BJD
British Journal of Dermatology

Patients with psoriasis have a dysbiotic taxonomic and functional gut microbiota*

Tanja Todberg,[1,2] Alexander Egeberg,[3] Claus Zachariae,[1,2] Nikolaj Sørensen,[4] Oluf Pedersen[5] and Lone Skov[1,2]

[1]Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, DK,2900,Denmark
[2]Copenhagen Research Group for Inflammatory Skin (CORGIS), Hellerup, Denmark
[3]Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark
[4]Clinical Microbiomics, Copenhagen, Denmark
[5]Novo Nordisk Foundation Centre for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Abstract

Background Accumulating evidence supports the findings of an altered gut microbiota in patients with autoimmune disease. However, existing studies on the role of the gut microbiota in patients with psoriasis have demonstrated conflicting results and have mainly been based on 16s rRNA gene sequencing analysis.

Objectives To examine whether the gut microbiota of patients with psoriasis was altered in composition and functional potentials compared with healthy controls, and as a second approach compared with healthy cohabitant partners. A further aim was to investigate relationships to disease severity, and seasonal impact on the gut microbiota.

Methods In a case–control study, 126 faecal samples were collected from a sample of 53 systemically untreated patients with plaque psoriasis; 52 healthy controls matched for age, sex and body mass index; and 21 cohabitant partners. A subpopulation of 18 patients with psoriasis and 19 healthy controls continued in a longitudinal study, where four to six faecal samples were collected over 9–12 months. The gut microbiota was characterized using shotgun metagenomic sequencing analysis.

Results A significantly lower richness ($P = 0{\cdot}007$) and difference in community composition ($P = 0{\cdot}01$) of metagenomic species was seen in patients with psoriasis compared with healthy controls, and patients with psoriasis had a lower microbial diversity than their partners ($P = 0{\cdot}04$). Additionally, the functional richness was decreased in patients with psoriasis compared with healthy controls ($P = 0{\cdot}01$) and partners ($P = 0{\cdot}05$). Increased disease severity was correlated with alterations in taxonomy and function, with a slight tendency towards a lower richness of metagenomic species, albeit not significant ($P = 0{\cdot}08$). The seasonal analysis showed no shifts in community composition in healthy controls or in patients with psoriasis.

Conclusions The findings of a different gut microbiota in composition and functional potentials between patients with psoriasis and healthy controls support a linkage between the gut microbiota and psoriasis. These findings need to be validated in larger studies, and a potential causal relationship between the gut microbiota and psoriasis still needs to be shown.

Correspondence
Tanja Todberg.
Email: tanja.todberg@regionh.dk

Accepted for publication
11 March 2022

Funding sources
This study was supported by Aage Bangs Foundation, Roberts Wehnerts and Kirsten Wehnerts Foundation, Liv Bryhns Foundation, Grosserer Fogts Foundation, the LEO Foundation and the Novo Nordisk Foundation Center for Basic Metabolic Research.

Conflicts of interest
The Conflicts of interest statement is listed in Appendix 1.

Data availability
The data are available upon request.

Ethics statement
Study approval was obtained from the Danish Data Protection Agency (VD-2018-415) and the ethics committees of the Capital Region of Denmark (H-18041455). The study was conducted in accordance with the Declaration of Helsinki.

*Plain language summary available online

DOI 10.1111/bjd.21245

It has become increasingly evident that the gut microbiota contributes to human health through multiple functions such as nutrient digestion, intestinal barrier protection and crosstalk with the immune system.[1] The association between the immune system and the gut microbiota has been an area of intense research as the microbiota is involved in the training and homeostasis of the immune system.[1] Accordingly, the gut microbiota may play a role in immune-mediated diseases such

as psoriasis. In support of this, germ-free murine models of psoriasis display decreased skin inflammation and fewer T helper (Th)17 cells in the lymphatic tissue compared with control mice,[2] suggesting a potential interaction between the gut microbiota and immune cells of psoriasis.

In humans, the gut microbiota comprises a large ecosystem of stable commensals; however, a possible mediator, such as diet, can induce rapid changes in the microbial profile.[3] In mice, a Western diet has been found to promote proinflammatory shifts and Th17-mediated dermatitis,[4] potentially giving support to the composition of the gut microbiota influencing the immune response of the host and thereby playing a role in psoriasis. Further, probably as a consequence of the chronic inflammation associated with psoriasis, cardiometabolic disorders are commonly observed in patients with psoriasis.[5]

Studies have suggested that the gut microbiota is altered in patients with psoriasis compared with that of healthy controls,[6–8] yet most of these studies were based on 16s rRNA gene marker analysis. Interest in the functional potential of the microbiota is increasing in an attempt to increase knowledge of how the gut microbiota interacts with the host in immune-mediated diseases.[1,9,10]

Here we examine the composition and the functional potential of the gut microbiota in patients with psoriasis compared with healthy controls using metagenomic shotgun sequencing analysis. As household conditions and lifestyle are known to impact the composition of gut microbiota,[11,12] cohabitant partners of the patients with psoriasis were included as a second group of healthy controls. As inflammatory diseases may be associated with instability of the gut microbiota,[13,14] potential seasonal shifts of the gut microbiota were investigated in a subpopulation of patients with psoriasis.

Patients and methods

Study approval was obtained from the Danish Data Protection Agency (VD-2018-415) and the ethics committees of the Capital Region of Denmark (H-18041455). The study was conducted in accordance with the Declaration of Helsinki.

Study population

Using a case–control design, potential taxonomic and functional differences of the gut microbiota between patients with psoriasis and healthy controls matched by age, sex and body mass index (BMI) were examined. For all patients who had a cohabiting partner, the partner was invited to participate in the study. In addition, a longitudinal study design was used to examine potential dynamics of the gut microbiota in a subpopulation of patients with psoriasis and healthy controls. The study designs are shown in Figure S1 (see Supporting Information).

