REVIEW ARTICLE

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Sex-related Variations in Comorbidities in Lichen Sclerosus: A Systematic Review and Meta-Analysis

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The comorbidities of lichen sclerosus (LS) are presumed but have not been analysed in detail. The purpose of this review was to identify evidence-based associated diseases in patients with LS and explore the potential need for sex-dependent screening protocols. A comprehensive search of the MEDLINE, Embase, and PsycINFO databases from inception to 29 February 2024 was conducted using the key search terms LS and all its synonyms. Pooled odds ratios and 95% confidence intervals of comorbidities were generated using the DerSimonian and Laird random-effects model. A total of 21 case-control studies met the inclusion criteria. Of the 75 comorbidities analysed, only 16 (21.3%) were studied in both sexes, revealing no contrasting associations based on sex. Both female and male LS patients showed significantly increased odds of common dermatological conditions (i.e., lichen planus, vitiligo, alopecia areata, atopic dermatitis, and psoriasis), various cardiovascular risk factors (i.e., essential hypertension, obesity, dyslipidaemia, diabetes mellitus, and diabetes mellitus type 2), genital warts, and hypothyroidism compared with controls. Overall, the scarcity of data currently does not support the implementation of sex-dependent screening strategies. The findings do, however, present significant associations with a range of potentially serious comorbidities, which warrants further elucidation and clinical vigilance.

SIGNIFICANCE

This study examines comorbidities and potential sex-based differences in lichen sclerosus (LS) across 21 case-control studies. Due to limited research, only a few comorbidities were common to both female and male LS patients, suggesting no distinct sex-based associations. This limited exploration discourages implementing sex-dependent screening strategies and underscores the importance of thorough skin examinations and regular screenings for cardiovascular risk factors and thyroid diseases in all LS patients to detect common comorbidities.

sively examine diseases associated with LS across both sexes, aiming to identify any sex-based discrepancies in comorbidity occurrence and advocate for potential sex-specific screening protocols. This examination of comorbidities in LS not only enhances care organization but also provides valuable insights into the underlying pathobiology of the disease.

MATERIALS AND METHODS

This systematic review was registered in PROSPERO (registration number CRD42022333520) and was performed according to the EQUATOR Reporting Guidelines. A comprehensive search of the MEDLINE, Embase, and PsycINFO databases from inception to 29 February 2024, was conducted through Ovid (https://www.wolterskluwer.com/en-gb/solutions/ovid) with the help of an experienced librarian using the key search terms lichen sclerosus and all its synonyms, later combined using *OR* to generate citations as can be seen in Appendix S1. All records retrieved by this search were screened for eligible studies independently by two authors (ŠŠB, KT) using Rayyan (https://www.rayyan.ai/). Any disagreement was discussed with a third author (GBEJ). After duplicate removal, titles and/or abstracts and, if necessary, full texts of the retrieved records were evaluated using the following inclusion criteria: (*i*) case-control study of comorbidities in LS written in English with at least 10 participants; (*ii*) comorbidities of LS, defined as any concurrent non-neoplastic diseases in individuals with LS, reported as absolute numbers or frequencies; (*iii*) the data disaggregated by sex; (*iv*) quality of the study, graded with the Newcastle-Ottawa Scale checklist at more than 3 stars (assessed by ŠŠB and KT). Later, the reference lists of relevant articles were additionally checked. Studies that reported outcomes regarding laboratory results rather than clinical diagnoses were excluded from the analysis. All authors agreed on the final studies for inclusion and, from each, data concerning authors, country, year of publication, study source, study population, sex, mean age,

Lichen sclerosus (LS) is a chronic inflammatory skin condition that primarily affects the anogenital region and can occur at any age in individuals of both sexes with a female-to-male ratio between 3:1 and 10:1. There are indications of sex-specific differences in comorbidity occurrence in LS. However, these are poorly described (1). Therefore, the primary objective of this systematic review and meta-analysis was to comprehen-

method of LS diagnosis, method of identification of comorbidities and comorbidities were extracted into an Excel sheet (Microsoft Corp, Redmond, WA, USA) (ŠŠB, KT).

