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# Risk Factors for Lichen Sclerosus: A Case-Control Study of 43,000 Finnish Women

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**Objectives:** Lichen sclerosus (LS) is an inflammatory skin disease probably arising from an interplay of genetics, local irritation, and autoimmune processes. We identified potential risk factors for the disease using data from nationwide Finnish registries.

**Methods:** We identified all women diagnosed with LS within specialized health care during 1998–2016 ( $n = 10,692$ ) and selected 3 age-matched population control women for each case. We calculated odds ratios (ORs) for possible risk factors using conditional logistic regression.

**Results:** Dermatological autoimmune conditions were strongly associated with LS (OR = 15.1, 95% confidence interval [CI] = 13.6–16.7 for morphea; OR = 10.3, 95% CI = 5.02–19.0 for lichen planus; OR = 6.86, 95% CI = 5.65–8.33 for alopecia; OR = 2.20, 95% CI = 1.88–2.56 for vitiligo). A diagnosis of Crohn or celiac disease increased the odds of LS (OR = 1.80, 95% CI = 1.71–1.89; OR = 1.49, 95% CI = 1.28–1.73, respectively) as did urge and stress incontinence (OR = 1.79, 95% CI = 1.71–1.87; OR = 1.28, 95% CI = 1.22–1.35, respectively).

The odds of LS were lower in women after a diagnosis of type 1 diabetes (OR = 0.43, 95% CI = 0.41–0.45), coronary artery disease (OR = 0.41, 95% CI = 0.38–0.43), and rheumatoid arthritis (OR = 0.38, 95% CI = 0.36–0.41).

Parous women had higher odds of LS (OR = 1.11, 95% CI = 1.04–1.17) than nulliparous ones, but increasing number of births decreased the risk. Lichen sclerosus was not associated with socioeconomic status nor the urbanicity level of the place of residence.

**Conclusions:** Certain autoimmune diseases and urinary incontinence were associated with LS.

**Key Words:** lichen sclerosus, risk factor, comorbid disease, etiology, autoimmune disease, socioeconomic status, place of residence, metabolic syndrome, thyroid disease, urinary incontinence

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Lichen sclerosus (LS) is an inflammatory skin disease mainly affecting the vulva. Patients are usually highly symptomatic, yet the diagnostic delay is often long.<sup>1,2</sup> Lichen sclerosus runs a chronic course and causes potential complications: scarring and malignant transformation.<sup>1–4</sup> Fortunately, LS usually responds well to topical immunosuppressant therapy. This treatment is suppressive rather than curative, and therefore often lifelong.<sup>3</sup>

Lichen sclerosus is characterized by lymphocyte-driven inflammation leading to scarring of the dermis,<sup>5</sup> but the events triggering this process remain uncertain. There is some evidence of LS-predisposing genetic haplotypes as well as autoimmune processes within the serum and the affected skin of patients.<sup>5–8</sup> Risk and triggering factors as well as associated conditions for LS have been sought, and previous local trauma has emerged as a possible trigger.<sup>9,10</sup> Associated diseases most frequently found in women living with LS include thyroid disorders and other autoimmune conditions.<sup>11,12</sup> Moreover, recent studies suggest a link between LS and the metabolic syndrome.<sup>13,14</sup>

To shed light on the etiology of LS, we identified sociodemographic and health-related factors related to LS using nationwide registry data from Finland.

## METHODS

This study uses data from the Care Register for Health Care (HILMO), the Population Information System (Population Registry), and census data at Statistics Finland. The registries have collected and used health-related data of the Finnish population for decades under legal mandate. We identified the cases and controls within the registries by means of personal identity codes provided to all Finnish citizens and permanent residents at birth or immigration.

The HILMO is maintained by the Finnish Institute for Health and Welfare. It includes all inpatient and outpatient diagnoses from public Finnish specialized health care classified with the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10) during the study period of 1998–2016. Cases for this study are women identified from the HILMO using the diagnostic code L90.0 (lichen sclerosus). Control women for each case were randomly selected from the Population Registry at a ratio of 3:1. The controls had to have a birth date as close to the birth date of the case as possible (a maximum of  $\pm 6$  months) and be alive and residing in Finland at the time of diagnosis of the respective case (“index date”).