Between February 2019 and September 2020, patients with psoriasis living in the capital region of Denmark were recruited from our outpatient clinics. All participants were highly selected to minimize exposure to confounding factors. Eligibility criteria were age 18–74 years, Psoriasis Area Severity Index (PASI) ≥ 8, BMI < 35 kg m^{-2}, and no use of systemic antipsoriatic or antibiotic treatment for $\geq$3 months. Patients with diabetes, autoimmune diseases, cancer or infections, and patients receiving other systemic anti-inflammatory treatment were excluded. Apart from the psoriasis-specific criteria, healthy controls, including partners, fulfilled the same eligibility criteria apart from psoriasis as did the patients with psoriasis.

Study visit and collection of samples

Patients with psoriasis underwent a clinical examination, including PASI. In addition, for all participants – patients, healthy controls and partners – details were registered of medical history, treatment, diet (Dietary Quality Score)[15] and physical activity (International Physical Activity Questionnaire).[16] A kit for collecting faecal samples at home was delivered to all participants.[17]

A subpopulation of patients with psoriasis and healthy controls continued in the longitudinal study and delivered a faecal sample every 2–3 months for a 9–12-month period. During collection, participants registered potential treatment, diet or lifestyle changes. If antibiotics had been administered, the time of sampling was increased by 3 months. Faecal samples were returned by post, where, upon arrival, they were stored at −80 °C until analysis.

Processing of samples

DNA was extracted from all samples and sequenced using metagenomic shotgun analysis. A detailed description is provided in Appendix S1 (see Supporting Information).

Statistics

Baseline characteristics are presented as the median and interquartile range (IQR), or frequency and percentage. P-values <0·05 were considered significant. Statistical comparisons were performed using the Mann–Whitney U-test, Kruskal–Wallis rank sum test and χ^2-test. Correlations between PASI and metagenomic species (MGS) and gut metabolic modules were based on Spearman correlation.

When performing statistical testing on multiple hypotheses, the Benjamini–Hochberg method was used to control the false discovery rate (FDR) at a level of 10%, thus an FDR-adjusted value of 0·1 was considered significant. The α-diversity was calculated as richness and as Shannon Index. The β-diversity was illustrated using principal coordinates analysis based on Bray–Curtis dissimilarity. To investigate whether psoriasis could be associated with a certain enterotype, community typing analysis at the genus level was performed using the Dirichlet multinomial mixtures approach.[18] In a subanalysis, specific taxa were selected based on prior study findings and

were examined for their relation to psoriasis. Multiple testing was not performed in predefined analyses based on an a priori hypothesis.

Results

Participant characteristics

In the case–control study, 126 faecal samples in total were received from 53 patients with psoriasis, 52 healthy controls and 21 partners. Patients had a median PASI of 10·0 (IQR 8·3–12·6), the median age at disease onset was 18·0 years (IQR 13·0–30·0) and the median disease duration was 23·0 years (IQR 10·0–36·0). In total, 32 patients (60%) received no antipsoriatic treatment, and the rest received topical treatment only. Eight patients (15%) also had psoriatic arthritis. Patients with psoriasis had a median age of 48·0 years (IQR 36·0–58·0) and a median BMI of 25·2 kg m^{-2} (IQR 22·9–27·4), and 29 (55%) were men. Healthy controls had a median age of 49·0 years (IQR 36·0–58·0) and a median BMI of 24·7 kg m^{-2} (IQR 22·9–27·2), and 29 (56%) were male. No significant differences in age, sex or BMI were detected between patients with psoriasis and healthy controls, or in age and BMI between patients with psoriasis and partners; however, significant differences in smoking and physical activity habits were found between patients with psoriasis and healthy controls ($P < 0·005$ and $P = 0·004$, respectively). Patients with psoriasis tended to smoke more, and more had the poorest physical activity level compared with the healthy controls. Smoking habits and physical activity did not differ between patients with psoriasis and their partners. Table 1 shows the demographics of all of the participants.

Patients with psoriasis exhibited a distinct gut microbiota profile

Adequate sequencing results were retrieved from all but two samples. The included samples had sequencing results with a minimum of 15·4 million reads per sample and an average of 22·8 million reads per sample. The remaining two samples collected from patients in the longitudinal study were excluded from analysis. The reads were matched to the HG03 gene catalogue, which allowed for a mapping match of at least 80·4% and an average of 86·6% (Figure S2; see Supporting Information).

Figure 1 provides an overview of the relative abundance aggregated at the family and genus levels for all groups. A significantly lower MGS richness was observed in patients with psoriasis than in healthy controls ($P = 0·007$), and a slight tendency was seen towards a lower richness in patients with psoriasis compared with their partners ($P = 0·09$) (Figure 2). The diversity of MGS (Shannon Index) differed significantly between the patients with psoriasis and their partners ($P = 0·04$) but not between patients with psoriasis and healthy controls (Figure 2). Moreover, β-diversity showed a significant separation between the samples from patients with psoriasis and the healthy controls, indicating that the microbial communities differed between the two groups ($P = 0·01$) (Figure 3).

At the genus level, participants were assigned to groups of dominating clusters, where three clusters of microbial variation were identified (clusters 1–3) (Figure S3; see Supporting Information). Patients with psoriasis were significantly more likely to belong to cluster 3 than healthy controls ($P = 0·04$), but there were no significant associations for clusters 1 or 2. Cluster 2 was characterized by a high proportion of *Prevotella*, whereas clusters 1 and 3 shared many of their main drivers, including a high proportion of *Bacteroides* (Figure S4; see Supporting Information).

