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Comorbidities in lichen planus by phenome-wide *association* study in two biobank population cohorts*

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Summary

Background Lichen planus (LP) is a relatively frequent mucocutaneous inflammatory disease affecting the skin, skin appendages and mucosae, including oral mucosae, and less frequently the anogenital area, conjunctivae, oesophagus or larynx.

Objectives To estimate the association of LP, with emphasis on dermatological and gastrointestinal conditions, in two large independent population cohorts.

Materials and methods We performed a phenome-wide association study (PheWAS) and examined conditions associated with LP in two unrelated cohorts, i.e. the multicentre, community-based UK Biobank (UKB: 501 381 controls; 1130 LP subjects) and the healthcare-associated Penn Medicine BioBank (PMBB; 42 702 controls; 764 LP subjects). The data were analysed in 2021. The 'PheWAS' R package was used to perform the PheWAS analyses and Bonferroni correction was used to adjust for multiple testing. Odds ratios (ORs) were adjusted for age, sex and body mass index.

Results In the UKB, PheWAS revealed 133 phenome codes (PheCodes) significantly associated with LP and most of them were confirmed in PMBB. Dermatological and digestive PheCodes were the most abundant: 29 and 34 of these disorders, respectively, were significantly overrepresented in LP individuals from both cohorts. The 29 dermatological and 12 oral disorders were often highly enriched, whereas hepatic, gastric, oesophageal and intestinal PheCodes displayed ORs in the range of 1·6–4·5. Several autoimmune disorders also exhibited OR > 5 in both cohorts.

Conclusions PheWAS in two large unrelated cohorts identified previously unknown comorbidities and may support clinical counselling of patients with LP.

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What is already known about this topic?

- Lichen planus (LP) is known to affect the skin, skin appendages and mucosae, including oral mucosae, and less frequently the anogenital area, conjunctivae, oesophagus or larynx.

What does this study add?

- Our data provide the most comprehensive collection of associated dermatological, digestive and autoimmune disorders to date.
- Our findings are expected to be useful for the evaluation and management of patients with LP.

Lichen planus (LP) is an inflammatory disease affecting the skin, skin appendages and mucosae. It is associated with a $CD8^+$ T-cell-mediated cytotoxic response.[1] Histologically, it is characterized by a band-like infiltration of lymphocytes along the dermal–epidermal junction and keratinocyte apoptosis, a histological pattern termed interface dermatitis.[2,3] With a prevalence of ~1%, LP is one of the most frequent idiopathic inflammatory diseases worldwide.[2] While skin and oral mucosa are the most frequently involved areas, hair follicles and nails as well as other mucous membranes, such as the anogenital area, conjunctivae, oesophagus or larynx, can also be affected.[2] There are small series and case reports describing LP of the oesophagus, which may result in dysphagia and oesophageal strictures, and increase the risk of oesophageal cancer.[3–5] For example, Kern *et al.* examined 32 consecutive patients with LP and found probable/definitive LP of the oesophagus in more than 50% of these patients.[5] The involvement of other gastrointestinal epithelia in LP in the form of gastritis, chronic duodenal ulcer and bulbitis was also suggested.[6,7] Smaller, inconclusive observations are also available for an association with ulcerative colitis or liver disease.[8,9] Finally, several studies described an enrichment of autoimmune disorders in subjects with LP.[10–12] However, most of these reports are anecdotal or small single-centre case series and therefore have a high risk of bias.

