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ORIGINAL RESEARCH

Dysbiosis of the Saliva Microbiota in Patients with Psoriasis: A Case-Control Study

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Purpose: Accumulating evidence supports the association between altered salivary microbiota and inflammatory diseases. The existing literature on the salivary microbiota in patients with psoriasis is limited. However, differences in the prevalence of *Candida* species and abundance of several bacterial taxa in saliva have been found between patients and controls. This study aimed to investigate the differences in the composition and functional potential of salivary microbiota in patients with psoriasis compared to their cohabiting partners and healthy controls.

Patients and Methods: Samples from 115 of 123 individuals qualified for statistical analysis: patients with psoriasis who did not receive systemic anti-psoriatic treatment (n=47); cohabiting partners (n=21); and age-, sex-, and BMI-matched healthy controls (n=47). One saliva sample was collected from each participant and analysed by shotgun metagenomic sequencing.

Results: A difference in the α-diversity of bacterial species was observed exclusively between patients and controls, with a lower diversity in patients (p=0.041). Variation in bacterial composition (β-diversity) was influenced by smoking (p=0.001) and diet (p=0.025) but not by group status. Using a linear regression model adjusted for smoking and diet, we identified four bacterial classes and five species that were significantly different between the patient, partner, and control groups. One Kyoto Encyclopedia of Genes and Genomes module differed significantly between patients with psoriasis and their partners. No differences in *Candida* species or abundance were found among the three groups.

Conclusion: Comparison of salivary microbiota at the levels of bacterial diversity, composition, and predicted function indicated that psoriasis cases are characterised by dysbiosis.

Keywords: psoriasis, dysbiosis, saliva, microbiota, shotgun sequencing

Introduction

Psoriasis is a chronic inflammatory skin disease affecting 0.5–11.6% of the adult population worldwide.[1] Psoriasis is characterised by well-demarcated red scaly plaques on the skin.

Patients with psoriasis have an increased risk of developing other inflammatory diseases such as inflammatory bowel disease and diseases of the oral cavity such as periodontitis.[2,3]

The pathogenesis of psoriasis is multifactorial as the disease manifests in genetically predisposed individuals when exposed to one or more environmental triggering factors. Known trigger factors include stress, smoking, obesity, excessive alcohol consumption, and streptococcal throat infection.[4]

Alterations in the gut microbiota have been associated with inflammatory diseases,[5–9] and associations between psoriasis and dysbiotic gut microbiota have been reported;[10] however, few studies have examined the role of the oral microbiota in psoriasis (Table 1).[11–21] While findings regarding bacterial prevalence and diversity at various taxonomic

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Table 1 Previous Studies on Psoriasis and Oral Microbiota. Adjusted Table From Systematic Review on Oral and Gut Microbiota in Psoriasis Patients[5]

Author (Year) Location	Sampling Method	Psoriasis Type	Anti-Psoriatic Treatment/Other Restrictions	Cases/ Controls	Methods	Main Findings
Waldman (2001) Israel [11]	Saliva	Plaque-type	• Not specified	50/50	Culture	• The prevalence and count of Candida species were significantly higher in patients with psoriasis than in healthy controls.
Bedair (2012) Jordan [12]	Swab, smear, and oral rinse	Not specified	• All psoriatic treatment allowed. • No antifungal/antibiotics for 2 months.	100/100	Culture	• The prevalence and count of Candida species were significantly higher in patients with psoriasis than in healthy controls. • No significant difference in prevalence of Candida in treated/untreated patients with psoriasis.
Sarvtin (2014) Iran [13]	Swab	Plaque-type	• No corticosteroids or antibiotics • Diabetes patients excluded.	100/50	Culture	• The prevalence and count of Candida species were significantly higher in patients with psoriasis than in healthy controls.
Lesan (2018) Iran [14]	Smear	Plaque-type	• No previous systemic anti-psoriatic treatment. • No antibiotics/antifungals/corticosteroids for 2 months. • Smokers and patients with systemic diseases excluded.	70/70	Culture	• The prevalence and count of Candida species were significantly higher in patients with psoriasis than in healthy controls. • There was a significant positive association between PASI and colony count.
Belstrøm (2019) Denmark [15]	Swab and stimulated saliva	Not specified	• No antibiotics for 3 months.	27/52	16S rRNA (V1–V3), 22 PCR cycles, Illumina Miseq Sequencing	• β-diversity (PCoA): no clustering. • 21 bacterial taxa at various levels differentiated between the groups.
Paksoy (2022) Turkey [16]	Subgingival	Plaque-type	• No cancer, cardiovascular, neurological, psychiatric or chronic inflammatory disease or any inflammatory or autoimmune skin disease. • No tobacco use. • No periodontal care for 6 months. • No immunosuppressive drugs or drugs that could affect saliva for 6 months. • No systemic anti-psoriatic treatment for 3 months. • No pregnant or lactating women.	20/20[a]	Light-Cycler 480 II qPCR, 40 cycles for bacteria, 50 cycles for candida albicans and EBV	• No significant difference between groups in prevalence of each species. • Higher mean amount of *Porphyromonas gingvalis* in periodontitis groups compared with healthy groups. • Higher mean amount of *Campylobacter rectus* in psoriasis patients with periodontitis compared with periodontally healthy psoriasis patients.