The following potential risk factors for LS were assessed: comorbid diagnoses (Supplementary Digital Content 1, <http://links.lww.com/LGT/A334>) between January 1, 1998, and index date (from the HILMO), parity, age at first birth before index date, socioeconomic status, and the urbanicity level of the place of residence.

Data on childbirths before the index date were retrieved from the Population Registry, where there are links from mother to child for most mothers born after the mid-1930s. Parity was categorized in 2 groups (nulliparous and parous), and the parous women were further classified according to the number of births (1, 2, 3, 4, or more). Age at first birth was divided into 4 categories: younger than 25, 25–29, 30–34, and 35 years or older.

Statistics Finland provided the data on the socioeconomic status (SES) of the cases and controls from population census information from 1970, 1975, 1980, and 1985. The data are based on occupation and are in our study divided into 6 categories. For persons with varying SES in the censuses, the following priority order was used: (1) farmers, (2) upper white-collar workers (i.e., upper level employees with administrative, managerial, professional, and related occupations), (3) lower white-collar workers (i.e., lower level employees with administrative and clerical occupations), (4) blue collar workers (i.e., manual workers), (5) other known occupations, and (6) unknown, students, and pensioners.

The municipality at index date was retrieved from the Population Registry. In 2023, Finland was divided into 309 municipalities, which are self-governing administrative units. For this study, the municipality at index date was classified into 3 classes using the newest available classification of the municipality: urban (>90% of the population lives in urban settlements or the population of the largest urban settlement exceeds 15,000), semiurban (60%–90% of the population lives in urban settlements and the population of the largest urban settlement is 4,000–15,000), and rural (more sparsely populated than the aforementioned) ([https://www.stat.fi/meta/kas/til\\_kuntaryhmit\\_en.html](https://www.stat.fi/meta/kas/til_kuntaryhmit_en.html)).

The odds ratio (OR) for each risk factor was calculated using conditional logistic regression models with 95% confidence intervals (CI). To study possible reverse causality, we calculated the ORs stratified by the temporal distance (less than or 5 years or more than) between the diagnosis of the comorbid disease and index date. The analyses were performed using Stata version 16 (StataCorp LP, College Station, TX).

We obtained permissions for the study from the Finnish Institute for Health and Welfare (THL/1890/5.05.00/2017), the Digital and Population Data Services Agency (VRK/44507/2017–2), and Statistics Finland (TK-53-1712-17). In Finland, no ethics committee approval is required for registry-based studies.

## RESULTS

Between 1998 and 2016, we identified 10,692 women diagnosed with LS within the Finnish specialized health care and 32,076 age-matched control women. The mean age of both the cases and controls at index date was 60.8 years (median = 64, range = 4–89; Table 1).

Lichen sclerosus was not associated with the urbanicity level of the place of residence at index date nor with the SES (Table 2). Women with LS were more often parous than controls (OR = 1.11, 95% CI = 1.04–1.17), and the OR was highest in women with 1 birth only (OR = 1.22, 95% CI = 1.12–1.31). Higher age at first birth increased the odds of LS (Table 2).

Some dermatological diseases with autoimmune etiology were strongly associated with LS (Table 3). Morphea showed an OR of 15.1 (95% CI = 13.6–16.7), lichen planus 10.3 (95% CI = 5.02–19.0), alopecia 6.86 (95% CI = 5.65–8.33), vitiligo 2.20 (95% CI = 1.88–2.56), and atopic dermatitis 1.14 (95% CI = 1.09–1.20), all statistically significant (Table 3). Women with LS had lower odds of having had psoriasis than controls (OR = 0.81, 95% CI = 0.78–0.84).

