and Microbial Metagenome Project (PRJEB3206). The study revealed that the abundance of *Porphyromonadaceae*, the bacterial family to which *Porphyromonas gingivalis* belongs, was markedly elevated in the faecal samples of individuals diagnosed with Crohn's disease when compared to those of healthy control volunteers. This finding points to a potential association between the presence of *Porphyromonas gingivalis* and the manifestation of clinical symptoms associated with Crohn's disease (11). It raises questions about the role of oral-derived microbes in the pathogenesis of gastrointestinal disorders and whether they may contribute to or exacerbate inflammatory processes in the gut. The mechanisms by which these periodontal pathogens might influence the development or progression of Crohn's disease remain to be fully understood. However, it is hypothesized that the systemic inflammation triggered by periodontal infections could play a role in the intestinal inflammation characteristic of Crohn's disease.

Given the complexity of microbial ecosystems and their interactions with host immunity, further research is essential to clarify the pathways through which periodontal bacteria may impact gut health. Such studies should consider the microbial interplay at various body sites, the immune responses elicited by these microbes, and the environmental factors that might facilitate their translocation. Understanding these dynamics could lead to novel therapeutic strategies for managing inflammatory bowel diseases and highlight the importance of maintaining oral health for overall well-being.

The intricate relationship between the oral and gut microbiomes is increasingly recognized as a critical component of systemic health. Previous studies have demonstrated correlations between

faecal microbiota and oral bacteria in individuals with periodontal disease, supporting a potential oral-gut axis mediated by microbial dynamics. Notably, *Fusobacterium nucleatum*, a keystone pathogen in periodontitis, is frequently enriched in faecal samples of affected individuals, highlighting its dual role in oral dysbiosis and potential systemic effects (12). This enrichment underscores the hypothesis that periodontal pathogens may influence gut microbiota composition, possibly through direct translocation or immune-mediated pathways.

The presence of oral microbial taxa in faecal samples, although limited, provides insights into how oral dysbiosis might contribute to systemic health issues. While oral taxa typically represent a minor proportion of the gut microbiota, their detection in faecal samples suggests transient colonization or direct seeding from the oral cavity, particularly in disease states. Studies have shown that periodontal conditions, such as gingivitis and periodontitis, are associated with specific microbial signatures, including increased salivary abundance of *Aggregatibacter actinomycetemcomitans*, *Parvimonas micra*, and *Fretibacterium species*, which correlate with clinical markers such as deep periodontal pockets and inflammation (12).

The microbial diversity observed in saliva samples from periodontitis patients also reveals significant dysbiosis. The increased biodiversity, while counterintuitive, reflects the presence of pathogenic bacteria that disrupt the ecological balance of the oral microbiome. Periodontopathic species such as *Porphyromonas gingivalis*, *Treponema denticola* and *Prevotella* intermedia dominate in disease states, contrasting with the relative abundance of health-associated genera such as *Streptococcus* and *Neisseria* in healthy individuals (13, 14). These findings highlight the dynamic nature of the oral microbiome and its role in maintaining oral and systemic health.

Comparisons between the oral and gut microbiomes in healthy individuals and those with periodontal disease further reveal distinct microbial compositions and diversity metrics. The Shannon diversity index, a measure of species richness and evenness, shows similar values between oral and faecal samples, indicating comparable levels of microbial diversity at these sites. However, beta diversity analyses reveal that faecal samples typically exhibit greater inter-individual variability, likely reflecting the influence of diet, host genetics, and systemic health factors (16). This aligns with findings that gut microbiota are more dynamic and responsive to external factors compared to the relatively stable oral microbiota.

Interestingly, while some pathogenic bacteria such as *Fusobacterium nucleatum* are enriched in both oral and faecal samples of periodontitis patients, other periodontopathic species remain exclusive to the oral cavity. This exclusivity suggests that while certain bacteria may traverse the gastrointestinal tract, others rely on the unique ecological niches of the oral environment for survival and proliferation (12, 19, 20). This distinction emphasizes the importance of niche-specific factors in shaping microbial communities.

Methodological advancements, such as the application of SHAMAN for metagenomic analysis, have enhanced our understanding of these microbiomes. This tool has been validated in studies of microbiomes across various primate body sites, demonstrating the uniqueness of the oral microbiome and its significant divergence from other body sites (15). Such tools allow for more nuanced analyses of microbial contributions to health and disease, particularly through metrics like the contribution spectrum, which quantifies the impact of specific taxa on health outcomes (17).

The interplay between oral and gut microbiomes has profound implications for systemic health.

Oral dysbiosis, characterized by increased diversity and the presence of periodontopathic species, may not only exacerbate periodontal disease but also influence gut health and systemic inflammation. The detection of shared microbial taxa between these niches suggests potential mechanisms of microbial exchange, whether through swallowing, immune interactions, or systemic circulation.

In conclusion, this study corroborates existing evidence that the oral and gut microbiomes, while distinct, are interconnected. Differences in microbial composition and diversity metrics between these sites reflect their unique ecological roles and interactions with host physiology. The findings also underscore the exclusivity of periodontopathic species to the oral cavity, emphasizing the localized nature of periodontal disease. Future research should focus on unravelling the mechanistic pathways linking oral dysbiosis to gut health and systemic diseases, with the potential to identify novel therapeutic targets for managing periodontal and systemic conditions.

AUTHOR CONTRIBUTION STATEMENT

All authors contributed to the conduct of this study.
Conceptualization and design: A.J.E. and B.P.P.
Literature review: A.J.E.
Methodology and validation: A.J.E and N.R.F.
Data analysis and interpretation: A.J.E and N.R.F.
Writing-original draft preparation: A.J.E., N.R.F. and B.P.P.
Writing-review & editing: A.J.E., N.R.F. and B.P.P.
Supervision: B.P.P.
Final approval of the manuscript: A.J.E., N.R.F. and B.P.P.

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