Orozco-Molina (2023) Mexico [17]	Subgingival	Plaque-type	• No systemic diseases other that plaque-type psoriasis that might influence periodontitis. • No antibiotics for 3 months. • No antioxidant drugs for 3 months. • No periodontal treatment in the past and > 20 natural teeth. • No history of smoking or excessive alcohol use. • No pregnant or lactating women.	52/43[a]	Checkerboard DNA-DNA hybridization	• Higher proportions of blue complex species in the group with both psoriasis and periodontitis. • Three blue complex species were higher in severe psoriasis compared to mild psoriasis. • Periodontitis patients with psoriasis had lower proportions of red complex species compared to those without. • Sixteen species were elevated in patients with psoriasis.
Zhao (2024) China[18]	Unstimulated saliva	Plaque-type	• No autoimmune disease, diabetes, obesity, neurological or psychiatric disorders, or infectious disease • No pregnant or lactating women. • No antibiotics, probiotics or immunosuppressants for 3 months	20/20	16S rRNA	• Higher alpha diversity in psoriasis group • Significant difference in beta diversity based on group status. • Several taxa differed between groups. • Psoriasis severity was positively correlated with *Alloprevotella, Porphyromonas* and *Neisseria* and negatively correlated with *Veillonella*.
Fan (2024) China[19]	Unstimulated saliva	Plaque-type	• No family history of psoriasis • No malignant tumours, diabetes, cardiovascular diseases, immune dysfunction, herpes infections, systemic autoimmune diseases, rheumatoid arthritis • No acute oral diseases such as herpes simplex, mucosal ulcers, local trauma or surgery within the past 3 months • No smoking or alcohol within 3 months.	44/16	16S rRNA (V3–V4), Illumina Hiseq 2000 Sequencing	• Analysis of similarities (ANOSIM) showed more difference between psoriasis and control groups than within each group. • 168 bacterial taxa differed between the psoriasis and control groups, including the class Campylobacteria that was found more abundant in the psoriasis group.

(*Continued*)

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Table 1 (Continued).

Author (Year) Location	Sampling Method	Psoriasis Type	Anti-Psoriatic Treatment/Other Restrictions	Cases/ Controls	Methods	Main Findings
Chen (2025) China[20]	Tonsillar swab	Not specified	• No antibiotics, probiotics or immunosuppressants for 3 months, • No serious health conditions, • No infectious disease for 1 month • No special dietary habits. • Only one ethnic group (Chinese)	28/24	16S rRNA	• No difference in alpha diversity • Significant difference in beta diversity due to psoriasis • Genus Bacteroidales, phylum Bacterioidota and family Prevotellaceae were increased in patients compared to healthy controls. Families Neisseriaceae, Micrococcaceae and Pasteurellaceae were reduced. Several species differed between the groups, highlighting *Rothia mucilaginosa* which differed significantly regardless of analysis method.
				8/10[b]	Metagenomic sequencing	• Lower Simpson and Shannon index in patients than healthy controls, higher ACE index and Chao1 index in patients than healthy controls. • Several taxa on phylum-, family-, genus- and species level were decreased in patients. *Solobacterium moorei* was increased in patients. • Functional analysis (KEGG) revealed changes in pathways related to decreased metabolism, environmental information processing, organismal systems and increased cellular processes in patients.
Kageyama (2020) Japan[21]	Unstimulated saliva	PPP	• No inflammatory diseases or allergic hypersensitivity. • Exclusion from control group if current or previous PPP or other major skin disease.	21/10	16S rRNA	• Lower Proteobacteria abundance in PPP patients. • Lower Neisseria abundance in PPP. • Several minor taxa were higher in PPP, some of which are associated with periodontal disease.

Note: [a] Cases and controls further divided based on periodontal status. [b] Subpopulation, selection method not specified.
Abbreviations: qPCR, quantitative polymerase chain reaction; EBV, Epstein-Barr virus; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPP, palmoplantar pustulosis.

levels have been inconsistent, all culture-based studies have consistently reported a significantly higher prevalence and load of Candida species in patients with psoriasis than in healthy controls.

The oral microbiota is the second largest and most diverse after the gut microbiota;[22] 90% of the total number of cells associated with our bodies are microbes, whereas the remaining 10% are human cells.[23] The microbiota is changeable, for example, owing to diet, which has been shown to cause changes in the gut microbiome within a few days of intervention,[24] and the oral microbiome is affected by a shared household environment.[25,26]

Saliva is a potential source of easily accessible material for sample collection. Saliva has been used to show differences in microbiota and cytokines in different diseases and study setups.[6,27,28] Therefore, saliva may have potential as a biological marker medium for evaluating not only oral health, but also the risk of systemic diseases.

The modulation of the microbiome may contribute to the management of inflammatory diseases. A systematic review and meta-analysis examining the use of oral probiotics as an adjunctive therapy in psoriasis reported a reduction in disease activity in the treatment group compared to placebo.[29]

The objective of this study was to evaluate i) whether the saliva microbiota of patients with psoriasis differs from that of healthy controls and non-related healthy controls living in the same household and ii) whether the saliva microbiota is influenced by lifestyle.

Materials and Methods

Design and Study Population

A case-control design was used to investigate potential taxonomic and functional differences in the salivary microbiota among patients with psoriasis, their cohabitant partners, and healthy controls matched for age, sex, and BMI. All participants also provided faecal and blood samples for the study of gut microbiota, and these data have been published.[10]

The inclusion criteria were age between 18–74 years, moderate-to-severe plaque psoriasis with a psoriasis area and severity index (PASI) ≥ 8, BMI < 35 kg/m^2, and no treatment with systemic anti-psoriatic or antibiotic treatments for 3 months. Patients receiving any other systemic anti-inflammatory treatment and those with diabetes, autoimmune diseases, cancer, or infections were excluded. If the patients had a cohabiting partner, the partner was invited to participate in the study. The healthy controls and cohabiting partners met the same eligibility criteria as the patients except for those specific to psoriasis.

Participants were recruited between February 2019 and September 2020 from the psoriasis outpatient clinic of the Department of Dermatology and Allergy at Herlev and Gentofte Hospital, Denmark. Written informed consent was obtained from all participants, and the study was approved by the Scientific Ethics Committee of the Capital Region of Denmark (H-18041455).