Validation of previously identified psoriasis-associated taxa

To test specific taxa that had previously been reported to associate with psoriasis, 31 MGS belonging to the genera of *Blautia*, *Faecalibacterium* and *Paraprevotella* and the species *Akkermansia muciniphila* were analysed. Two species {[*Ruminococcus*] *torques* and [*Ruminococcus*] *gnavus*} belonging to the genus *Blautia* showed a higher abundance ($P < 0·05$), and one species (*Faecalibacterium sp.* OF04-11AC) belonging to the genus *Faecalibacterium* displayed a lower abundance in patients with psoriasis than in healthy controls (Figures S5–S7; see Supporting Information).

Lower functional potential in the gut microbiome of patients with psoriasis

Patients with psoriasis displayed lower functional richness compared with healthy controls ($P = 0·01$) and compared with their partners ($P = 0·05$). Evenness of gut metabolic modules was similar between all groups (Figure 4). The β-diversity analysis of functional capacity showed that patients with psoriasis were significantly separated from the healthy control ($P = 0·02$), but not from their partners (Figure 5). The gut metabolic modules of glutamate degradation, isoleucine degradation, asparagine degradation and nitrate reduction, and the Entner–Doudoroff pathway displayed significantly higher abundance in patients with psoriasis than in healthy controls (FDR < 0·1).

Impact of lifestyle factors and medication on the microbial community

No impact of smoking or physical activity on the taxonomic or functional potential of the gut microbiome could be observed. Too few participants were receiving concomitant treatment for a meaningful analysis of the confounding effect of treatment (Table 1).

Severity of psoriasis may correlate with microbial composition

Patients with severe psoriasis tended to display a lower MGS richness ($P = 0·08$) (Figure S8; see Supporting Information). No

Table 1 Baseline demographics of participants

	Psoriasis (n = 53)	Controls (n = 52)	P-value	Partners (n = 21)	P-value
Age (years) median (IQR)	48·0 (36·0–58·0)	49·0 (36·0–58·0)	0·95	47·0 (40·0–56·0)	0·89
Sex (male)	29 (55)	29 (56)	0·91	8 (38)	0·20
BMI (kg m^{-2}), median (IQR)	25·2 (22·9–27·4)	24·7 (22·9–27·2)	0·93	24·4 (22·8–27·9)	0·74
Psoriasis characteristics					
PASI, median (IQR)	10 (8·3–12·6)				
Age at onset (years), median (IQR)	18·0 (13·0–30·0)				
Duration of disease, median (IQR)	23·0 (10·0–36·0)				
Ongoing psoriasis treatment					
None/topical emollient	32 (60)				
Topical treatment (corticosteroid ± vitamin D)	21 (40)				
Previous psoriasis treatment					
None/topical emollient	2 (4)				
Topical corticosteroid	25 (48)				
Topical corticosteroids with vitamin D	26 (49)				
Tar	19 (36)				
Ultraviolet B	42 (79)				
Psoralen plus ultraviolet A	9 (17)				
Systemic (methotrexate, biologics)	27 (51)				
Time since systemic treatment (years), median (IQR)	3 (2·5–4·5)				
Family history of psoriasis					
Yes	20 (38)				
No	33 (62)				
Psoriatic arthritis (physician diagnosed)					
Yes	8 (15)				
No	41 (77)				
Unknown	4 (8)				
Comorbidities					
Active or history of periodontitis	8 (15)	8 (15)	0·37	4 (18)	0·63
Hypertension	7 (12)	2 (4)	0·092	3 (14)	0·75
Other nonpsoriasis treatment					
Time since treatment with antibiotics (years), median (IQR)	2·0 (1.0–5·0)	3·0 (1.0–5·0)	0·40	2·0 (0·75–4·5)	0·74
Motility affecting treatment	0 (0)	0 (0)		0 (0)	
Statins	6 (11)	3 (6)	0·31	1 (5)	0·39
Other nonsystemic anti-inflammatory	1 (2)	2 (4)	0·55	1 (5)	0·49
Antidepressants	2 (4)	1 (2)	0·16	0 (0)	0·36
Proton pump inhibitors	2 (4)	0 (0)		0 (0)	
Smoking					
Yes	11 (21)	3 (6)	< 0·001	4 (19)	0·26
Former	27 (51)	12 (23)		7 (33)	
No	15 (28)	37 (71)		10 (71)	
Use of alcohol (units per week)					
0	15 (28)	11 (21)	0·34	3 (14)	0·066
1–7	28 (53)	30 (58)		13 (62)	
8–14	3 (6)	8 (15)		5 (24)	
15–21	5 (9)	2 (4)		0 (0)	
> 21	2 (4)	1 (2)		0 (0)	
Level of physical activity					
Low	16 (30)	3 (6)	0·004	4 (19)	0·61
Moderate	25 (47)	30 (58)		12 (57)	
High	12 (23)	19 (36)		5 (24)	
Dietary habits					
Unhealthy	3 (6)	3 (6)	0·62	1 (5)	0·19
Moderate	39 (77)	34 (65)		18 (86)	
Healthy	11 (21)	15 (29)		2 (10)	
High-sensitivity C-reactive protein (mg L^{-1}), median (IQR)	1·2 (0·5–3·0)	0·9 (0·3–1·5)	0·058	0·7 (0·5–3·5)	0·61

The data are presented as n (%) unless stated otherwise. BMI, body mass index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index.