All comorbidities associated with LS were compared with the control group, with separate analyses conducted for males and females, using odds ratios (OR) and 95% confidence intervals (CI). These OR and CI were calculated for each comorbidity using the DerSimonian and Laird random-effects model, which assigns more weight to studies with less variability and adjusts for additional variability across studies. Each study is weighted based on the inverse of its variance and a between-study variance component. Heterogeneity among the studies was evaluated using the I^2 (%) statistic and the Q test (p-value) when a comorbidity had at least 3 included studies. Publication bias was evaluated through funnel plots and Egger's test, with statistical significance set at a p-value <0.05. All analyses were performed by custom Python scripts, using "statsmodels" and "scipy" libraries. The recommendations were graded by the Quality Rating Scheme for Studies and Other Evidence provided by the Oxford Centre for Evidence-Based Medicine.

RESULTS

Study selection and data synthesis

Initially, a total of 9,936 records were identified. After assessing the full texts of 198 articles for eligibility against all inclusion criteria, 21 case-control studies were ultimately included in the meta-analysis (2–22). PRISMA flow diagram can be seen in **Fig. 1**. Included studies collectively involved 13,765 females with LS and 21,702,053 females without it, as well as 1,589 males with LS and 8,900 non-LS male controls. Further details, such as the Newcastle-Ottawa quality of study assessment (Table SI), a summary of the key characteristics of the included studies (Table SII), and the PRISMA checklist (Table SIII), are available under Supplementary material. The diagnosis of LS was established through clinical examination, histological confirmation, or a combination of both methods in 17 studies, but the method was not clearly specified in the remaining 4. A total of 75 comorbidities were identified, but only 16/75 (21.3%) were studied in both sexes, while the remaining were investigated exclusively within 1 sex. All meta-analysis results are presented in **Fig. 2**, with comorbidities examined in both sexes highlighted in **Fig. 3**. Only significant findings common to both sexes are listed in the results section. Assessment of heterogeneity and

publication bias including the Q statistic, I^2, and p-value of Egger's test are presented in Table SIV (for women) and Table SV (for men). The included studies employed diverse terminology for defining certain diseases, rendering their data integration challenging, but we made concerted efforts to merge them coherently.