Study Visits and Collection of Samples

Patients underwent clinical examination to assess PASI. Through medical interviews and questionnaires, data on medical history, medical treatment, periodontal status, diet (Dietary Quality Score, DQS, Figure S10),[30] and physical activity (International Physical Activity Questionnaire, IPAQ)[31] were collected from all participants. One saliva sample was collected from each participant using the OM-501 kit from DNA Genotek according to the manufacturer's instructions. The participants were instructed to abstain from eating, smoking, chewing gum, and brushing their teeth for at least two hours before sample collection.

Processing of Saliva Samples

DNA was extracted from saliva samples, fragmented, amplified by PCR, and sequenced (NovaSeq/Illumina) by Clinical Microbiomics A/S (Fruebjergvej 3, 2100 Copenhagen, Denmark). A detailed description of the methods used for processing the samples is provided in the Supplementary Information.

Bioinformatics

Sequencing data processing was performed by Clinical Microbiomics A/S. Raw FASTQ files were filtered to remove human genomic contamination by discarding read pairs in which either read mapped to the human reference genome GRCh38.p14 with Bowtie2[32] in local alignment mode. Reads were then trimmed to remove adapters and bases with a Phred score below 30 using AdapterRemoval.[33] Sequences were mapped to the Clinical Microbiomics Human Microbiome Reference HMR05 gene catalogue derived primarily from high-quality (HQ) prokaryotic metagenome-assembled genomes (MAGs) identified from 30,382 human microbiome samples collected from nine distinct human body sites. Species quantification was based on the core signature genes selected for each species. High-quality non-host reads (host-filtered read pairs with lengths > 100 base pairs) were retained and mapped to the gene catalogue using BWA mem.[34]

Species relative abundance and the Kyoto Encyclopedia of Genes and Genomes (KEGG) module relative abundance were calculated. The expected read counts for signature genes in each species in each sample were modelled with a negative binomial distribution as follows. First, if ≥50 of the signature genes for a species had non-zero read counts and ≥99% of genes were expected to have non-zero read counts given the total read count for that species (1-(((n_genes-1)/n_genes)^n_reads)≥0.99), then signature genes with zero reads were ignored in that sample. Second, the expected 99% quantile (between 0.5% and 99.5%) of read counts were calculated for each gene based on a negative binomial distribution with a mean proportional to the effective gene length (accounting for read length and mapping alignment criteria) and dispersion defined as log2(effective gene length). The abundance of each species was then calculated as the mean read count normalised by effective gene length based on reads mapping to signature genes with observed read counts within the expected 99% quantile. Species abundances were set to zero if less than 5 genes with non-zero read counts were within the 99% quantile. Furthermore, species with <66% of genes with non-zero read count within the 99% quantile were set to zero, unless the median abundance of signature genes was non-zero, in which case the median gene-length- corrected abundance of non-zero genes was used. Abundances were then normalized sample-wise such that the total abundance of all species sums to 100%. For further description, see Supplementary Information.

Statistics

Baseline characteristics of the study population were summarised using descriptive statistics. The median and inter-quartile range (IQR), frequency, and percentage were used to present continuous and categorical variables, respectively. Mann–Whitney *U*, Kruskal-Walli's rank-sum, and Fisher's tests were used for statistical comparisons. Statistical significance was set at $P < 0.05$.

α-Diversity was calculated as the richness (number of species observed in a sample) and Shannon index (accounting for the abundance and evenness of the species). Subsequently, pairwise Mann–Whitney *U*-tests were used to compare richness and Shannon indices between the study groups. β-Diversity was evaluated using the Bray-Curtis dissimilarity and presented as a principal coordinate analysis (PCoA) for visual interpretation. β-Diversity was further evaluated using permutational analysis of variance (PERMANOVA).

Changes in microbiota composition and functional potential between the study groups were assessed using both the Mann–Whitney *U*-test and a linear regression model.[35] For each sample individually, the zero-omitted relative taxon abundances were transformed with a centred log-ratio transformation (CLR) to account for the compositional structure of the data. To be robust against outliers in the data, winsorization was performed, capping the CLR-transformed abundances at their 3rd and 97th percentile. Linear regression analyses were performed and adjusted for smoking and diet for each taxon present in at least 5 samples in each group. KEGG module abundance was used for functional testing.

The p-values for abundance differences were controlled for false discovery rate (FDR) due to multiple testing using the Benjamini-Hochberg procedure, and results were considered significant if FDR < 0.1. The statistical methods used are described in the Supplementary Information.

Results

Saliva samples were obtained from 123 participants in groups of patients with psoriasis (n=52), healthy cohabitating partners (n=21), and healthy controls (n=50).

Characteristics of the Study Population

The demographics of all participants are presented in Table 2. The participants were similar in terms of age, sex, body mass index (BMI), and oral health status across study groups. However, there were significant differences in smoking status ($p<0.0001$) and physical activity ($p=0.0071$) between patients and healthy controls, with a higher proportion of smokers and poorer physical activity levels among patients than among healthy controls. This difference was not observed when patients were compared with cohabitant partners.