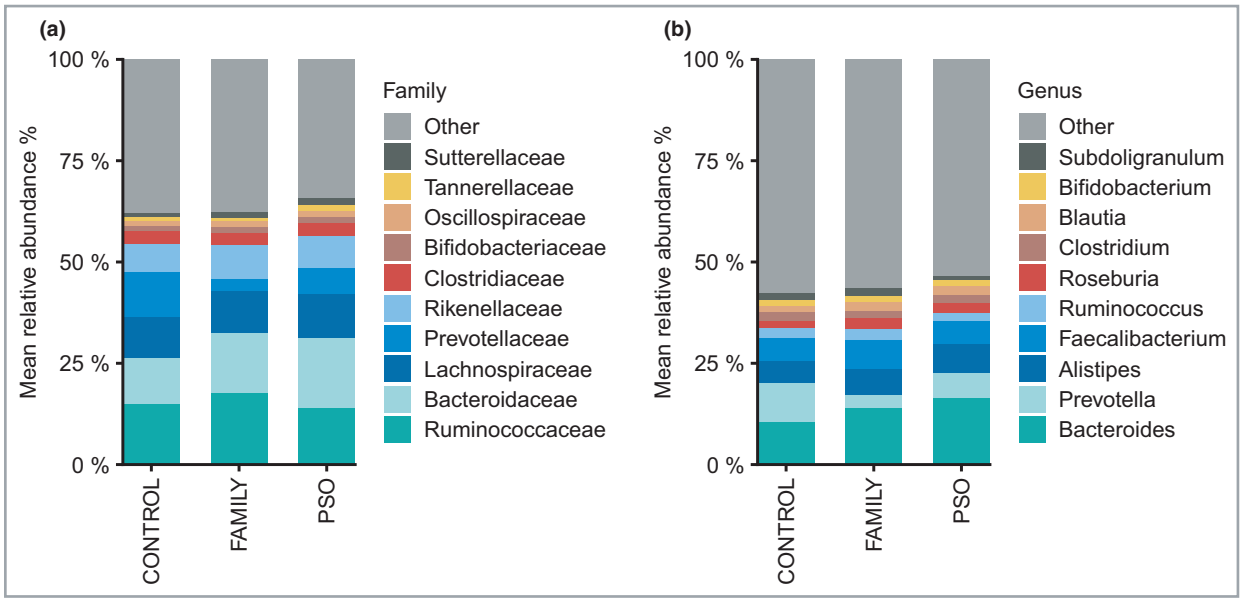

Figure 1 Mean relative abundance aggregated at (a) the family level and (b) the genus level. PSO, patients with psoriasis (n = 53); CONTROL, healthy controls (n = 52); FAMILY, healthy partners (n = 21).

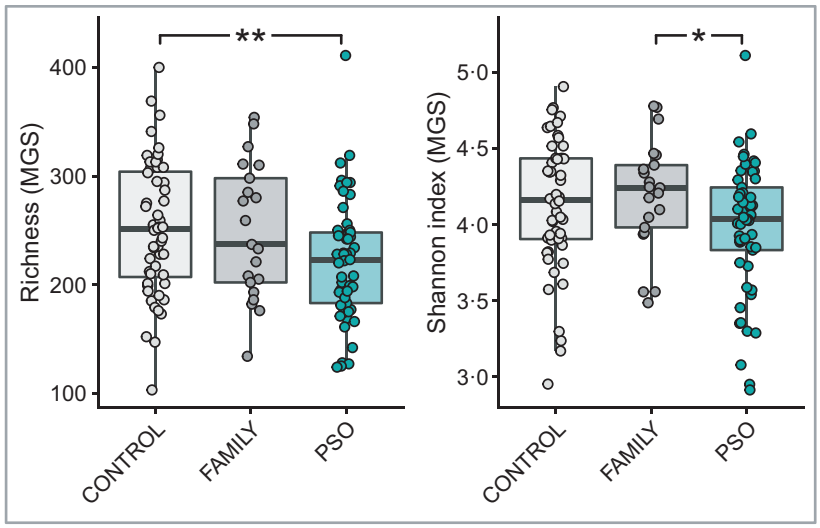

Figure 2 The gut microbiota of patients with psoriasis differed from that of healthy controls in metagenomic species (MGS) richness (P = 0·0073) and in diversity from partners (P = 0·039). A tendency towards a lower richness in patients with psoriasis compared with partners was seen (P = 0·093). The boxplots display microbial α-diversity assessed as richness and evenness (Shannon Index) of metagenomic species. PSO, patients with psoriasis (n = 53); CONTROL, healthy controls (n = 52); FAMILY, healthy partners (n = 21). *P < 0·05, **P < 0·01.

correlation was seen between PASI and richness of gut metabolic modules (Figure S9; see Supporting Information). The phyla Actinobacteria and Euryarchaeota and the family *Methanobacteriaceae* were significantly increased in those with more severe disease (FDR-corrected P = 0·059, 0·059 and 0·092, respectively). In addition, increased methanogenesis and decreased butyrate production were associated with higher PASI, although these were borderline significant (FDR-corrected P = 0·13 and 0·13). No correlation could be identified between any functional pathway and having a comorbidity of psoriatic arthritis, having a family disposition to psoriasis, or age at onset.

Seasonal changes induced no alteration in microbiota

In the longitudinal study, 193 faecal samples were collected from the subpopulation comprising 18 patients with psoriasis and 19 healthy controls (four to six samples per participant). Table S1 (see Supporting Information) shows the baseline characteristics of the participants.