Of other autoimmune diseases, celiac disease and Crohn disease were statistically significantly associated with LS (OR = 1.49, 95% CI = 1.28–1.73 and OR = 1.80, 95% CI = 1.71–1.89, respectively) (Table 3). In contrast, the OR was reduced in women with type 1 diabetes mellitus (OR = 0.43, 95% CI = 0.41–0.45), rheumatoid arthritis (OR = 0.38, 95% CI = 0.36–0.41), and colitis ulcerosa (OR = 0.64, 95% CI = 0.61–0.70).

Thyroid diseases were not associated with LS, whereas the OR for urinary incontinence of either type was elevated (OR =

**TABLE 1.** Descriptive Characteristics of the Lichen Sclerosus Cases and Controls

	Cases (n = 10,692)	Controls (n = 32,076)
Date of birth		
1903–1930	1,672 (15.6%)	5,016 (15.6%)
1931–1940	2,411 (22.6%)	7,233 (22.6%)
1941–1950	2,808 (26.3%)	8,424 (26.3%)
1951–1960	1,820 (17.0%)	5,460 (17.0%)
1961–2014	1,981 (18.5%)	5,943 (18.5%)
Index date		
1998–2000	1,347 (12.6%)	4,041 (12.6%)
2001–2003	1,143 (10.7%)	3,429 (10.7%)
2004–2006	1,380 (12.9%)	4,140 (12.9%)
2007–2009	1,650 (15.4%)	4,950 (15.4%)
2010–2012	1,916 (17.9%)	5,748 (17.9%)
2013–2016	3,256 (30.5%)	9,768 (30.5%)
Age at index date		
≤40	1,278 (12.0%)	3,834 (12.0%)
41–50	1,008 (9.4%)	3,024 (9.4%)
51–60	2,115 (19.8%)	6,345 (19.8%)
61–70	2,893 (27.1%)	8,679 (27.1%)
71–80	2,403 (22.5%)	7,209 (22.5%)
>80	995 (9.3%)	2,985 (9.3%)

1.28, 95% CI = 1.22–1.35 for stress incontinence; OR = 1.79, 95% CI = 1.71–1.87 for urge incontinence) (Table 3).

Type 2 diabetes mellitus (OR = 0.83, 95% CI = 0.79–0.87), the metabolic syndrome (OR = 0.86, 95% CI = 0.77–0.96), hypertension (OR = 0.63, 95% CI = 0.61–0.65), myocardial infarction (OR = 0.62, 95% CI = 0.60–0.64), and history of coronary artery disease (OR = 0.41, 95% CI = 0.38–0.43) were associated with reduced odds of LS (Table 3).

When stratified according to the time period between comorbidity and index date, the ORs for systemic lupus erythematosus (SLE), Sjögren syndrome, atopic dermatitis, and vitiligo were only increased when the diagnoses were made more than 5 years before the index date (Table 3). The ORs for interstitial cystitis and autoimmune thyroiditis were increased when the diagnoses were made less than 5 years before the index date (Table 3).

## DISCUSSION

We found that having given birth and being diagnosed with autoimmune diseases or urinary incontinence were associated with later LS. The ORs for SLE, Sjögren syndrome, atopic dermatitis, and vitiligo were markedly elevated when the time period between those diagnoses and LS was long. In contrast, the ORs were reduced for coronary artery disease, its risk factors (hypertension and diabetes), and its complication myocardial infarction. The risk of LS was not associated with the SES nor with the place of residence of patients.

Physical trauma to the genital skin has been suggested to trigger the development of LS.<sup>9</sup> We found that parous women are diagnosed with LS more often than nulliparous, which could be explained by childbirth-related injuries triggering LS later in life. Similarly, an Italian study of 75 LS women showed an increased risk of LS in women who had given birth.<sup>15</sup> In our study, the OR was highest in women with 1 birth only. A difficult obstetric tear at first birth may prevent women from having more children.