Table 2 Study Population Characteristics

	Psoriasis (n=52)	Control (n=50)	P-value (Psoriasis vs Control)	Partner (n=21)	P-value (Psoriasis vs Partner)
Age, years, median (IQR)	48.7 (38.5–57.9)	49.1 (38.8–58.2)	0.987	47.6 (42.8–55.1)	0.947
Sex (male)	28 (53.8%)	29 (58.0%)	0.824	9 (42.9%)	0.554
BMI, kg/m2, median (IQR)	25.3 (22.9–27.3)	24.9 (23.1–27.2)	0.933	24.4 (23.4–26.8)	0.692
Psoriasis characteristics					
PASI, median (IQR)	10.9 (8.3–12.4)	–		–	
Age at debut, median (IQR)	18.0 (13.0–29.5)	–		–	
Duration of disease, years, median (IQR)	23.9 (11.0–34.9)	–		–	
Ongoing psoriasis treatment					
None/topical emollient	32 (61.5%)	–		–	
Topical treatment (corticosteroid ± calcipotriol)	19 (36.5%)	–		–	
Previous psoriasis treatment					
None/ topical emollient	2 (38.5%)	–		–	
Topical corticosteroid	25 (48.1%)	–		–	
Topical corticosteroids with calcipotriol	25 (48.1%)	–		–	
Tar	19 (36.5%)	–		–	
UVB	41 (78.7%)	–		–	
PUVA	9 (17.3%)	–		–	
Systemic (methotrexate, biologics)	27 (51.9%)	–		–	
Time since systemic treatment, years, median (IQR)	4.3 (1.3–5.0)	–		–	
Family history of psoriasis[a]	20 (38.5%)	–		–	
Psoriatic arthritis (physician diagnosed)[b]	8 (15.4%)	–		–	
Oral health					
Active or history of periodontitis	8 (15.4%)	8 (16.0%)	0.583	4 (19.0%)	0.869
Loose teeth	6 (11.5%)	1 (2.0%)	0.113	0 (0.0%)	0.173
Dentures or missing teeth	21 (40.1%)	15 (30%)	0.305	5 (23.8%)	0.280
Gum bleeding	7 (13.5%)	2 (4.0%)	0.161	1 (4.8%)	0.425
Bad breath	8 (15.4%)	4 (8.0%)	0.293	3 (14.3%)	1

(*Continued*)

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Table 2 (Continued).

	Psoriasis (n=52)	Control (n=50)	P-value (Psoriasis vs Control)	Partner (n=21)	P-value (Psoriasis vs Partner)
Other non-psoriasis treatment					
Time since treatment with antibiotics, years (median, IQR)	2.0 (1.0–5.0)	3.0 (1.0–5.0)	0.372	2.0 (1.0–4.0)	0.692
Motility affecting treatment	0 (0.0%)	0 (0.0%)	–	0 (0.0%)	–
Statins	6 (11.5%)	3 (6.0%)	0.488	1 (4.8%)	0.665
Other non-systemic anti-inflammatory	1	2 (4.0%)	0.614	1 (4.8%)	0.495
Antidepressants	2 (3.8%)	1 (2.0%)	1	0 (0.0%)	1
Proton-pump inhibitors	2 (3.8%)	0 (0.0%)	0.495	0 (0.0)	1
Smoking			<0.0001*		0.219
Current	11 (21.2%)	3 (6.0%)		4 (19.0%)	
Former	27 (51.9%)	12 (24.0%)		7 (33.3%)	
Never	14 (26.9%)	35 (70.0%)		10 (47.6%)	
Use of alcohol/units/week			0.451		0.084
0	15 (28.8%)	11 (22.0%)		3 (14.3%)	
1-7	27 (51.9%)	29 (58.0%)		13 (61.9%)	
8-14	3 (5.8%)	7 (14.0%)		5 (23.8%)	
15-21	5 (9.6%)	2 (4.0%)		0 (0.0%)	
>21	2 (3.8%)	1 (2.0%)		0 (0.0%)	
Level of physical activity			0.007*		0.745
Low	15 (28.8%)	3 (6.0%)		4 (19.0%)	
Moderate	25 (48.1%)	28 (56.0%)		12 (5.7%)	
High	12 (23.1%)	19 (38.0%)		5 (23.9%)	
Dietary habits			0.363		0.515
Unhealthy	3 (5.8%)	1 (2.0%)		1 (4.8%)	
Moderate	38 (73.1%)	32 (64.0%)		18 (85.7%)	
Healthy	11 (21.2%)	15 (30.0%)		2 (9.5%)	

Notes: [a]Family history was defined as at least one parent or one child with psoriasis. [b] 4 patients (7.7%) did not know if they had been diagnosed with psoriatic arthritis by a physician. *P-value < 0.05.

Abbreviations: IQR, interquartile range; BMI, body mass index; PASI, Psoriasis Area Severity Index; UVB, ultraviolet-B radiation; PUVA, psoralen plus ultraviolet-A radiation.

The patients had moderate-to severe psoriatic disease expressed by a median PASI of 10.9 and IQR of 8.3–12.4, the median duration of disease was 23.9 years (IQR 11.0–34.9). At the time of sample collection, 32 (61.5%) patients received no anti-psoriatic treatment or only a topical emollient, whereas 19 (36.5%) patients received topical treatment only, with corticosteroids with or without calcipotriol. Previous treatment included systemic antipsoriatic treatment in 27 (51.9%) patients. Psoriatic arthritis was diagnosed in 8 (15.4%) patients.

Patients with Psoriasis Have a Lower Saliva Bacterial Diversity and the Overall Bacterial Composition Is Influenced by Smoking and Diet

Of the 123 collected samples, 115 were successfully sequenced and of sufficient quality to be included in statistical analysis. These samples comprised of patients with psoriasis (n=47), cohabitating partners (n=21), and healthy controls (n=47). The sequencing quality results (Table S1–2 and Figure S1–4), and a taxonomic overview (Figures S5 and S6) are presented in the Supplementary Information.

The α-diversity was lower in the psoriasis group than in the healthy control group when expressed as Shannon index (p=0.041) (Figure 1). No difference in Shannon index was found when comparing patients with cohabiting partners. For β-diversity, no significant differences were observed between the groups (p=0.168), but smoking (p=0.001) and diet (p=0.022) caused shifts in microbiota composition (Figure 2 and Table 3). No significant difference in β-diversity was observed based on physical activity level (p=0.460) The unadjusted PERMANOVA analyses for group, smoking, and diet, along with PCoA plots colour-coded by group, smoking, and diet status, are provided in the Supplementary Information (Table S3–5 and Figure S7–9).

