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

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participants provided written informed consent for the study. The UKB study has approval from the Northwest Multicenter research ethics committee.

Ethics statement: Not applicable

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 anogenital area, conjunctivae, esophagus, or larynx.

What does this study add?

Our data provide the hitherto most comprehensive collection of associated dermatologic, digestive, and autoimmune disorders. Our findings are expected to be useful for the evaluation and management of patients with lichen planus.

ABSTRACT

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

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

Methods: We performed a phenome-wide association study (PheWAS) and examined conditions associated with LP in two unrelated cohorts, i.e., the multicenter, community-based United Kingdom Biobank (UKB; 501,381 controls; 1130 LP subjects) and the healthcare-associated Penn Medicine Biobank (PMBB; 42702 controls; 764 LP subjects). The data were analyzed in 2021. The "PheWAS" R package was used to perform the PheWAS analyses and Bonferroni correction was utilized to adjust for multiple testing. Odds ratios (ORs) were adjusted for age, sex, and BMI.

Results: In the UKB, PheWAS revealed 133 PheCodes significantly associated with LP and most of them were confirmed in PMBB. Dermatologic and digestive PheCodes were the most abundant: 29 resp. 34 of them were significantly overrepresented in LP individuals from both cohorts. The 29 dermatologic and 12 oral disorders were often highly enriched, whereas hepatic, gastric, esophageal, and intestinal PheCodes displayed ORs in the range of 1.6-4.5. Several autoimmune disorders also exhibited OR>5 in both cohorts.

Conclusion: PheWAS in two large unrelated cohorts identified previously unknown comorbidities and may support clinical counseling of LP patients.

INTRODUCTION

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 anogenital area, conjunctivae, esophagus, or larynx, can also be affected.[2] There are small series and case reports describing LP of the esophagus (ELP), which may result in dysphagia and esophageal strictures, and increase the risk of esophageal cancer.[3-5] For example, Kern et al. examined 32 consecutive LP patients and found probable/definitive ELP in more than 50% of them.[5] The involvement of other gastrointestinal epithelia in LP in form of gastritis, chronic duodenal ulcer, and bulbitis was also suggested.[6,7] Smaller, inconclusive observations are also available for association with ulcerative colitis or liver disease.[8,9] Finally, several studies described an enrichment of autoimmune disorders in LP subjects.[10-12] However, most of these reports are anecdotal or small single-center 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 a large multicenter, community-based United Kingdom Biobank and validated the findings in a second independent healthcare-associated Biobank cohort. 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 (GWAS),

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 United Kingdom Biobank (UKB) represents a population-based cohort study conducted in the United Kingdom from 2006 to 2010 that recruited >500,000 individuals. They all 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 codes (ICD-10 codes), were identified by using inpatient hospital records beginning in 1996. The research has been conducted using the UK Biobank Resource under application number 47527.

Participants in the Penn Medicine BioBank (PMBB) were recruited from clinical practice sites throughout the University of Pennsylvania Health System. They all consented for access to electronic health record (EHR) 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 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).

PheWAS analysis

In 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 removed. The

ICD-10 codes were then converted to 9505 associated 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 only performed for PheCodes with a minimum number of 200 cases to ensure adequate statistical power.[17] In cohort 3, subjects harboring 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±standard deviations. Odds ratios (ORs) were shown with their corresponding 95% confidence intervals (CI). Multivariable logistic regression was used to test for independent associations and all multivariable analyzes were adjusted for age, sex, and body mass index (BMI). Bonferroni correction was utilized to adjust for multiple testing in PheWAS analyses. Differences were considered to be statistically significant when $p < 0.05$. The data were analyzed using SPSS Statistics version 27 (IBM; Armonk, NY, USA), 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 UKB and PMBB, LP was diagnosed in 1130 and 764 individuals, respectively (Table 1, Figure 1). Compared to controls, LP subjects were significantly older and more often female, had slightly higher body mass index 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 S1-4), the majority of which was confirmed in PMBB (Cohort 2). As expected, dermatological PheCodes were particularly enriched, but digestive diseases were also markedly

overrepresented (Figure 2A). Together, they made >50% of overrepresented PheCodes, while other categories all remained below 10% (Tables S1-4).