Skin diseases

Both female and male LS patients exhibited significantly elevated odds of developing lichen planus (females, OR=10.19, 95% CI=5.95–17.45; males, OR=16.84, 95% CI=9.30–30.50), vitiligo (females, OR=7.33, 95% CI=2.34–22.96; males, OR=64.66, 95% CI=3.71–1126.03), alopecia areata (females, OR=6.16, 95% CI=1.54–24.62; males, OR=15.26; 95% CI=3.21–72.42), atopic dermatitis (females, OR=3.95, 95% CI=2.37–6.60; males, OR=2.43, 95% CI=1.61–3.67), and psoriasis (females, OR=3.17, 95% CI=1.61–6.26; males, OR=3.44, 95% CI=2.02–5.83) compared with non-LS controls.
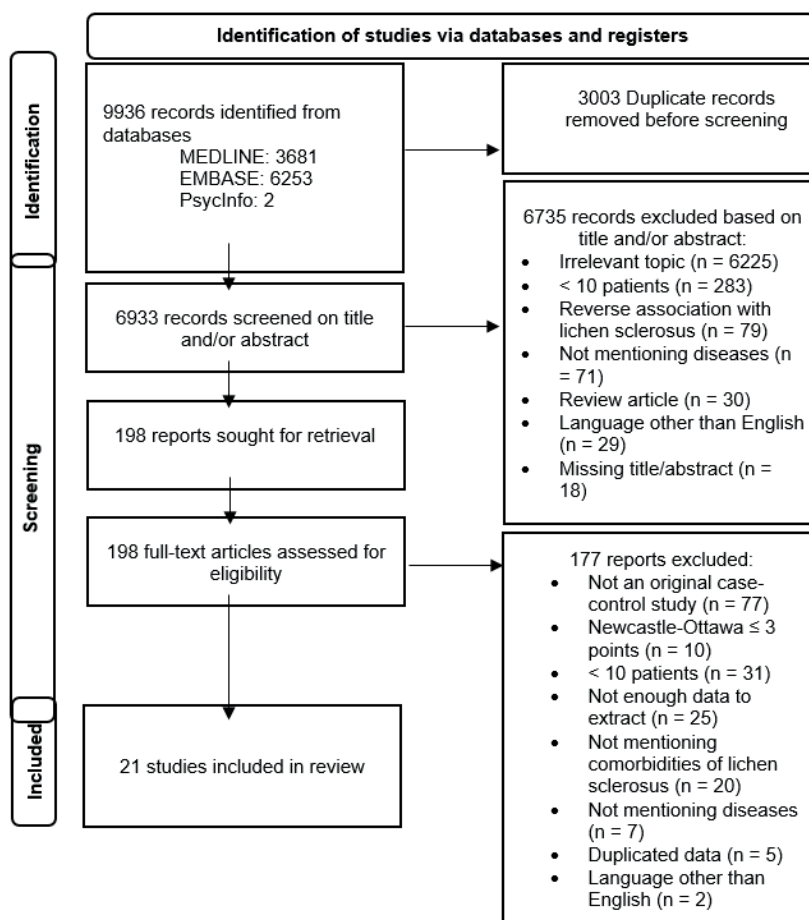

Fig. 1. PRISMA flow diagram illustrating the selection process of studies included in the meta-analysis.

Skin diseases
- Localized scleroderma (morphea)
- Discoid lupus erythematosus
- Androgenetic alopecia
- Lichen planus
- Cutaneous lupus erythematosus
- Bullous pemphigoid
- Vitiligo
- Hypertrichosis
- Alopecia areata
- Atopic dermatitis
- Seborrhoeic dermatitis
- Psoriasis
- Alopecia
- Dermatitis
- Skin disorder

Rheumatic diseases
- Felty syndrome
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Immune connective tissue disorders
- Fibromyalgia
- Behcet disease
- Reactive arthritis

Sexually transmitted, infectious, and urologic diseases
- Genital warts
- Urinary incontinence
- Recurrent urinary tract infection
- Pelvic infections
- Balanoposthitis
- Anogenital herpes simplex infection
- Genital candidiasis
- Nongonococcal urethritis
- Lyme disease
- Gonorrhoea

Kidney, gastrointestinal, cardiovascular, and hematologic diseases
- Renovascular hypertension
- Coeliac disease
- *Helicobacter pylori* infection
- Peripheral vascular disease
- Hypertensive heart disease
- Coagulopathy
- Pernicious anemia
- Holecystectomy
- Atrioventricular block
- Functional intestinal disorders
- Liver problems
- Diverticular disease
- Kidney problems
- Peptic ulcer disease or gastroesophageal reflux disease
- Essential hypertension
- Stroke
- Inflammatory bowel disease
- Chronic peripheral venous insufficiency
- Phlebitis and tromboflebitis
- Angina pectoris
- Coronary artery disease
- Cerebrovascular disease

Pulmonary, allergic, and otorhinolaryngology diseases
- Atopy
- Chronic rhinitis, nasopharyngitis or pharyngitis
- Chronic pulmonary disease
- Hay fever
- Vasomotor and allergic rhinitis
- Sleep apnea

Endocrine and metabolic diseases
- All autoimmune thyroid diseases
- Obesity
- Thyroid disease
- Diabetes mellitus
- Thyrotoxicosis (hyperthyroidism)
- Hypothyroidism (including Hashimoto thyroiditis)
- Diabetes mellitus type II