Changes in Abundances of Several Bacterial Taxa Were Associated with Psoriasis

When applying pairwise Mann–Whitney *U*-test for differential abundance between groups, a difference was observed between the psoriasis and healthy control groups for the family *Leptotrichiaceae* (false discovery rate, FDR = 0.059) and for the species *Leptotrichia* (FDR = 0.079). Both were more abundant in healthy controls than in the psoriasis group. No statistically significant differences were found between the patients and their partners. The top 10 results for the species, families, and KEGG modules are presented in Table S6–8.

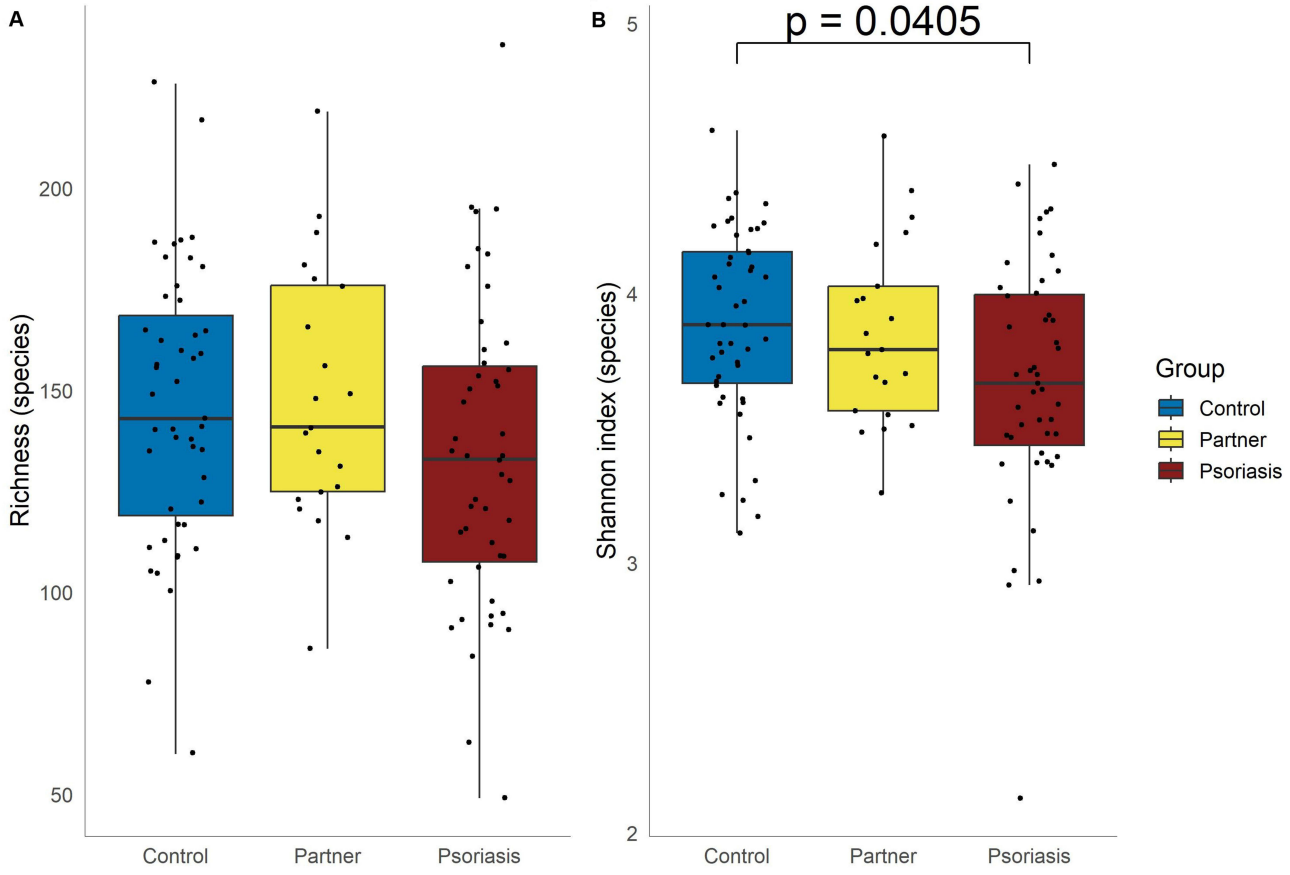

Figure 1 Boxplot showing differences in species richness (**A**) and Shannon diversity (**B**) grouped by psoriasis status and family. All groups were compared pairwise by Mann–Whitney U-test, and significant differences (p<0.05) are indicated above the groups.