To test whether the association with digestive disorders is specific for LP or is seen in other dermatologic disorders as well, we performed multivariable PheWAS analyses for individuals with atopic dermatitis (L20), seborrheic dermatitis (L82), and urticaria (L50) (Figure 1; Table S5). In atopic and seborrheic dermatitis, dermatologic 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) (Figures S1A-C, Tables S6-8). Subjects with atopic dermatitis also frequently displayed infectious diseases, musculoskeletal disorders, and respiratory PheCodes (each >10% of associated PheCodes), whereas neoplasms (29% of PheCodes) were commonly enriched in seborrheic dermatitis (Figures S1A-C, Tables S6-8). Notably, digestive PheCodes accounted for less than 10% of hits in all these PheWAS analyses (Tables S6-8).

Associated dermatological PheCodes are often LP-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 dermatologic 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”, “seborrheic 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 dermatologic disorders,

i.e., infectious cellulitis (L03), follicular cysts (L72), seborrheic keratosis (L82), or other not elsewhere classified disorders of skin and subcutaneous tissue (L98) (Figure 2B; Table S9). This analysis yielded 52 Bonferroni-significant PheCodes with 28 of them being dermatological conditions (Figure 2B; Table S10).

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 to controls (Figure 3; Tables S3-4). Among them, oral PheCodes/symptoms known to be associated with LP such as "glossodynia", "glossitis", "stomatitis and mucositis", or "leukoplakia" displayed the highest ORs. Involvement of other digestive organs (esophagus, 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). Out 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 non-oral digestive PheCodes among LP subjects were "disease of esophagus, "esophagitis, GERD 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 LP

Since LP is considered a T cell-medicated autoimmune disease, we systematically assessed our LP-PheWAS for presence of other immune-mediated disorders.[18] Several of them 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 dermatologic, autoimmune, and digestive PheCodes in LP individuals. An important advantage of our study is the availability of large datasets that allows 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 LP individuals. This is not surprising since skin and oral mucosa are the most frequently affected sites in LP.[2,19] The enrichment of dermatologic PheCodes was even more prominent among LP subjects in UKB compared to PMBB, which was somewhat surprising since UKB is based primarily on inpatient data. In contrast, PMBB consists of the more co-morbid, overweight population with higher rate of diabetes and presumably a higher utilization of health-care 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. This might be for example responsible for a strong enrichment of psoriasis and sarcoidosis given that both conditions are potential differential diagnosis of LP.[20,21] To address a potential overrepresentation of dermatological PheCodes due to a 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 utilization of healthcare system, we performed PheWAS for individuals with atopic dermatitis (L20), seborrheic dermatitis (L82), and urticaria (L50) in the UKB. All three of them showed only very few associated digestive disorders thereby supporting the specificity of association seen in LP.

In both UKB and PMBB, we observed a clear enrichment of esophageal, gastric, and upper gastrointestinal PheCodes. However, their occurrence seems to be lower than in previously published studies.[5,7] Since the latter ones constitute mainly small, single-center reports from tertiary centers, it is conceivable that the latter observations are skewed towards more severe cases with multi-organ involvement. Although systematic endoscopic and histological

examinations revealed higher rates of esophageal changes (such as detachment/tearing of mucosa/epithelium, T-cell infiltrate, etc.), these alterations may remain a-/oligosymptomatic 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. non-oral) malignancies is somewhat unexpected, since 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 entirely encompass 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 are only relying on inpatient data, lacking information from outpatient and general practitioners (GP) records; whereas PMBB collects in- and outpatient data and is missing GP data. The lack of outpatient and GP data in UKB likely leads to underdiagnoses of dermatological diseases that do not frequently lead to hospitalization. In this respect, PMBB likely has a more complete coverage of these disorders since 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 are supported only by case reports/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 LP individuals and yield an enrichment of dermatologic, 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 LP subjects. Analyses including general practitioner data would be useful to provide an even more complete picture.

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FIGURE LEGENDS

Figure 1: Overview of the analyzed cohorts in United Kingdom Biobank (UKB) and Penn Medicine BioBank (PMBB).

Cohort 1: Population-based study examining participants from the UKB aged 37-73 years at baseline examination. Cohort 2: PMBB analyzing 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.

Abbreviations: UBK, United Kingdom Biobank; PMBB, Penn Medicine BioBank.

Figure 2: Manhattan plot visualizing PheCodes significantly associated with the diagnosis of Lichen planus in UKB individuals (cohort 1 and cohort 3).

(A) Manhattan plots showing Bonferroni-significant PheCodes associated with 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.