No significant seasonal variation of the microbiota in patients with psoriasis or in healthy controls could be observed at a taxonomic (P = 0·72 and 0·97) (Figures S10 and S11; see Supporting Information) or functional level

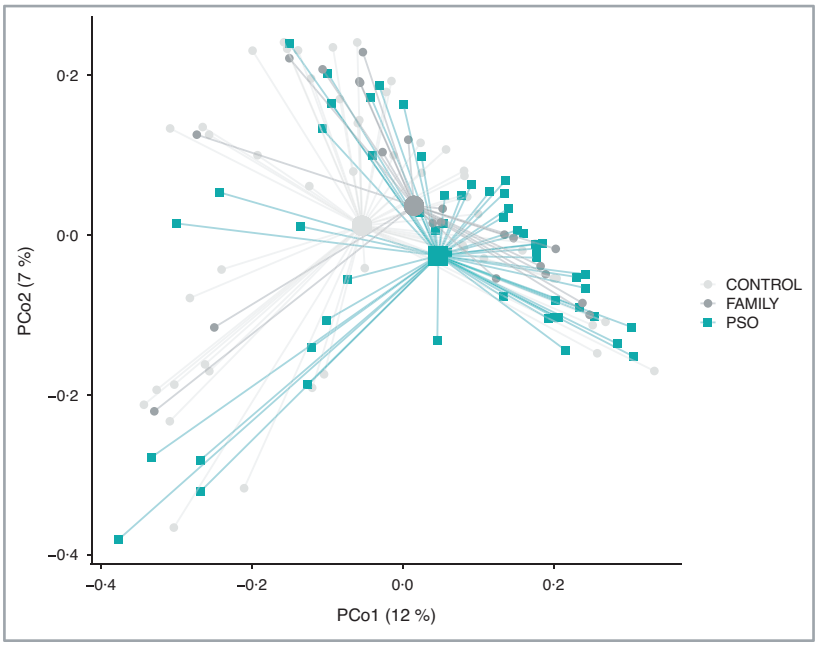

Figure 3 Community composition of patients with psoriasis differed from that of healthy controls (P = 0·014). Principal coordinates analysis (PCoA) based on Bray–Curtis dissimilarities among samples based on metagenomic species abundances. The mean (centroid) of samples in each group is indicated with a larger dot. Percentages on the *x*-axis and *y*-axis indicate microbial variance explained by the first two principal coordinates. PSO, patients with psoriasis (n = 53); CONTROL, healthy controls (n = 52); FAMILY, healthy partners (n = 21).

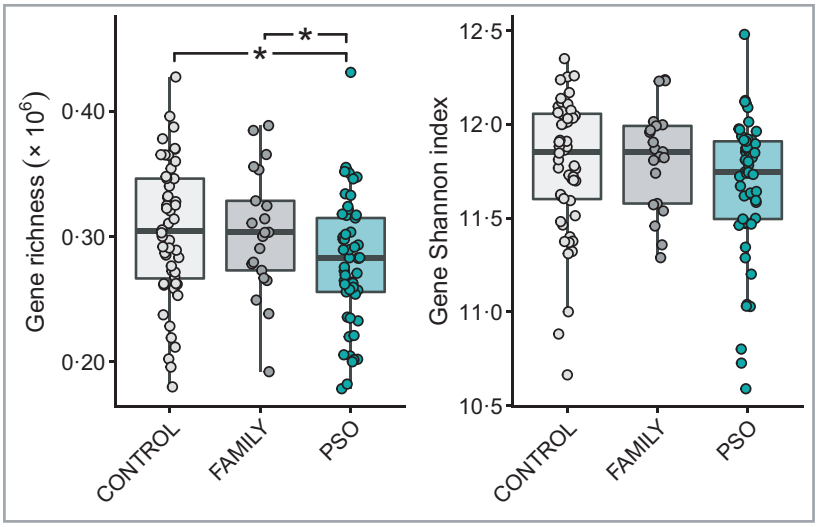

Figure 4 The function of the gut microbiota of patients with psoriasis differed in richness from that of healthy controls (P = 0·012) and partners (P = 0·051). The boxplots show differences in functional richness and Shannon Index. PSO, patients with psoriasis (n = 53); CONTROL, healthy controls (n = 52); FAMILY, healthy partners (n = 21). *P < 0·05.

(P = 0·49 and 0·89) (Figures S12 and S13; see Supporting Information).

Discussion

Using metagenomic shotgun sequencing analysis, we found that the gut microbiota of patients with psoriasis displayed lower richness of MGS and functional potentials and differed in community composition compared with that of healthy controls. Further, we observed a tendency towards lower MGS richness in patients with psoriasis compared with their cohabitant partners. In a subanalysis, we showed that severity of psoriasis displayed a slight tendency towards a lower richness, as well as alternations in taxonomy and in function. We observed no fluctuation according to season in the microbial composition in patients with psoriasis.

In agreement with previous studies examining the gut microbiota in patients with psoriasis, we provide evidence of an aberrant gut microbiota profile in patients with psoriasis compared with healthy controls.[6,7,19] Our findings are supported by a recent study using 16S rRNA gene-based microbial profiling analysis by Hidalgo-Cantabrana *et al.*, who demonstrate a reduced richness (defined as the number of operational taxonomic units) in patients with psoriasis (n = 19) compared with healthy controls (n = 20).[7] In contrast, Codoñer *et al.*, also using 16S rRNA gene-based microbial profiling analysis, found that patients with psoriasis (n = 52) had a more diverse gut microbiota than healthy controls (n = 52).[6] The different findings in the two studies may be due to their studies including nongeographically matched control individuals and not including information on other medical treatment, BMI, diabetes or use of antibiotics; therefore, there was most likely not an adequate match between patients and control individuals.