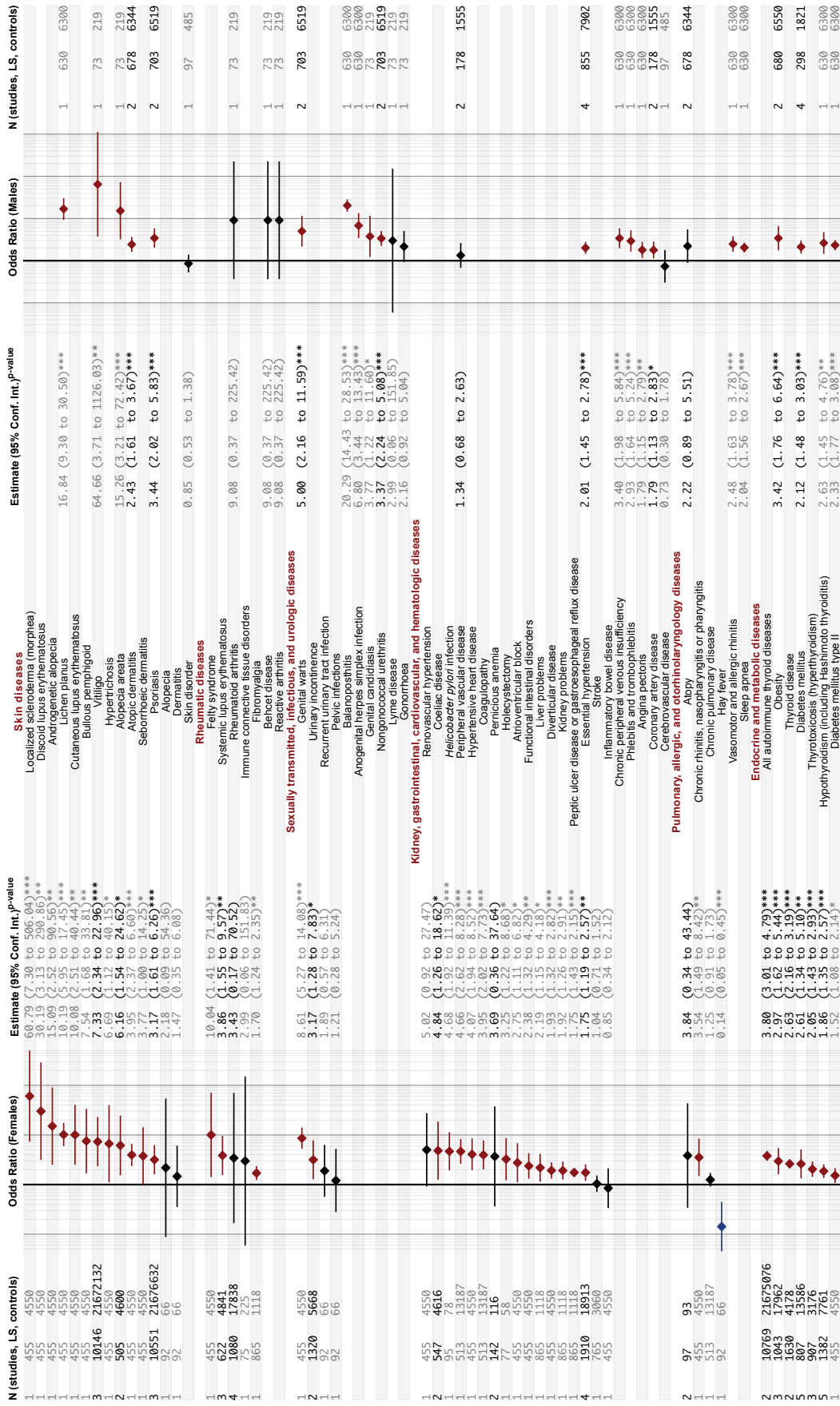**Fig. 2. Forest plot displaying pooled odds ratios and 95% confidence intervals for comorbidities associated with lichen sclerosus, separated by sex.** Significant ORs greater than 1 are shown in red, significant ORs less than 1 are shown in blue, and non-significant ORs are shown in black. Numbers and estimates that rely on data from more than 1 study are emphasized, indicating stronger evidence. Legend: N: number, OR: odds ratio, *p < 0.05, **p < 0.01, ***p < 0.001.
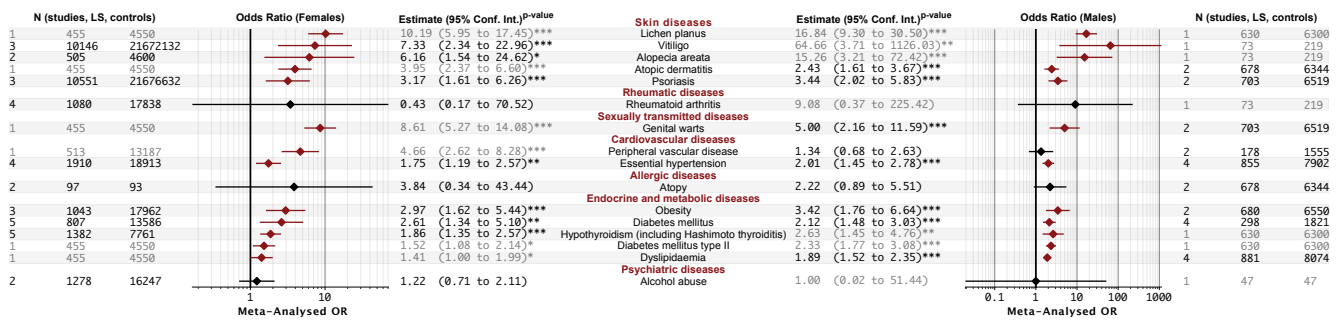
N (studies, LS, controls)	Odds Ratio (Females)	Estimate (95% Conf. Int.) p-value		Estimate (95% Conf. Int.) p-value	Odds Ratio (Males)	N (studies, LS, controls)
			Skin diseases			
1 455 4550		10.19 (5.95 to 17.45)***	Lichen planus	16.84 (9.30 to 30.50)***		1 630 6300
3 10146 21672132		7.33 (2.34 to 22.96)***	Vitiligo	64.66 (3.71 to 1126.03)**		1 73 219
2 505 4600		6.16 (1.54 to 24.62)*	Alopecia areata	15.26 (3.21 to 72.42)***		1 73 219
1 455 4550		3.95 (2.37 to 6.60)***	Atopic dermatitis	2.43 (1.61 to 3.67)***		2 678 6344
3 10551 21676632		3.17 (1.61 to 6.26)***	Psoriasis	3.44 (2.02 to 5.83)***		2 703 6519