To gain better insight into comorbidities of LP and to guide more comprehensive management strategies, we have here estimated the association of other disorders with LP by performing a systematic phenome-wide association study (PheWAS) in the large multicentre, community-based UK Biobank (UKB) and validated the findings in a second, independent healthcare-associated biobank cohort (Penn Medicine BioBank, PMBB). The PheWAS analysis represents a novel, unbiased approach to discover interrelated phenotypes and to explore the association between a selected condition and a broad spectrum of phenotypes in large cohorts.[13] Its approach is analogous to genome-wide associations studies; however, instead of genetic variants, it assesses the association with the recorded phenotypic features ('phenome wide'). Therefore, both analyses are complementary, but start from different perspectives.[14]

Materials and methods

Study populations

The UKB is a long-term population-based cohort study conducted in the UK that recruited > 500 000 individuals between 2006 and 2010. All participants underwent an initial examination (questionnaires, physical and laboratory examination, etc.), and gave informed consent for genotyping and data linkage to medical reports. Diagnoses according to the International Classification of Diseases 10th revision (ICD-10) were identified by using inpatient hospital records beginning in 1996. The research has been conducted using the UKB resource under application number 47527.

Participants in the PMBB were recruited from clinical practice sites throughout the University of Pennsylvania Health System. All participants gave consent for access to electronic health record data. The inpatient and outpatient records up to July 2020 were used to identify diagnoses according to ICD-10 codes.

PheWAS analyses for L43 (lichen planus) were performed in both the UKB (cohort 1) and PMBB (cohort 2), while PheWAS for other dermatological diagnoses, i.e. L20 (atopic dermatitis), L82 (seborrhoeic keratosis) and L50 (urticaria) were carried out in cohort 1 only (Figure 1). To compare LP cases with subjects suffering from other dermatological disorders, an additional PheWAS was performed on the UKB participants by considering individuals with L03 (cellulitis), L72 (follicular cysts of skin and subcutaneous tissue), L82 (seborrhoeic keratosis) or L98 (other disorders of skin and subcutaneous tissue, not elsewhere classified) as controls (cohort 3).

Phenome-wide association studies: analysis

For each UKB and PMBB participant, clinical diagnoses based on the World Health Organization's ICD-10 coding system were collected throughout the study period and duplicates were removed. The ICD-10 codes were then converted to 9505 associated phenome codes (PheCodes),[15,16] and a series of case–control tests was performed: (1) the cohort of cases was generated by including individuals with the tested PheCode; (2) the absence of this specific PheCode led to assignment to the control group; (3) statistical analysis was performed only for PheCodes with a minimum number of 200 cases to ensure adequate statistical power.[17] In cohort 3, subjects harbouring both LP and the 'control' disorder were excluded. The PheWAS R package (R foundation) was used to perform PheWAS analyses.

Statistical analysis

Categorical variables were displayed as absolute and relative frequencies, and continuous variables were presented as means ± SD. Odds ratios (ORs) were shown with their corresponding 95% confidence intervals. Multivariable logistic regression was used to test for independent associations and all multivariable analyses were adjusted for age, sex and body mass index (BMI). Bonferroni correction was used to adjust for multiple testing in PheWAS analyses. Differences were considered to be statistically significant when $P < 0{\cdot}05$. The data were analysed using SPSS Statistics version 27 (IBM; Armonk, NY, USA) and R version 3.5.2 (The R Foundation), and visualized with Prism version 8 (GraphPad, LaJolla, CA, USA).

Results

Lichen planus associates with gastrointestinal disorders

In the UKB and PMBB, LP was diagnosed in 1130 and 764 individuals, respectively (Table 1, Figure 1). Compared with controls, LP subjects were significantly older and more often