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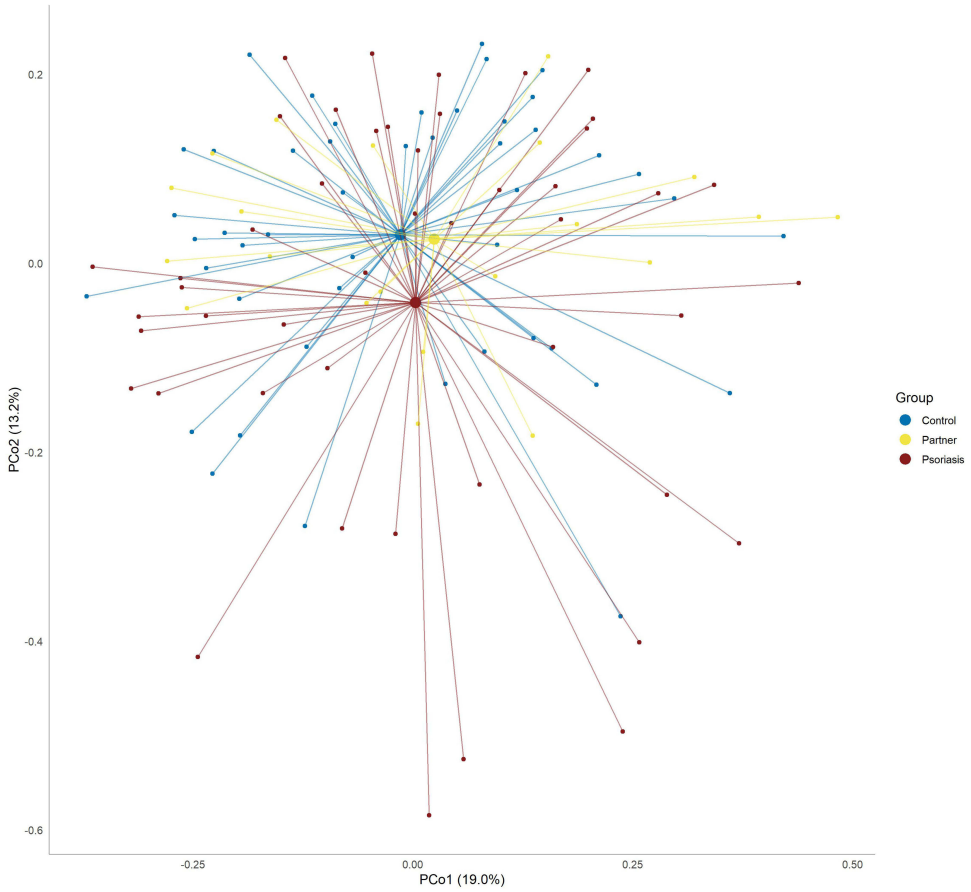

Figure 2 Principal coordinates analysis based on Bray-Curtis dissimilarities among samples, calculated based on the species abundances. Samples are colour coded by group variable. The x- and y-axis indicate the microbial variance explained by the first two principal coordinates.

When fitted to a linear regression model adjusted for smoking and diet (Figure 3), the following five bacterial species were more abundant (FDR < 0.1) in the psoriasis group than in the healthy control group: *Granulicatella sp015264885* (FDR=0.060), *Streptococcus sp905221385* (FDR=0.060), *Centipeda timonae* (FDR=0.081), *Peptostreptococcus sp900759325* (FDR=0.081), and *Rothia mucilaginosa hMGS.05786* (FDR=0.081). There was no difference in abundance at the species level when comparing the patients with their partners. Partners and healthy controls had different abundances

Table 3 Permutational Multivariate Analysis of Variance (PERMANOVA) Test of Differences in β-Diversity with Adjustment for Diet, Smoking and Physical Activity

	Sum of Squares	R^2	P-value
Group	0.518	2.1%	0.168
Smoking	0.764	3.1%	0.001*
Diet	0.412	1.7%	0.022*
Physical activity	0.204	0.8%	0.460
Residual	22.812	92.5%	NA
Total	24.654	100%	NA

Note: *P-value < 0.05.

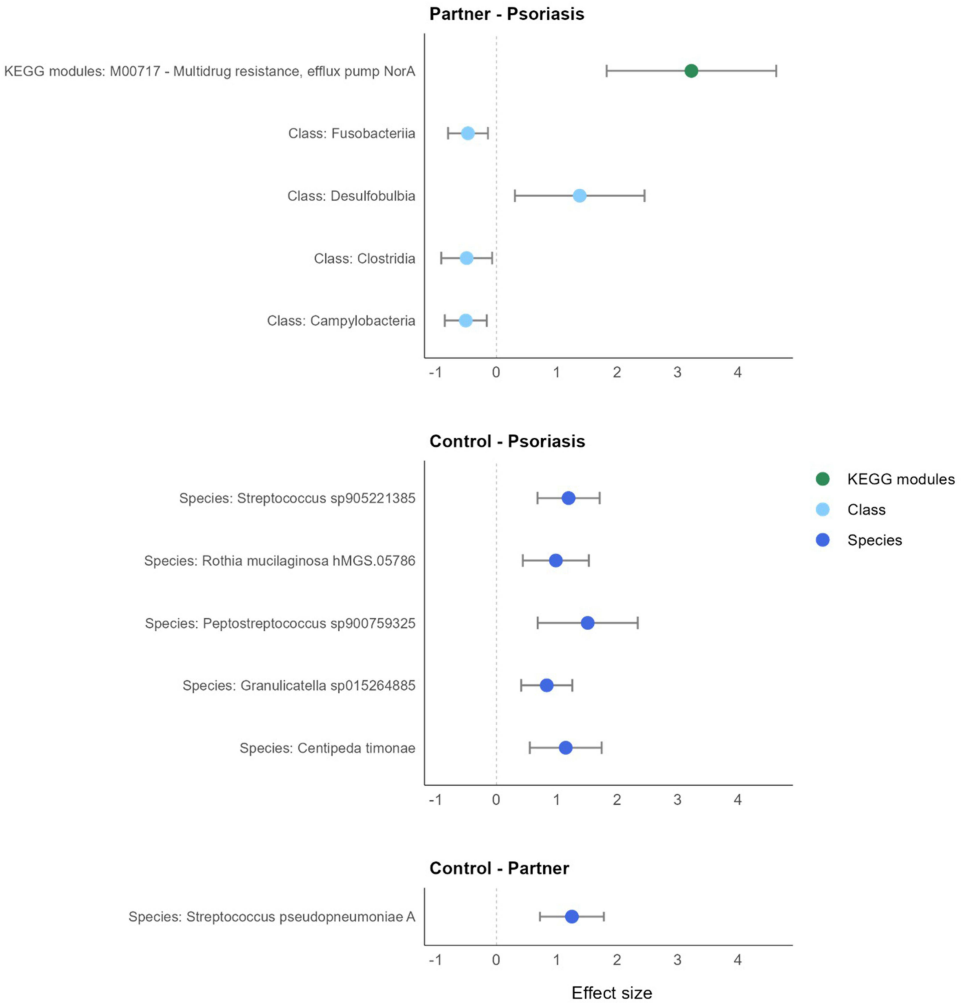

Figure 3 Effect sizes of the group variable for the taxa whose change in abundance differed significantly between the psoriasis and control groups including error bars representing 95% confidence interval of the estimated effect size. A positive effect size means that abundance of the taxon increased from in the first mentioned group compared to the second mentioned group. A negative effect size can be interpreted as the opposite.