Figure 3: Overview of digestive PheCodes overrepresented in UKB subjects and PMBB participants with lichen planus.

Odds ratios were adjusted for age, sex, and body mass index and compare the occurrence of the corresponding PheCodes in individuals with vs. without Lichen planus. Blue font color represents the results from UKB, orange font color from PMBB. PheCodes were divided into five groups according to their location within the gastrointestinal tract: mouth/teeth, esophageal, liver, stomach/small intestine, and large intestine.

Abbreviations: UBK, United Kingdom Biobank; PMBB, Penn Medicine BioBank; OR, odds ratio.

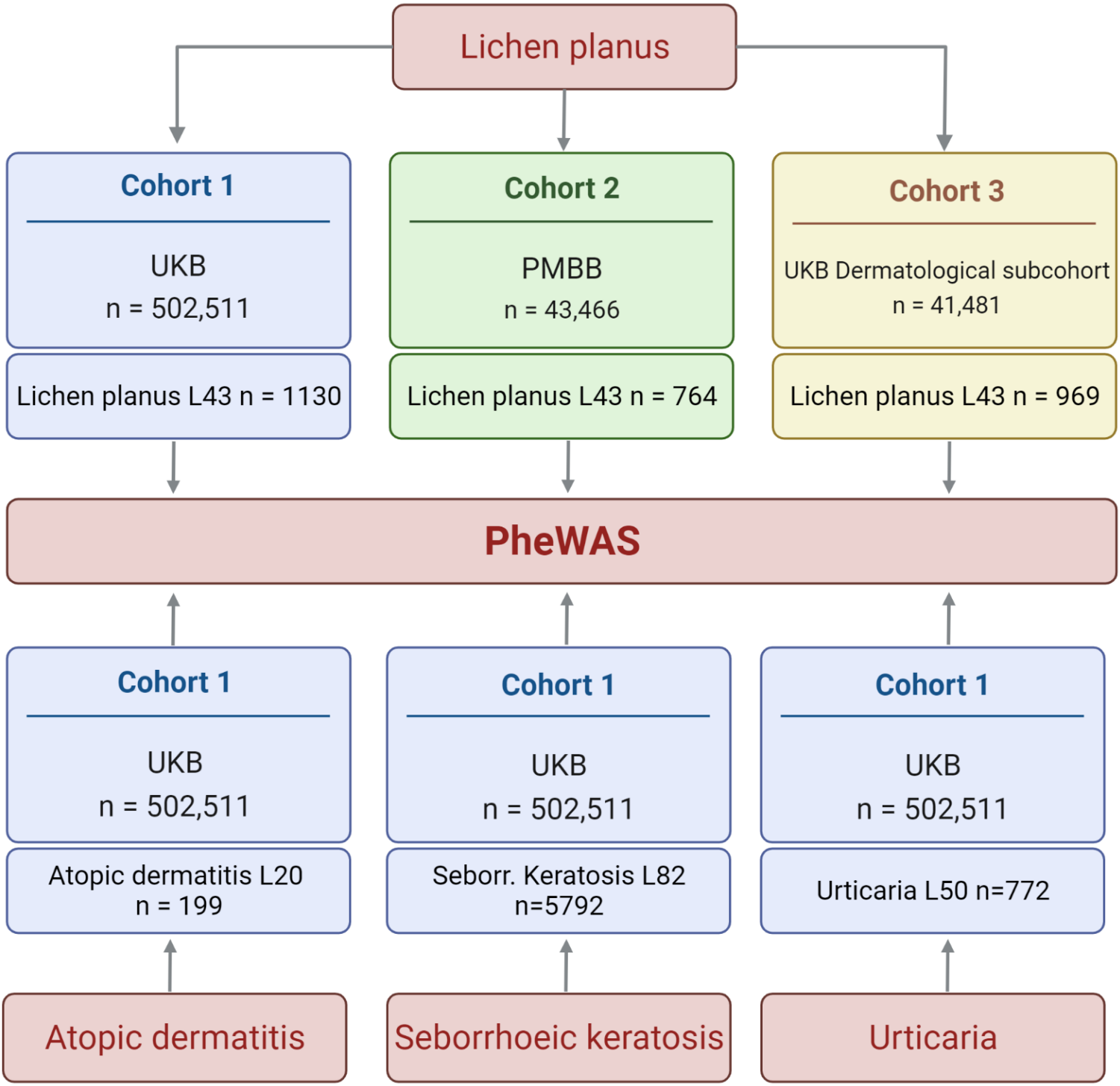
TABLES

Table 1: Basic characteristics of UKB individuals and PMBB participants with and without lichen planus.