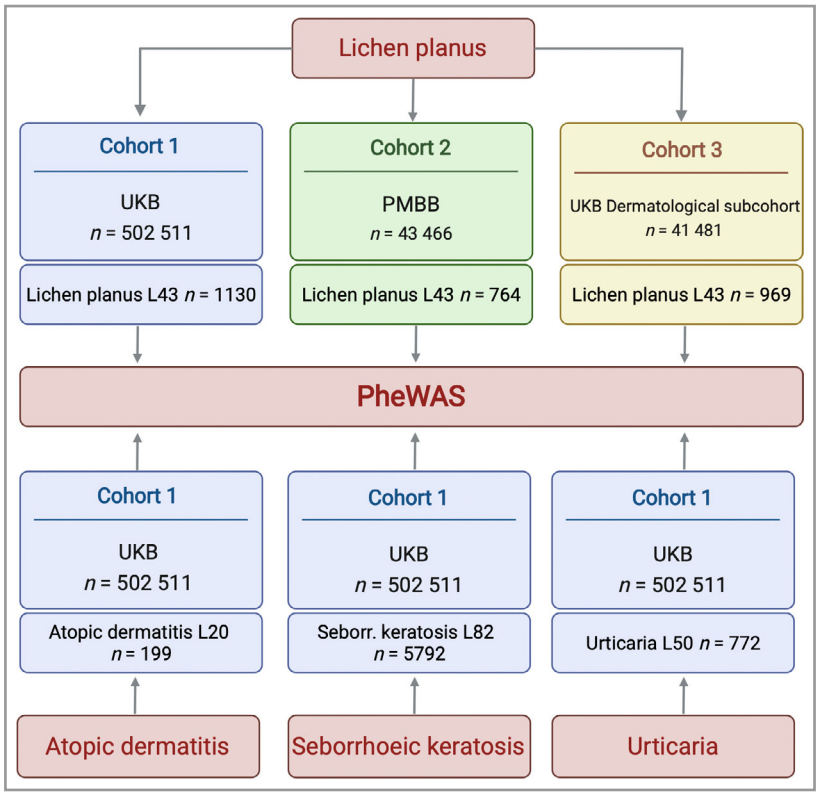

Figure 1 Overview of the analysed cohorts in UK Biobank (UKB) and Penn Medicine BioBank (PMBB). Cohort 1 (UKB): population-based study examining participants from the UKB aged 37–73 years at baseline examination. Cohort 2 (PMBB): analysis of individuals recruited throughout the University of Pennsylvania Health System. Cohort 3 (dermatological subcohort of the UKB): considering individuals with L03 (cellulitis), L72 (follicular cysts of skin and subcutaneous tissue), L82 (seborrhoeic keratosis) or L98 (other disorders of skin and subcutaneous tissue, not elsewhere classified) as controls.

Table 1 Basic characteristics of UK Biobank (UKB) individuals and Penn Medicine BioBank (PMBB) participants with and without lichen planus (LP)

Characteristics	UKB			PMBB		
	Controls n = 501 381	LP n = 1130	P-value	Controls n = 42 702	LP n = 764	P-value
Age (years)	56·5 ± 8·1	59·0 ± 7·2	**< 0·001**	55·2 ± 10·2	58·7 ± 14·3	**< 0·001**
Women (%)	54·4	68·1	**< 0·001**	50·0	57·8	**< 0·001**
Body mass index (kg m^{-2})	27·4 ± 4·8	27·8 ± 4·9	**0·006**	29·4 ± 7·8	30·8 ± 8·2	**< 0·001**
Diabetes mellitus (%)	5·3	7·6	**< 0·001**	18	35	**< 0·001**

Quantitative measures are expressed as mean with SD or relative frequency (%).

female, had slightly higher BMI and were more often diagnosed with diabetes mellitus (Table 1).

To determine diseases associated with LP, we performed multivariable PheWAS analysis. In the UKB cohort (cohort 1), LP individuals displayed 133 Bonferroni-significant PheCodes (Figure 2a; Tables S1–S4; see Supporting Information), the majority of which were confirmed in the PMBB (cohort 2). As expected, dermatological PheCodes were particularly enriched, but digestive diseases were also markedly overrepresented (Figure 2a). Together, they comprised > 50% of overrepresented PheCodes, while other categories all remained below 10% (Tables S1–S4).