Another suggested trigger for LS is chronic irritation of genital skin by urine.<sup>10</sup> In our study, both stress and urge incontinence increased the likelihood of a subsequent LS diagnosis. In contrast,

**TABLE 2.** Odds Ratios (OR) and 95% Confidence Intervals (CI) for the Place of Residence, Socioeconomic Status, and Parity Associated With Subsequent Risk for Lichen Sclerosus, Derived From Multivariate Analyses

Place of residence at index date	Cases	Controls	OR	95% CI
Urban	6,610	19,766	1.00	Reference
Semiurban	1,793	5,149	0.92	0.85–1.01
Rural	2,095	6,594	1.05	0.97–1.13
Unknown	194	567	1.00	0.83–1.15
<b>Socioeconomic status at index date</b>				
Upper white collar	912	2,768	1.00	Reference
Lower white collar	3,437	10,409	0.99	0.91–1.09
Blue collar	3,169	9,427	0.98	0.90–1.06
Farmers	801	2,407	0.99	0.88–1.11
Other known occupations	404	1,235	1.00	0.88–1.15
Unknown, pensioners, students	1,969	5,830	0.97	0.89–1.07
<b>Parity</b>				
0	1,820	5,039	1.00	Reference
≥1	6,322	19,387	1.11	1.04–1.17
1	1,265	4,382	1.22	1.12–1.31
2	2,592	7,929	1.09	1.03–1.14
3	1,485	4,401	1.04	1.01–1.23
≥4	980	2,675	0.97	0.93–1.05
<b>Age at first birth</b>				
<25 y	3,427	10,137	1.00	Reference
25–29 y	1,823	6,059	1.07	1.02–1.14
30–34 y	630	1,935	1.12	1.00–1.18
≥35 years	442	1,256	1.08	0.98–1.19

a recent meta-analysis based on 8 studies with altogether 1,248 LS patients did not find a difference in the prevalence of urinary incontinence between LS patients and controls.<sup>16</sup>

Possible autoimmune etiology of LS has directed research into identification of comorbid autoimmune diseases—especially those of the thyroid gland. A recent large study comparing the medical records of 10,000 women with LS to 21 million controls found an increased prevalence of all autoimmune thyroid diseases in women with LS.<sup>17</sup> In the present study, the diagnoses of hypothyroidism, Hashimoto thyroiditis, or Graves disease were equally prevalent in LS women and controls.

Of autoimmune dermatological diseases, alopecia, vitiligo, and morphea were strongly associated with LS. These associations are well known,<sup>11–13,17</sup> and probably due to similar pathophysiological processes. There are less reports of psoriasis or lichen planus in LS women.<sup>13,17–19</sup> We found an increased OR for lichen planus and a reduced OR for psoriasis.

Of autoimmune gastrointestinal diseases, Crohn disease and celiac disease were associated with increased odds of LS, whereas women with ulcerative colitis were diagnosed with LS less frequently than controls. Previous studies based on only 92 and 190 women with LS found no increased risk of celiac disease among patients with LS.<sup>12,19</sup> Inflammatory bowel disease has rarely been reported in LS patients.<sup>20</sup>

The odds of some autoimmune diseases were reduced; these included type 1 diabetes and rheumatoid arthritis. These conditions have infrequently been described in women with LS, usually with prevalence not different from that among reference populations.<sup>11–13,19</sup> The low odds of these autoimmune diseases in our study could arise from their potentially difficult complications, which may prevent patients from seeking medical help for LS. Alternatively, the reduced odds might result from immunosuppressive medications used in the treatment of rheumatoid arthritis.

A recent cohort study with 5,680 women and men diagnosed during 2001–2021 with LS in Sweden found similar age-adjusted ORs for some comorbid autoimmune diseases: 2.2 for alopecia, 2.8 for vitiligo, 6.9 for morphea, 7.9 for lichen planus, and 2.0 for Crohn disease.<sup>21</sup> In contrast to our results, the ORs for ulcerative colitis and type 1 diabetes were elevated (1.8 and 1.9, respectively), and the prevalence of rheumatoid arthritis was equal to that of the control population. The study settings in the Swedish study and our study are similar, with the exception that the Swedish study has not considered the temporal relation of LS and comorbid disease—how long the period between the diagnoses was, and whether symptoms and diagnostics of one disease may increase the probability of diagnosing another.