	UKB			***PMBB***		
	Controls (n= 501 381)	**Lichen planus** (n= 1130)	***P value***	**Controls** (n= 42 702)	**Lichen planus** (n= 764)	***P value***
Characteristics						
Age (years)	56.5±8.1	59.0±7.2	**<.001**	55.2±10.2	58.7±14.3	**<.001**
Women (%)	54.4	68.1	**<.001**	50.0	57.8	**<.001**
BMI (kg/m^2)	27.4±4.8	27.8±4.9	**.006**	29.4±7.8	30.8±8.2	**<.001**
Diabetes mellitus (%)	5.3	7.6	**<.001**	18	35	**<.001**

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

Abbreviations: UKB, United Kingdom Biobank; PMBB, Penn Medicine BioBank; BMI, body mass index.



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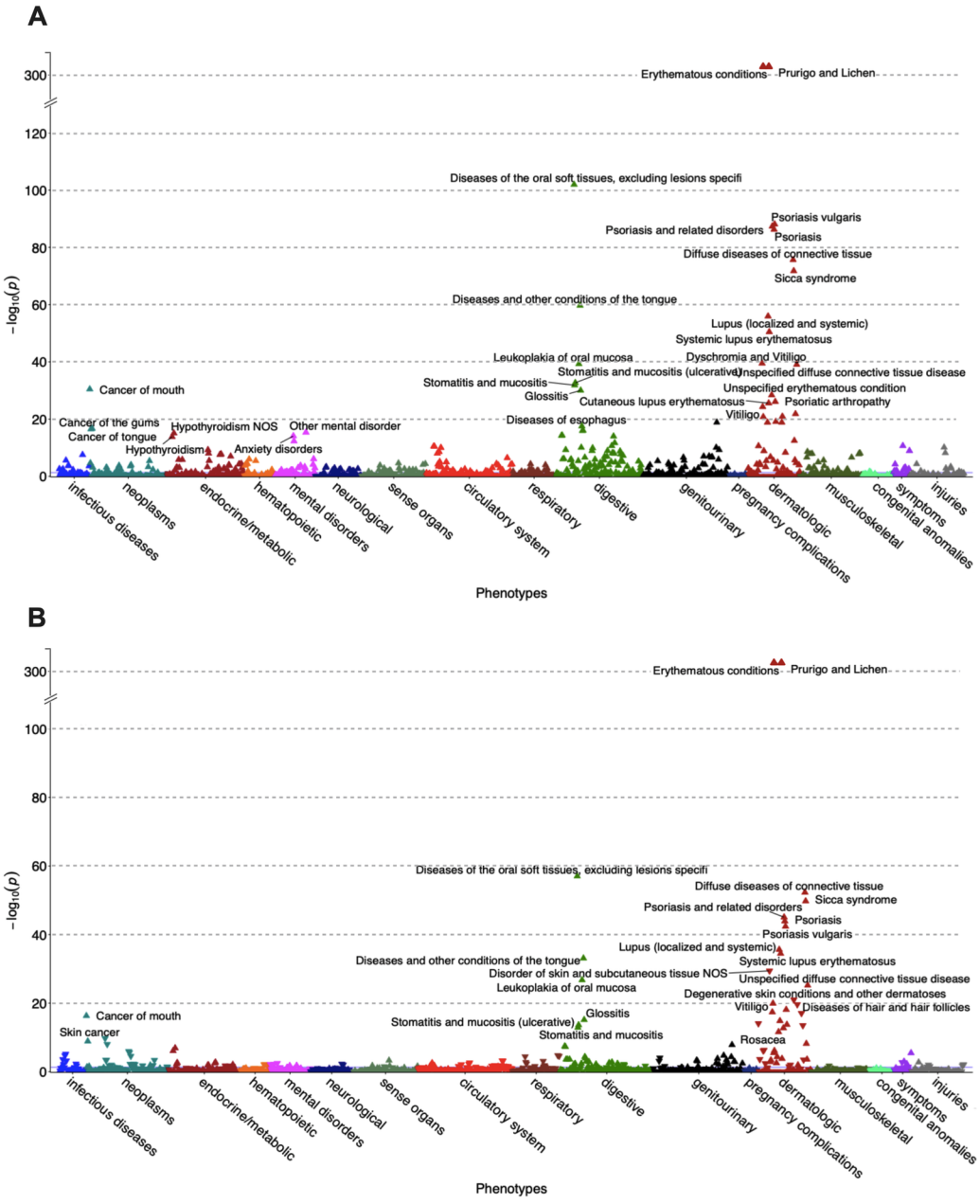