To test whether the association with digestive disorders is specific for LP or is seen in other dermatological disorders as well, we performed multivariable PheWAS analyses for individuals with atopic dermatitis (L20), seborrhoeic dermatitis (L82) and urticaria (L50) (Figure 1; Table S5; see Supporting Information). In atopic and seborrhoeic dermatitis, dermatological disorders represented the most prominently associated disease group and accounted for 25% and 32% of PheCodes, respectively, while disorders of the circulatory system were most commonly enriched in individuals with urticaria (19% of PheCodes) (Figure S1a–c, Tables S6–S8; see Supporting Information). Subjects with atopic dermatitis also frequently

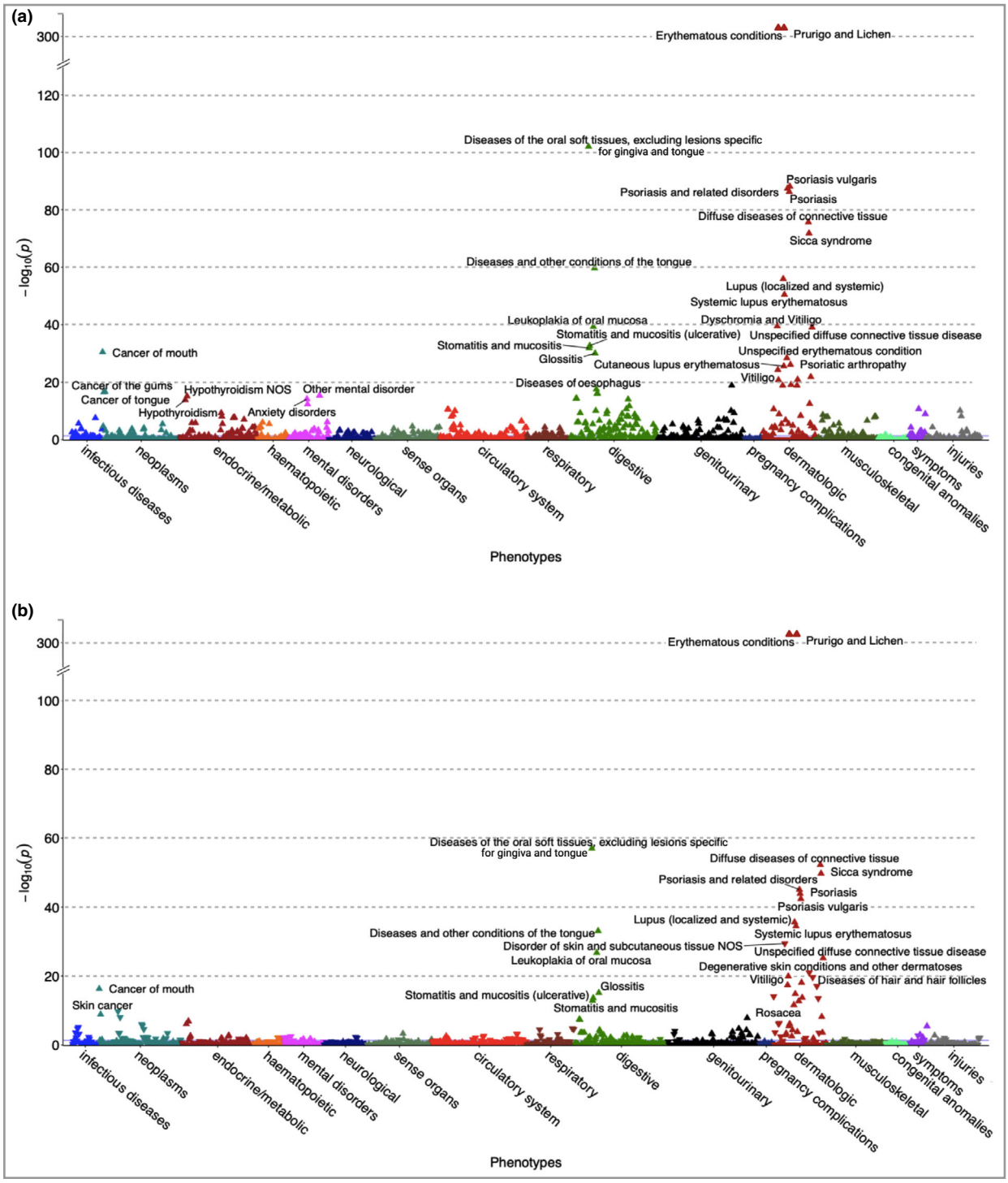

Figure 2 Manhattan plot visualizing PheCodes significantly associated with the diagnosis of lichen planus in UK Biobank (UKB) individuals (cohorts 1 and 3). (a) Manhattan plots showing Bonferroni-significant PheCodes associated with lichen planus (LP) in all UKB participants (cohort 1). (b) PheCodes enriched in LP subjects in a dermatological subgroup (cohort 3). Upwards/downwards pointing triangles refer to PheCodes that are over-/underrepresented. All analyses are adjusted for sex, age and body mass index and P-values are displayed in a −log10 format.

displayed infectious diseases, musculoskeletal disorders and respiratory PheCodes (each > 10% of associated PheCodes), whereas neoplasms (29% of PheCodes) were commonly enriched in seborrhoeic dermatitis (Figure S1a–c, Tables S6–S8). Notably, digestive disease PheCodes accounted for less than 10% of hits in all these PheWAS analyses (Tables S6–S8).

Associated dermatological PheCodes are often lichen planus-specific