			Rheumatic diseases			
4 1080 17838		0.43 (0.17 to 70.52)	Rheumatoid arthritis	9.08 (0.37 to 225.42)		1 73 219
			Sexually transmitted diseases			
1 455 4550		8.61 (5.27 to 14.08)***	Genital warts	5.00 (2.16 to 11.59)***		2 703 6519
			Cardiovascular diseases			
1 513 13187		4.66 (2.62 to 8.28)***	Peripheral vascular disease	1.34 (0.68 to 2.63)		2 178 1555
4 1910 18913		1.75 (1.19 to 2.57)**	Essential hypertension	2.01 (1.45 to 2.78)***		4 855 7902
			Allergic diseases			
2 97 93		3.84 (0.34 to 43.44)	Atopy	2.22 (0.89 to 5.51)		2 678 6344
			Endocrine and metabolic diseases			
3 1043 17962		2.97 (1.62 to 5.44)***	Obesity	3.42 (1.76 to 6.64)***		2 680 6550
5 807 13586		2.61 (1.34 to 5.10)**	Diabetes mellitus	2.12 (1.48 to 3.03)***		4 298 1821
5 1382 7761		1.86 (1.35 to 2.57)***	Hypothyroidism (including Hashimoto thyroiditis)	2.63 (1.45 to 4.76)**		1 630 6300
1 455 4550		1.52 (1.08 to 2.14)*	Diabetes mellitus type II	2.33 (1.77 to 3.08)***		1 630 6300
1 455 4550		1.41 (1.00 to 1.99)*	Dyslipidaemia	1.89 (1.52 to 2.35)***		4 881 8074
			Psychiatric diseases			
2 1278 16247	Meta-Analysed OR	1.22 (0.71 to 2.11)	Alcohol abuse	1.00 (0.02 to 51.44)	Meta-Analysed OR	1 47 47