of the species *Streptococcus pseudopneumoniae A* (FDR=0.0288). The following bacterial classes differed between the psoriasis and partner groups: Fusobacteria (FDR=0.044), Campylobacteria (FDR=0.044), and Clostridia (FDR=0.088) were lower in patients with psoriasis than in their partners. In contrast, Desulfobulbia was higher in the patients (FDR=0.088).

No differences were found in abundances of bacterial genera, families, orders, or phyla, or in the abundances of fungi. The following fungi were included in the analysis: *Candida auris, C. albicans, C. parapsilosis, C. tropicalis, C. orthopsilosis, C. dubliniensis, C. intermedia, C. maltose, C. duobushaemulonis, C. viswanathii*, and *Debaryomyces hansenii*. Only three fungal species were present in the saliva samples, *C. dubliniensis, C. parapsilosis, C. tropicalis*, and no differences were observed between the three groups.

Patients with Psoriasis Have a Different Microbial Functional Potential

The functional potential analysis revealed a higher abundance of the KEGG module M00717, Multidrug resistance, efflux pump NorA (FDR=0.0375) in patients than in their partners. No differences in KEGG modules were found between psoriasis cases and the healthy control group.

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Discussion

Using metagenomic sequencing, we observed a lower Shannon index of saliva microbiota in patients with psoriasis than in healthy controls, a shift in β-diversity due to smoking and diet, as well as differences in the abundance of four bacterial classes, one KEGG module between psoriasis and partner groups, and five bacterial species between the psoriasis and control groups, as presented in Figures 1–3.

The Shannon index (Figure 1) revealed a general trend of decreasing values, with the control group exhibiting the highest index followed by the partner group, and the psoriasis group displaying the lowest values. A statistically significant difference was observed only between the psoriasis group and the healthy control group. Alterations in the oral microbiota can occur due to dietary changes[24] and shared household environment.[25,26] Our findings suggest that the combination of living habits and psoriasis may have an additive effect on salivary microbiota diversity, as neither living habits alone nor psoriasis alone appeared to result in significant shifts in the Shannon index.

Although the β-diversity analysis revealed no differences between the groups in the present study of the salivary microbiota, it revealed shifts in microbiota composition attributed to smoking and diet, highlighting the impact of lifestyle on the saliva microbiota and the relevance of investigating the impact of lifestyle by including cohabitant partners to the patients in our study. Notably, we found that the relative abundance of one bacterial taxon was different between our two healthy control groups, which could possibly be explained by lifestyle differences.

Differences in the oral microbiome have been linked to periodontitis and periodontitis has also been linked to psoriasis, as periodontitis is more common in patients with psoriasis and is correlated with psoriasis severity and psoriatic arthritis.[36] The prevalence of periodontitis increases with the severity of psoriasis.[37] This suggests an association between psoriasis and inflammation in the oral cavity, which is supported by the detection of salivary biomarkers associated with psoriasis disease activity and therapeutic response.[38]

The change in β-diversity due to smoking status in the present study supports the previously demonstrated relationship between smoking status, the subgingival microbiota,[39] and periodontitis.[40,41]

Table 1 summarises the results of previous studies that investigated the oral microbiota of patients with psoriasis. Four of these studies focused on fungi by culture,[11–14] and five analysed bacteria by 16S rRNA,[15,19] qPCR,[16] checkerboard DNA-DNA hybridisation,[17] and both 16S rRNA and shotgun sequencing.[20]

Previous studies on the relationship between oral fungi and psoriasis have all revealed a significantly higher prevalence of *Candida* species in patients with psoriasis than that in healthy controls. The lack of this finding in our population is likely due to the difference in the methods used, as culturing may be superior for detecting low-abundance fungi.[42,43] Although none of the tested fungi in our study were found to be significantly different between the groups, this finding may stem from saliva DNA extraction and distal analysis not being optimized for fungal species, as evidenced by their sparse representation (Table S9). Proper analysis of these species requires fungus-targeted DNA extraction and sequencing. The same applies to investigations of viral species.

Five saliva-based studies focused on bacteria and 16S rRNA amplicon sequencing analysis was performed. An altered oral microbiota composition was observed in the salivary microbiota of patients with palmoplantar pustulosis, and it was revealed that the abundance of genera within Firmicutes and Synergistetes was higher in the patient group and that the abundance of genus *Neisseria* was lower.[21] It has been suggested that a relatively low amount of *Neisseria* may permit the growth of pathogenic bacteria. Belstrøm et al identified 21 species that differed between patients with psoriasis and healthy controls.[15] Zhao et al found a higher α-diversity in the psoriasis group and a significant difference in β-diversity between the groups, as well as species associated with periodontal disease,[44] positively correlated with psoriasis severity.[18] None of these differences were reproduced in our study, highlighting the importance of the choice of experimental methods and underlining the need for an international consensus for a higher degree of standardised specimen sampling, DNA extraction differentially enriched for identifying bacteria, archaea, viruses, or fungi, sequencing depth, and bioinformatics pipelines.[45–48]

One KEGG module-based study of the functional potential of the saliva microbiota have previously been reported on the tonsillar microbiota in patients with psoriasis.[20] Changes were found in pathways related to decreased metabolism,

environmental information processing, organismal systems, and increased cellular processes in patients. These functional changes suggest a possible mechanism of interaction between the altered tonsillar microbiota and psoriasis.