In the UKB cohort (cohort 1), 32 dermatological PheCodes were significantly enriched in LP subjects vs. controls. Notably, half of them were disease-specific in that they were not associated with any other dermatological conditions described above. Among them, autoimmune disorders such as dermatitis herpetiformis, lupus erythematosus, sicca syndrome, or poly-/dermatomyositis were particularly prevalent (data not shown). Moreover, 29 of the dermatological PheCodes detected among UKB participants were also significantly overrepresented among the PMBB LP cases although the ORs tended to be lower. In both cohorts, 'erythematous conditions' and 'prurigo and lichen' were the PheCodes with the highest ORs (Table S2). 'Dyschromia/vitiligo', 'rosacea', 'dermatitis herpetiformis', 'other erythematous conditions', 'seborrhoeic dermatitis', 'specified diseases of connective tissue' and 'vascular disorders of the skin' were the other PheCodes that displayed ORs > 10 (Table S2).

To test whether the enrichment of dermatological PheCodes is due to the fact that the LP individuals were more frequently seen by dermatologists, we performed an additional analysis comparing LP individuals with subjects affected by unrelated, prevalent dermatological disorders, i.e. infectious cellulitis (L03), follicular cysts (L72), seborrhoeic keratosis (L82) or other not elsewhere classified disorders of skin and subcutaneous tissue (L98) (Figure 2b; Table S9; see Supporting Information). This analysis yielded 52 Bonferroni-significant PheCodes with 28 of them being dermatological conditions (Figure 2b; Table S10; see Supporting Information).

Gastroenterological PheCodes are not restricted to oral cavity

With regard to gastrointestinal involvement, 41 digestive PheCodes were significantly more common among UKB LP cases compared with controls (Figure 3; Tables S3 and S4). Among them, oral PheCodes/symptoms known to be associated with LP such as 'glossodynia', 'glossitis', 'stomatitis and mucositis',