In line with these results, studies examining the gut microbiota in patients with other inflammatory diseases, such as inflammatory bowel disease[20] and multiple sclerosis,[21] have presented varying results, hence other factors may influence and contribute to alterations of composition of the gut microbiota.[22] Despite several studies showing different outcomes, accumulating evidence supports the potential of the gut microbiota to play a role in both inflammatory and metabolic diseases such as type 2 diabetes and obesity.[23,24] For example, the microbial profile of monozygotic twins with divergent BMI has been associated with a lower abundance of fibre-degrading bacteria in obese compared with lean individuals.[24] Also, the obesity-associated gut microbiota causes obesity when transferred to germ-free mice.[25]

Metabolic disorders including dyslipidaemia, type 2 diabetes and obesity are common comorbidities in patients with psoriasis;[5,26] however, the current study comprised lean patients without type 2 diabetes, hence the observation of a decreased richness and functionality in gut microbiota in our study sample of patients with psoriasis is not related to dysglycaemia or obesity and may overall support the hypothesis of an aberrant gut microbiota per se in patients with psoriasis. Nevertheless, reduced insulin sensitivity has also been observed in patients with psoriasis without type 2 diabetes compared with BMI-matched controls,[27] thus psoriasis may belong to the long list of insulin-resistant states that often feature altered gut microbiota profiles.[28] In support of this, we identified an enriched functional potential in the abundance of isoleucine degradation, which has been linked with increased insulin resistance;[29] however, the role of the identified pathways in psoriasis needs further investigation. Systemic inflammation and obesity have been linked with an enterotype configuration characterized by a high presence of *Bacteroides* and low presence of *Faecalibacterium*;[30] however, community typing analysis did not associate our patients with this enterotype.

In studies examining the gut microbiota of patients with other inflammatory diseases, a variety of taxa have been highlighted as characteristic features of the diseases.[8,31] In the analysis of preselected taxa, we could confirm the presence of some species, including an increase in those belonging to the genus *Blautia*, whereas we were unable to assign other

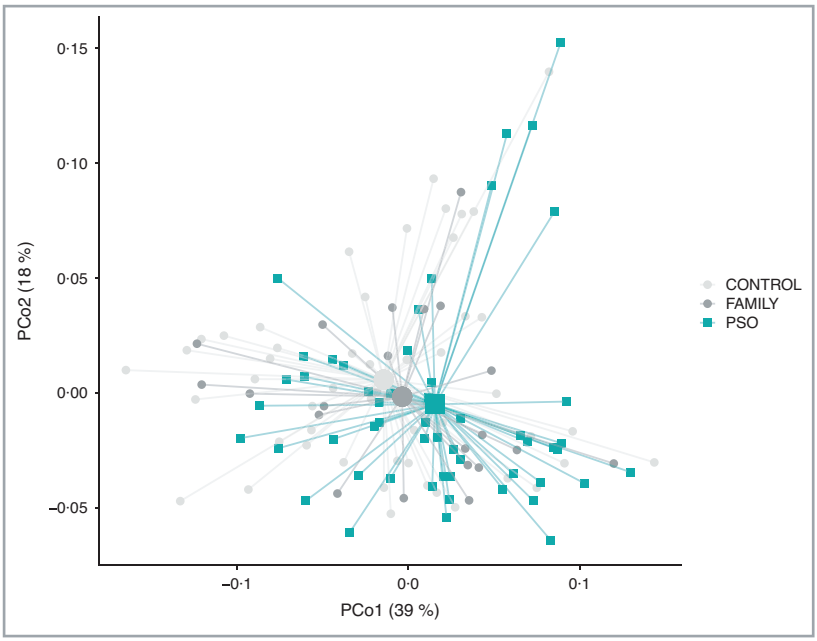

Figure 5 Functional community composition of patients with psoriasis differed from that of healthy controls (P = 0·01). Principal coordinates analysis (PCoA) based on Bray–Curtis dissimilarities among samples based on gut metabolic module abundances. The mean (centroid) of samples in each group is indicated with a larger dot. Percentages on the *x*-axis and *y*-axis indicate microbial variance explained by the first two principal coordinates. PSO, patients with psoriasis (n = 53); CONTROL, healthy controls (n = 52); FAMILY, healthy partners (n = 21).

preselected taxa to psoriasis. However, the fluctuating course and activity of the disease might impact the results. In keeping with this, and as shown by others,[32] we identified a correlation between the severity of psoriasis and an altered microbial profile. Here, we found that the abundance of the family *Methanobacteriaceae* and decreased gut microbiome butyrate production potential were directly correlated with psoriasis severity. Butyrate is a short-chain fatty acid known to impact regulatory T cells, playing a role in immune suppression by regulating the Th17 reponse.[33] In peripheral blood mononuclear cells from patients with psoriasis, the suppressive function of regulatory T cells has been shown to be impaired compared with healthy controls.[34]

Spondylarthritis is another inflammatory disease that has been linked with gut dysbiosis and that shares immunology with psoriasis.[35] Evidence of microscopic inflammation in the intestinal wall of patients with spondylarthritis has been provided, and a positive correlation between intestinal inflammation and disease severity has been reported.[36] Because psoriasis and spondylarthritis are strongly associated and are due to the chronic inflammation seen in psoriasis, patients with psoriasis might also have intestinal inflammation, which in turn might contribute to a dysbiotic microbiota.

One method to study the association between inflammation and the gut microbiota is the use of longitudinal designs in diseases with flares. Halfvarson and colleagues[13] examined the gut microbiota in cases of inflammatory bowel disease (IBD) (n = 109) and healthy controls (n = 9), showing that although the gut microbiota in healthy controls displayed intraindividual variation over time, the microbial shifts were more prominent in those with IBD. Interestingly, in our study, no volatility in taxonomy or in functional potentials of the gut microbiota could be identified in patients with psoriasis or healthy controls. Although psoriasis is characterized by flares, the negative findings may be explained by only a minor fluctuation of the course of psoriasis severity in our group during sample collection. In contrast to patients with psoriasis, patients with IBD are often affected by extraintestinal symptoms such as fever and malaise mediated by an altered immune response, which may be associated with dynamic changes of the gut microbiota.[37,38]

Although we could not identify a shift in gut microbiota, the variation between patients with psoriasis and their partners supports the linkage between the psoriasis and the microbiota. Previously it has been shown that cohabitant individuals have a more similar microbiota than monozygotic twins, suggesting that environmental conditions have a greater impact than genes on the microbial community.[11,12] Therefore, the identified microbial variation between patients with psoriasis and their partners may be prescribed to the psoriasis, as the lifestyles of the cohabitant partners were similar.