In our study, we observed that the abundance of M00717, the multidrug resistance efflux pump NorA, was higher in the psoriasis group than in the partner group. The NorA efflux pump is a gene in *Staphylococcus aureus* responsible for the efflux of various substances, including different antibiotic drugs and common disinfectants.[49,50] Although the exact role remains unclear, it could be speculated that patients with psoriasis received more antibiotics which might lead to increased expression of the NorA efflux pump.

Psoriasis severity could also be a factor to consider when investigating salivary microbiota. However, in our study, nearly all patients had moderate to severe psoriasis, with PASI values of 8 to 12 and a median value of 10.9 (IQR 8.3–12.4). Therefore, investigating the possible association between PASI and salivary microbiota is not relevant to our study.

Since our study participants had both saliva and stool samples sampled on the same day[10] and had both sets of metagenomes analysed, it was possible to compare diversity indices from the same patients at different sampling sites. While the salivary microbiota Shannon index was significantly lower in patients with psoriasis than in healthy controls and partners, the gut microbiota Shannon index was significantly lower only when compared to partners.[10] Chu et al reviewed the literature on the microbiome in patients with rheumatoid arthritis and found that the α-diversity of the gut microbiome was either not changed or decreased, and that the α-diversity of the oral microbiome was either unchanged or increased.[51] However, a case-control study on Kawasaki disease found coherence between the oral and gut microbiome α-diversity differences,[52] and a case-control study on axial spondylarthritis found no difference in gut α-diversity, but lower oral α-diversity in patients.[53] The lack of coherence between the changes in the oral and gut microbiotas in our population continues in terms of β-diversity, as the gut microbiome study found a shift in β-diversity due to group status.

We acknowledge that the outcome of the present study on non-stimulated salivary microbiota does not address the question of whether a more pronounced dysbiosis exists in the oral microbiota of psoriasis patients. Within the oral cavity, there are different microbial compositions in the teeth: gingiva, sulcus, tongue, buccal mucosa, floor of the mouth, lip, retromolar trigone, hard palate, and soft palate.[6,54] Therefore, careful specimen sampling from each of these sites in the oral cavity and subsequent microbiota analyses may reveal differences between cases and controls relevant to the pathogenesis or pathophysiology of psoriasis.

Although this research is at an early stage, the knowledge about the differences in microbiota between patients with inflammatory diseases and healthy individuals, along with insight into how environmental factors affect microbiota, will hopefully lead to new strategies for preventing disease development, new approaches to treatment and stratification of treatment to fit the individual patient.

Strengths and Limitations

Patients with psoriasis were relatively homogeneous, with a PASI of at least 8, indicative of moderate to severe disease activity, increasing the likelihood of positive findings being associated with psoriasis.

A major strength of this study was the use of shotgun metagenomic sequencing, a sequencing method with high taxonomic resolution[55] and limited selection bias, as all microbes in the samples are sought identified.

Knowing the impact of diet on the microbiome, our elaborate diet questionnaire sought to minimise dietary effects on the results through a diet-adjusted statistical analysis. Another strength of this study is the inclusion of cohabitant partners as controls, thereby eliminating household environment as a confounder.

However, this study has several limitations, including the lack of an estimation of bacterial cell load in saliva samples and therefore no possibility of quantifying the absolute abundance of taxa, and relatively small sample sizes making conclusions less robust, and the results need to be verified in larger-scale studies.

Furthermore, the study participants were not subjected to oral examinations for the presence of dental caries, gingivitis, or periodontal disease. However, they were asked whether they had previously been diagnosed with periodontitis by a dentist. Consequently, the reliability of our data on periodontal status was inferior to that of studies that have performed oral examinations. In the present study, periodontal status was found to be statistically insignificant in terms of its impact on oral microbiome composition. However, it should be noted that the limited accuracy of the periodontal status classification may have introduced residual confounding in the analysis.[56] Future research should include more

elaborate and standardized assessments of periodontal status to facilitate a clearer understanding of its potential influence on the results.

Conclusions

Previous findings in oral microbiota studies of psoriasis cases have been inconsistent, likely because of differences in sampling techniques, sequencing methods, bioinformatics pipelines, and statistical approaches.

The pattern of association between psoriasis and alterations in microbiota was different in saliva and faecal samples from the same participants, but both sites showed microbiota dysbiosis.

The results of the present study provide insights into the association between microbiota and psoriasis, and through comparison of the salivary microbiota of patients with psoriasis and controls, it was found that having psoriasis is associated with differences in oral microbiota diversity, composition, and functional potential when compared to healthy controls, and that the saliva microbiota is influenced by lifestyle.

While the cause-and-effect relationship requires further investigation, our findings contribute to a growing understanding of how alterations in oral microbiota may be linked to immune activation and the risk of systemic inflammatory diseases.

Data Sharing Statement

The raw sequencing data generated in this study have been deposited in the European Nucleotide Archive (ENA) under the accession number PRJEB90572 and are publicly available. All data is available upon request from the corresponding author.

Ethics Statement

The Danish Data Protection Agency (VD-2018-415) and the Scientific Ethics Committee of the Capital Region of Denmark (H-18041455) approved the study. Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

T.T. has been an investigator of Novartis, Abbvie, Dr. Wolff, Galderma, and Almirall. C.Z. has been a scientific consultant, advisor, investigator, and speaker for Eli Lilly, Jansen Cilag, Novartis, AbbVie, Takeda, Amgen, Almirall, CSL, UCB, Regeneron, MSD, and Leo Pharma. L.S. has been an investigator, speaker, and/or advisor of AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Novo Nordisk, Pfizer, Sanofi Genzyme, Takeda, and UCB. The other authors report no conflicts of interest in this work.

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