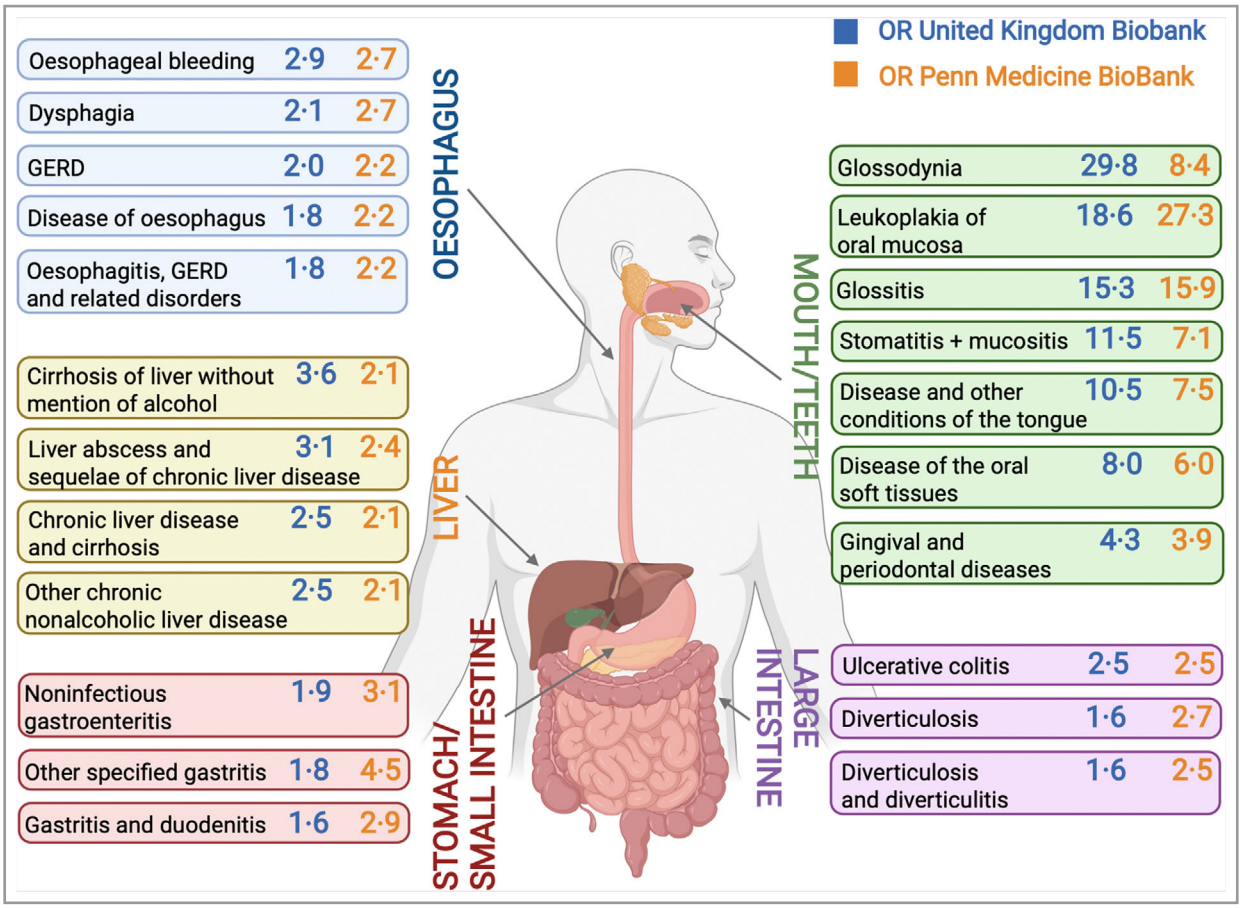

Figure 3 Overview of digestive PheCodes overrepresented in UK Biobank (UKB) subjects and Penn Medicine BioBank (PMBB) participants with lichen planus. Odds ratios (ORs) were adjusted for age, sex and body mass index and the occurrences of the corresponding PheCodes in individuals with vs. without lichen planus were compared. Blue numbers show the results from the UKB, orange numbers from the PMBB. PheCodes were divided into five groups according to their location within the gastrointestinal tract: mouth/teeth, oesophagus, liver, stomach/small intestine and large intestine. GERD, gastro-oesophageal reflux disease.

or 'leukoplakia' displayed the highest ORs. Involvement of other digestive organs (oesophagus, stomach/small intestine, large intestine, liver) presented with lower, but still significantly elevated ORs, mostly in the range of 1·6–3·6 (Figure 3; Table S3). Of these digestive PheCodes, 34 were also significantly enriched among LP subjects in the PMBB and the ORs found in both cohorts were similar (Figure 3).