A strength of this study is the enrolment of a carefully selected group of patients with psoriasis who were matched with the control persons on age, sex and BMI. We did not include patients receiving systemic antipsoriatic treatment or drugs known to affect the gut microbiota. Concomitant treatment including use of antibiotics, and lifestyle habits were registered and we found no statistical evidence on confounding. In addition, we included a group of cohabitant partners.

Among the limitations of the study are its small size for microbiota assessment. In addition, our library did not include MGS of eukaryotic viruses, phages or fungi. Although we used metagenomic shotgun sequencing, this is limited by detecting bacterial DNA, which may include detection of dead material. Another limitation includes the faecal samples serving as a proxy for the microbial profile of the gut content. Moreover, participants may have differences in their dietary habits that were not registered despite using the Dietary Quality Score. This may affect the microbiota independently of psoriasis.

In conclusion, the identified dysbiotic composition and functional gut microbiota in patients with psoriasis support an association between the gut microbiota and psoriasis. However, microbiome research is still at an early stage, where much remains to be elucidated, hence important steps include validating the findings in large independent studies, which may provide deeper insights into the gut microbiota patterns of patients with psoriasis. Potentially, this could lead to studies examining the modulatory effects on the gut microbiota in patients with psoriasis as a step towards clinical integration of the findings.

References

1 Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. *N Engl J Med* 2016; **375**:2369–79.
2 Zakostelska Z, Malkova J, Klimesova K *et al.* Intestinal microbiota promotes psoriasis-like skin inflammation by enhancing Th17 response. *PLOS ONE* 2016; **11**:e0159539.
3 Hansen LBS, Roager HM, Søndertoft NB *et al.* A low-gluten diet induces changes in the intestinal microbiome of healthy Danish adults. *Nat Commun* 2018; **9**:4630.
4 Shi Z, Wu X, Yu S *et al.* Short-term exposure to a Western diet induces psoriasiform dermatitis by promoting accumulation of IL-17A-producing γδ T cells. *J Invest Dermatol* 2020; **140**:1815–23.
5 Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. *Lancet* 2021; **397**:1301–15.
6 Codoñer FM, Ramírez-Bosca A, Climent E *et al.* Gut microbial composition in patients with psoriasis. *Sci Rep* 2018; **8**:3812.
7 Hidalgo-Cantabrana C, Gomez J, Delgado S *et al.* Gut microbiota dysbiosis in a cohort of patients with psoriasis. *Br J Dermatol* 2019; **181**:1287–95.
8 Tan L, Zhao S, Zhu W *et al.* The *Akkermansia muciniphila* is a gut microbiota signature in psoriasis. *Exp Dermatol* 2018; **27**:144–9.
9 Quince C, Walker AW, Simpson JT *et al.* Shotgun metagenomics, from sampling to analysis. *Nat Biotechnol* 2017; **35**:833–44.
10 Pérez-Cobas AE, Gomez-Valero L, Buchrieser C. Metagenomic approaches in microbial ecology: an update on whole-genome and marker gene sequencing analyses. *Microb Genom* 2020; **6**:mgen00409.
11 Dill-McFarland KA, Tang ZZ, Kemis JH *et al.* Close social relationships correlate with human gut microbiota composition. *Sci Rep* 2019; **9**:703.
12 Rothschild D, Weissbrod O, Barkan E *et al.* Environment dominates over host genetics in shaping human gut microbiota. *Nature* 2018; **555**:210–15.