Fig. 3. Forest plot highlighting pooled odds ratios and 95% confidence intervals for comorbidities associated with lichen sclerosus, analysed across both sexes. Significant ORs greater than 1 are shown in red, and non-significant ORs are shown in black. Numbers and estimates that rely on data from more than 1 study are emphasized, indicating stronger evidence. Legend: N: number, OR: odds ratio, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Sexually transmitted diseases

Both female and male LS patients showed significantly increased odds of having genital warts (females, OR = 8.61, 95% CI = 5.27–14.08; males, OR = 5.00, 95% CI = 2.16–11.59) compared with non-LS controls.

Cardiovascular diseases

Both female and male LS patients exhibited significantly elevated odds of developing essential hypertension (females, OR = 1.75, 95% CI = 1.19–2.57; males, OR = 2.01, 95% CI = 1.45–2.78) compared with non-LS controls.

Endocrine and metabolic diseases

Significantly higher odds were observed in both sexes with LS compared with the non-LS control group for obesity (females, OR = 2.97, 95% CI = 1.62–5.44; males, OR = 3.42, 95% CI = 1.76–6.64), diabetes mellitus (females, OR = 2.61, 95% CI = 1.34–5.10; males, OR = 2.12, 95% CI = 1.48–3.03), diabetes mellitus type 2 (females, OR = 1.52, 95% CI = 1.08–2.14; males, OR = 2.33, 95% CI = 1.77–3.08), hypothyroidism (including Hashimoto thyroiditis; females, OR = 1.86, 95% CI = 1.35–2.57; males, OR = 2.63, 95% CI = 1.45–4.76), and dyslipidaemia (females, OR = 1.41, 95% CI = 1.00–1.99; males, OR = 1.89, 95% CI = 1.52–2.35).

DISCUSSION

This systematic review indicates that a broad range of diseases may be associated with LS. Both female and male LS patients showed significantly increased odds of common dermatological conditions (i.e., lichen planus, vitiligo, alopecia areata, atopic dermatitis, and psoriasis), various cardiovascular risk factors (i.e., essential hypertension, obesity, dyslipidaemia, diabetes mellitus, and diabetes mellitus type 2), genital warts, and hypothyroidism, including Hashimoto thyroiditis compared with non-LS controls. The subsequent exploration of potential different screening protocols for LS comorbidities based on sex found no contrasting associations between men and women, highlighting that certain health risks are similar for both sexes. Due to selection bias, where 13 out of 21 case-control studies focused on female comorbidities, male comorbidities were largely unexplored. This may explain the perceived sex-dependent difference in comorbidities in LS, emphasizing the need to prioritize and intensify research efforts towards understanding comorbidities in male LS patients (1).

As additional diseases were not investigated in both sexes, a direct analysis of further comorbidities in LS based on sex is limited. By focusing on associations examined in more than 1 study, which increases statistical power despite being restricted to 1 sex, females with LS additionally showed significant associations with systemic lupus erythematosus, urinary incontinence, coeliac disease, depression, and other thyroid diseases, while males with LS were significantly associated with nongonococcal urethritis and coronary artery disease. Further evidence from individual studies corroborated the association of LS with diverse cardiovascular conditions in both sexes and additional genital infections in males with LS.