When considering the absolute numbers, the most common nonoral digestive PheCodes among LP subjects were 'disease of oesophagus', 'oesophagitis, GERD [gastro-oesophageal reflux disease] and related disorders', 'gastritis and duodenitis', 'diverticulosis' and 'diverticulosis and diverticulitis', which were found in 15–25% of them. Oral neoplasms, such as cancer of the gums, lips and tongue were markedly overrepresented (Table S1); however, no significant enrichment of other digestive malignancies was seen.

Immune-related disorders associated with lichen planus

Because LP is considered a T-cell-mediated autoimmune disease, we systematically assessed our LP-PheWAS for the presence of other immune-mediated disorders.[18] Several displayed ORs > 5 in both cohorts, i.e. psoriasis, sicca syndrome, lupus erythematosus, dyschromia/vitiligo, sarcoidosis, systemic sclerosis or dermatitis herpetiformis (Table S2). Altogether, among the PheCodes that displayed an OR > 5 in both LP-PheWAS analyses, ~ 50% belonged to (auto)immune diseases.

Discussion

Our study represents PheWAS analyses of individuals with LP and other dermatological disorders, and reveals a marked overrepresentation of dermatological, autoimmune and digestive PheCodes in LP individuals. An important advantage of our study is the availability of large datasets, allowing the assessment of less frequent conditions, as well as the fact that these datasets were collected by physicians of multiple different disciplines. As expected, we found a strong overrepresentation of dermatological and oral PheCodes in individuals with LP. This is not surprising as skin and oral mucosa are the most frequently affected sites in LP.[2,19] The enrichment of dermatological PheCodes was even more prominent among subjects with LP in the UKB compared with the PMBB, which was somewhat surprising as the UKB is based primarily on inpatient data. In contrast, PMBB consists of the more comorbid, overweight population with higher rates of diabetes and presumably a higher use of the healthcare system.

An important limitation of this analysis is that it is based on ICD-10 codes assigned during the entire patient journey by various physicians and this fact may introduce some degree of misclassification. For example, this might be responsible for a strong enrichment of psoriasis and sarcoidosis given that both conditions are potential differential diagnoses of LP.[20,21] To address a potential overrepresentation of dermatological PheCodes due to surveillance bias, we performed an additional analysis that used only individuals with selected dermatological diagnoses as controls. This analysis yielded similar results, thereby corroborating skin as the organ primarily affected by LP. To further test whether the association of LP with digestive disorders is specific or whether it might be in part due to a higher use of the healthcare system, we performed PheWAS for individuals with atopic dermatitis (L20), seborrhoeic dermatitis (L82) and urticaria (L50) in the UKB. All three showed only very few associated digestive disorders, thereby supporting the specificity of association seen in LP.

In both the UKB and the PMBB, we observed a clear enrichment of oesophageal, gastric and upper gastrointestinal PheCodes. However, their occurrence seems to be lower than in previously published studies.[5,7] Because the published data stem from small, single-centre reports from tertiary centres, it is conceivable that they are skewed towards more severe cases with multi-organ involvement. Although systematic endoscopic and histological examinations revealed higher rates of oesophageal changes (such as detachment/tearing of mucosa/epithelium, T-cell infiltrate, etc.), these alterations may remain a-/oligo-symptomatic and might therefore be underdiagnosed.