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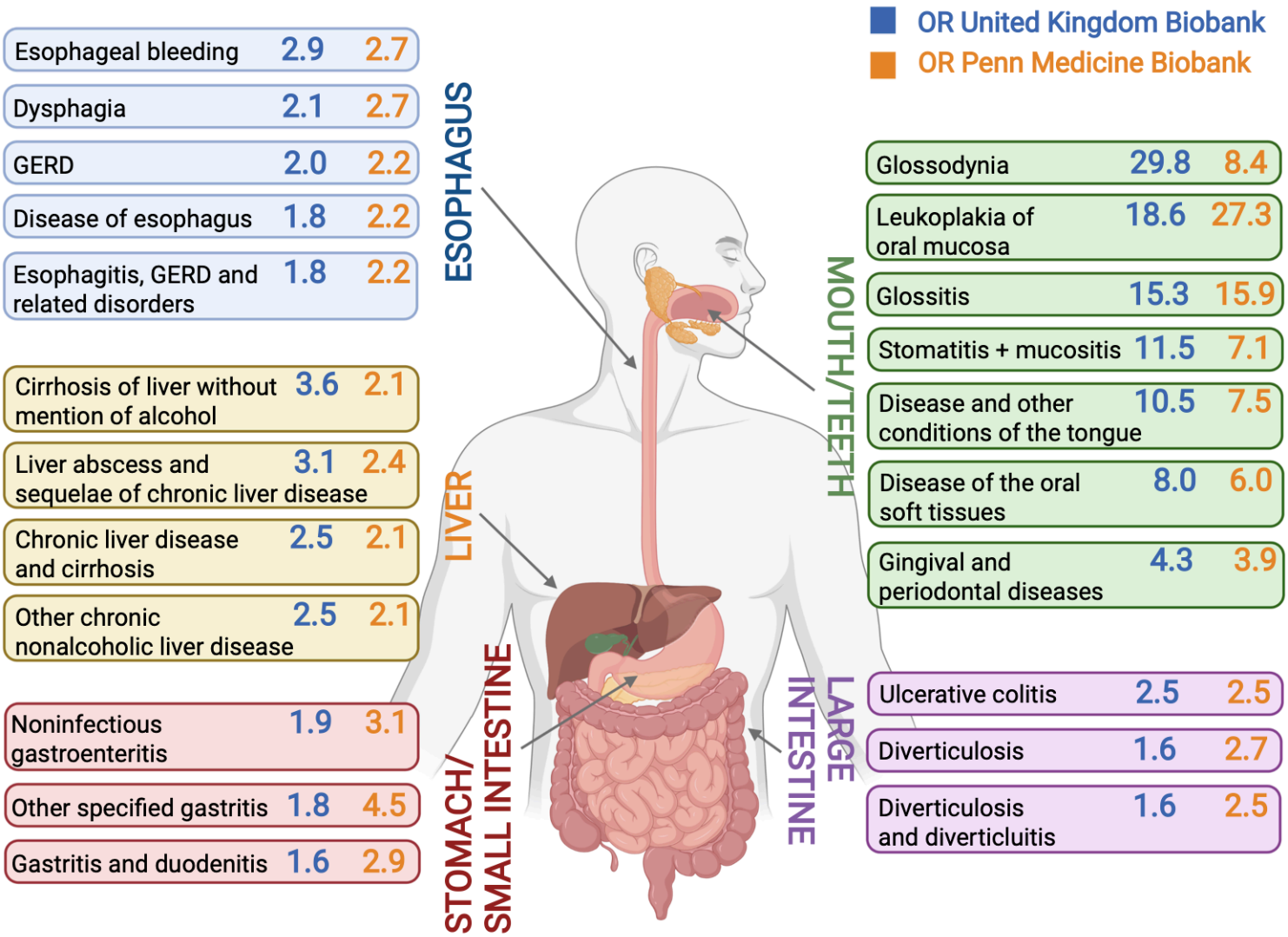

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