13 Halfvarson J, Brislawn CJ, Lamendella R *et al*. Dynamics of the human gut microbiome in inflammatory bowel disease. *Nat Microbiol* 2017; **2**:17004.
14 Braun T, Di Segni A, Benshoshan M *et al*. Individualized dynamics in the gut microbiota precede Crohn's disease flares. *Am J Gastroenterol* 2019; **114**:1142–51.
15 Toft U, Kristoffersen LH, Lau C *et al*. The Dietary Quality Score: validation and association with cardiovascular risk factors: the Inter99 study. *Eur J Clin Nutr* 2007; **61**:270–8.
16 Craig CL, Marshall AL, Sjöström M *et al*. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; **35**:1381–95.
17 Szopinska JW, Gresse R, van der Marel S *et al*. Reliability of a participant-friendly fecal collection method for microbiome analyses: a step towards large sample size investigation. *BMC Microbiol* 2018; **18**:110.
18 Holmes I, Harris K, Quince C. Dirichlet multinomial mixtures: generative models for microbial metagenomics. *PLOS ONE* 2012; **7**:e30126.
19 Shapiro J, Cohen NA, Shalev V *et al*. Psoriatic patients have a distinct structural and functional fecal microbiota compared with controls. *J Dermatol* 2019; **46**:595–603.
20 Pittayanon R, Lau JT, Leontiadis GI *et al*. Differences in gut microbiota in patients with versus without inflammatory bowel diseases: a systematic review. *Gastroenterology* 2020; **158**:930–46.
21 Mirza A, Forbes JD, Zhu F *et al*. The multiple sclerosis gut microbiota: a systematic review. *Mult Scler Relat Disord* 2020; **37**:101427.
22 Dein EJ, Wigley FM, McMahan ZH. Linaclotide for the treatment of refractory lower bowel manifestations of systemic sclerosis. *BMC Gastroenterol* 2021; **21**:174.
23 Allin KH, Tremaroli V, Caesar R *et al*. Aberrant intestinal microbiota in individuals with prediabetes. *Diabetologia* 2018; **61**: 810–20.
24 Tims S, Derom C, Jonkers DM *et al*. Microbiota conservation and BMI signatures in adult monozygotic twins. *ISME J* 2013; **7**:707–17.
25 Ridaura VK, Faith JJ, Rey FE *et al*. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 2013; **341**:1241214.
26 Norden A, Rekhtman S, Strunk A, Garg A. Risk of psoriasis according to body mass index: a retrospective cohort analysis. *J Am Acad Dermatol* 2022; in press; https://doi.org/10.1016/j.jaad.2021.06.012.
27 Gyldenløve M, Storgaard H, Holst JJ *et al*. Patients with psoriasis are insulin resistant. *J Am Acad Dermatol* 2015; **72**:599–605.
28 Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol* 2020; **19**:55–71.
29 Pedersen HK, Gudmundsdottir V, Nielsen HB *et al*. Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature* 2016; **535**:376–81.
30 Vieira-Silva S, Falony G, Belda E *et al*. Statin therapy is associated with lower prevalence of gut microbiota dysbiosis. *Nature* 2020; **581**:310–15.
31 Maeda Y, Takeda K. Role of gut microbiota in rheumatoid arthritis. *J Clin Med* 2017; **6**:60.
32 Dei-Cas I, Giliberto F, Luce L *et al*. Metagenomic analysis of gut microbiota in non-treated plaque psoriasis patients stratified by disease severity: development of a new Psoriasis-Microbiome Index. *Sci Rep* 2020; **10**:12754.
33 Nussbaum L, Chen YL, Ogg GS. Role of regulatory T cells in psoriasis pathogenesis and treatment. *Br J Dermatol* 2021; **184**:14–24.
34 Schwarz A, Philippsen R, Schwarz T. Induction of regulatory T cells and correction of cytokine disbalance by short-chain fatty acids: implications for psoriasis therapy. *J Invest Dermatol* 2020; **141**:95–104.
35 Scher JU, Littman DR, Abramson SB. Microbiome in inflammatory arthritis and human rheumatic diseases. *Arthritis Rheumatol* 2016; **68**:35–45.
36 Van Praet L, Jans L, Carron P *et al*. Degree of bone marrow oedema in sacroiliac joints of patients with axial spondyloarthritis is linked to gut inflammation and male sex: results from the GIANT cohort. *Ann Rheum Dis* 2014; **73**:1186–9.
37 Vogelaar L, de Haar C, Aerts BR *et al*. Fatigue in patients with inflammatory bowel disease is associated with distinct differences in immune parameters. *Clin Exp Gastroenterol* 2017; **10**:83.
38 Singh S, Blanchard A, Walker JR *et al*. Common symptoms and stressors among individuals with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2011; **9**:769–75. 1

Appendix

Conflicts of interest

T.T. has been an investigator for Novartis, AbbVie, Dr Wolff, Galderma and Almirall. A.E. has received research funding from Pfizer, Eli Lilly, Novartis, Bristol Myers Squibb, AbbVie, Janssen Pharmaceuticals, the Danish National Psoriasis Foundation, the Simon Spies Foundation, and the Kgl Hofbundtmager Aage Bang Foundation; and honoraria as a consultant and/or speaker from AbbVie, Almirall, LEO Pharma, Galápagos NV, Sun Pharmaceuticals, Samsung Bioepis Co., Ltd, Pfizer, Eli Lilly and Company, Novartis, Galderma, Dermavant, UCB, Mylan, Bristol Myers Squibb and Janssen Pharmaceuticals. C.Z. has been an advisor, investigator and speaker for AbbVie, Eli Lilly, Novartis, Sanofi, LEO Pharma, UCB, CSL and Almirall. L.S. has been an advisor, investigator and speaker for AbbVie, Eli Lilly, Novartis, Sanofi, Celgene, LEO Pharma, BMS, UCB and Almirall, outside the submitted work. L.S. reports nonfinancial support from AbbVie, Sanofi and Janssen, and grants from Novartis, Janssen, BMS and Sanofi. The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent research centre at the University of Copenhagen that is partially funded by an unrestricted donation from the Novo Nordisk Foundation. The funding sources had no role in the study design, data collection, data analysis, data interpretation or writing of the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Supplementary methods.

Figure S1 Overview of the study designs.

Figure S2 Bar plots summarizing read quality and read mapping for all samples.

Figure S3 Faecal community types clustering based on Dirichlet multinominal mixture modelling.

Figure S4 Heatmap of the community composition of each cluster.

Figure S5–S7 Abundance of preselected taxa in patients with psoriasis vs. healthy controls and partners.

Figure S8 Spearman correlation showed a tendency of correlation ($P = 0{\cdot}08$) between severity of psoriasis and decreased richness of metagenomic species.

Figure S9 Spearman correlation showed no correlation between severity of psoriasis and richness of gut metabolic modules ($P = 0{\cdot}89$).

Figure S10 and S11 Season had no impact on metagenomic species ($P = 0{\cdot}72$) or gut metabolic modules ($P = 0{\cdot}49$) in longitudinally collected samples from patients with psoriasis ($n = 19$).

Figures S12 and S13 Season had no impact on taxonomic (metagenomic species; $P = 0{\cdot}89$) or functional community composition (gut metabolic modules; $P = 0{\cdot}97$) in longitudinally collected samples from healthy controls ($n = 18$).

Table S1 Baseline demographics of participants in the longitudinal study.