The association between LP and ulcerative colitis as well as liver disease, as seen in our analysis, is supported by several case report series and smaller studies.[9,22] On the other hand, the lack of association with digestive (i.e. nonoral) malignancies is somewhat unexpected, as LP was suggested to predispose to malignant transformation, particularly when chronic erosive lesions are present.[2] An underrepresentation of individuals with malignant disorders in the assessed cohorts may account for this lack of association. In that respect, both the UKB and the PMBB do not encompass entirely representative population samples and this fact represents an important limitation of our study. In the UKB, approximately 94% of all participants are white British individuals from higher income classes. This limitation is partially offset by the PMBB, where 30% of all subjects are African Americans.[23] Moreover, ICD-codes of the UKB rely only on inpatient data, lacking information from outpatient and general practitioner (GP) records; whereas PMBB collects inpatient and outpatient data and is missing GP data. The lack of outpatient and GP data in the UKB is likely to lead to underdiagnoses of dermatological diseases that do not frequently lead to hospitalization. In this respect, the PMBB probably has a more complete coverage of these disorders because it also contains outpatient data. Nonetheless, the fact that both biobanks yielded highly reproducible findings supports the validity of our observations.[24]

Another intriguing observation is the association of LP with several immune-related disorders. Among them, an overlap with lupus erythematosus is well described in the literature,[10] while co-existence with others such as systemic sclerosis, vitiligo or sarcoidosis is supported only by case reports or report series.[25–27] These diseases share a type 1 immune bias with LP, which may explain in part the association.[28] Such an immune bias may be either genetically predetermined or the consequence of epithelial damage secondary to LP.[25,26]

Collectively, our data comprehensively characterize the phenotype of individuals with LP and yield an enrichment of

dermatological, autoimmune and digestive disorders. While PheWAS analysis is well suited to identify LP-associated conditions, it cannot distinguish between causes and consequences and the missing temporal information may introduce reverse causality bias. Therefore, further studies are needed to confirm our findings and to enable a better, evidence-based evaluation and management of subjects with LP. Analyses including GP data would be useful to provide an even more complete picture.

Acknowledgments

This research has been conducted using the UK Biobank resource. Figures were created by BioRender.com. Open Access funding enabled and organized by Projekt DEAL.

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Conflict of interest

C.S. has received honoraria as adviser for Abbvie, LEO Pharma, Lilly and Novartis and has received research funding from PPM Services/Nogra Pharma.

Ethics statement

Not applicable.

Data availability

The data sets used in this study have not been deposited in a public repository but are available after approval of a reasonable application at https://www.ukbiobank.ac.uk. All participants provided written informed consent for the study. The UK Biobank study has approval from the Northwest Multicentre research ethics committee.

Supporting Information

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

Figure S1 Manhattan plot visualizing Bonferroni-significant PheCodes enriched in UKB individuals with atopic dermatitis, seborrhoeic keratosis, and urticaria (cohort 1).
Table S1 Bonferroni-significant PheCodes (all but dermatological and digestive) associated with the diagnosis of lichen planus in the UK Biobank.
Table S2 Overview of dermatological PheCodes enriched in individuals with lichen planus in the UKB and PMBB cohorts.
Table S3 Digestive PheCodes significantly enriched in UKB subjects and PMBB individuals with the diagnosis of lichen planus.
Table S4 Overview of oral PheCodes overrepresented in individuals with lichen planus in the UKB and PMBB cohorts.
Table S5 Basic characteristics of UKB individuals with and without atopic dermatitis, seborrhoeic dermatitis and urticaria.
Table S6 Bonferroni-significant PheCodes associated with the diagnosis of atopic dermatitis in the UK Biobank.
Table S7 Bonferroni-significant PheCodes enriched in UKB individuals with the diagnosis of seborrhoeic keratosis.
Table S8 Bonferroni-significant PheCodes associated with the diagnosis of urticaria in the UK Biobank.
Table S9 Overview of basic characteristics of UKB participants with and without lichen planus in a dermatological subcohort (L03, L72, L98, L82) of the UKB.
Table S10 Overview of significantly enriched PheCodes in individuals with the diagnosis of lichen planus in a subgroup of dermatological disorders (L03, L72, L98, L82) in the UK biobank.

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