While some associated diseases in LS may be incidental (e.g., genital infections and skin diseases found due to surveillance bias) or the result of a previous incorrect diagnosis carried forward (e.g., lichen planus in classification bias), they nevertheless represent a clinically relevant catalogue (see Fig. 2 for all results). It is suggested that these diseases are brought to clinicians' attention when doing a work-up of LS patients. Our findings especially suggest the need for thorough skin examinations and regular screenings for cardiovascular risk factors and thyroid diseases in all LS patients to detect common comorbidities.

Finally, understanding comorbid diseases provides valuable insights into the complex nature of LS. For example, comorbid autoimmune diseases may contribute to the diminished suppressive function of regulatory T cells, triggering an immune response against extracellular matrix self-antigens observed in LS (23–27). Additionally, cardiovascular risk factors and diseases may exacerbate

endothelial dysfunction and decrease microvascular density in LS tissue (28, 29).

Limitations

In addition to selection and potential surveillance and classification biases, this study has several other limitations. First, while all cases and controls were sex-matched, only 15/21 studies were additionally age-matched, leading to potential bias in reporting comorbidity frequencies. Additionally, race was matched in only 6/21 studies, while socioeconomic status was not standardized. If any of these factors are independently associated with LS and were not evenly distributed among groups, this could potentially affect the results. Moreover, the majority (13/21) of controls originated from the same institution but were diagnosed with conditions other than LS. The control group came from the community in only in 2 studies, while others were sourced from various health facilities or insurance company databases. This may not accurately represent the overall population. Next, in 17/21 studies, LS was confirmed either histologically or clinically, while in 4 studies the method of confirmation was not specified. Conversely, only 1 study excluded LS histologically in the control group, and in 10/21 studies the exclusion method was not specified. This lack of specification raises concerns that subclinical LS diagnoses may have been missed in the control group, potentially introducing bias into the results. Additionally, data reliance on various sources such as International Classification of Diseases codes (7/19), chart reviews (6/19), questionnaires/interviews (7/19), and/or clinical examination/other tests (4/19) may have led to the omission of unrecognized comorbidities, recall bias, or underreporting due to coding errors. What is more, the increased occurrence of comorbidities in LS might stem from frequent doctor's visits prompted by these conditions rather than direct associations with LS, or LS may be more readily diagnosed when patients seek medical attention for other reasons. Conversely, individuals who avoid seeking medical advice may not be accurately represented in medical records. It is also possible that patients with LS who seek medical attention may have a higher disease burden and, thus, more comorbidities. Additionally, sex-related medical help-seeking behaviours may contribute to the underreporting of certain medical conditions.

Despite our efforts to limit heterogeneity in this meta-analysis, heterogeneity remained considerable for hypothyroidism (including Hashimoto thyroiditis), psoriasis, essential hypertension, vitiligo, and obesity in females and essential hypertension in males. On the other hand, the *p*-values of Egger's test were far above the significant threshold of 0.05, indicating a low likelihood of publication bias in the meta-analysis results. However, with only a small number of available studies that were included in the meta-analysis, the ability to explore and explain heterogeneity and publication bias is limited. The rating of quality of evidence for this meta-analysis is categorized as Grade 3a, according to the Quality Rating Scheme for Studies and Other Evidence provided by the Oxford Centre for Evidence-Based Medicine, as it combines data from case-control studies.

Conclusion

Our meta-analysis underscores the significant association between LS and various skin, sexually transmitted, cardiovascular, metabolic, and endocrine diseases in both males and females. It is suggested that these diseases are brought to clinicians' attention when doing a work-up of LS patients. In practical terms, the findings of this study indicate the need to conduct thorough skin examinations and routinely screen all LS patients for cardiovascular risk factors and thyroid diseases to identify common comorbidities. However, further prospective case-control studies are needed to validate the findings of this meta-analysis and to enhance our understanding of the complex comorbidities associated with LS.

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