Two recent studies of 585 and 455 women with LS found hypertension and type 2 diabetes more often in LS women than in controls.<sup>13,14</sup> In the present study, the odds of LS were reduced for hypertensive disorders, type 2 diabetes, and the metabolic syndrome, as well as for coronary artery disease and myocardial infarction. Our results may contradict those of Ranum and Hieta<sup>13,14</sup> because of the unclear temporal relationship of lichen and comorbid condition in the 2 previous studies. Moreover, it may be speculated that the prevalence of cardiovascular diseases increases after the LS diagnosis.

Vulvar pain and dyspareunia are known symptoms of LS. In addition, Berger et al.<sup>22</sup> showed that the prevalence of some chronic pain syndromes, such as fibromyalgia and interstitial cystitis, was increased in LS women compared with the general population. We found interstitial cystitis more often in LS women compared with controls when it was diagnosed less than 5 years before LS diagnosis.

Studies concerning the SES of LS patients are few. Sideri et al.<sup>15</sup> did not observe differences in the length of education in LS women compared with controls, whereas in the study by Virgili et al.,<sup>18</sup> LS patients had higher educational level compared with population controls. We used an occupation-based indicator

**TABLE 3.** Odds Ratios (ORs) and 95% CI of Selected Diagnoses Associated With Subsequent Risk for Lichen Sclerosus, Stratified by Time Between the Preceding Diagnosis and Index Date, Derived From Multivariate Analyses

Preceding diagnosis	Time difference between the preceding comorbid diagnosis and index date											
	<5 y				≥5 y				Any			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Autoimmune diseases												
Pernicious anemia	2	6	1.02	0.65–1.63	4	19	0.72	0.53–0.95	6	25	0.81	0.63–1.02
Diabetes mellitus, type 1	92	492	0.61	0.57–0.65	91	737	0.33	0.31–0.35	183	1,229	0.43	0.41–0.45
Celiac disease	37	68	1.84	1.65–2.06	56	135	1.18	1.08–1.29	93	203	1.49	1.28–1.73
Crohn disease	80	135	1.91	1.76–2.07	110	173	1.74	1.62–1.86	190	308	1.80	1.71–1.89
Colitis ulcerosa	63	271	0.74	0.69–0.80	71	332	0.58	0.54–0.63	134	603	0.64	0.61–0.70
Seropositive rheumatoid arthritis	26	236	0.36	0.32–0.41	61	422	0.39	0.36–0.42	87	658	0.38	0.36–0.41
Systemic lupus erythematosus	8	83	0.32	0.27–0.40	57	135	1.12	1.03–1.22	65	218	0.86	0.79–0.93
Sjögren syndrome	30	135	0.74	0.66–0.83	57	122	1.26	1.15–1.38	87	257	1.01	0.94–1.08
Skin diseases												
Atopic dermatitis	63	239	0.86	0.80–0.94	133	277	1.37	1.29–1.45	196	516	1.14	1.09–1.20
Psoriasis	147	605	0.80	0.76–0.85	159	534	0.85	0.81–0.89	306	1,139	0.81	0.78–0.84
Lichen planus	62	27	8.82	6.09–18.4	135	50	12.23	8.41–26.5	197	77	10.3	5.02–19.0
Alopecia	8	4	7.22	5.21–10.0	16	6	6.64	5.20–8.47	24	10	6.86	5.65–8.33
Vitiligo	7	27	0.92	0.73–1.16	13	2	17.2	11.9–24.8	20	29	2.20	1.88–2.56
Morphea	70	17	21.9	18.5–25.8	76	12	11.7	10.2–13.3	146	29	15.1	13.6–16.7
Thyroid diseases												
Hypothyroidism	113	361	1.04	0.97–1.10	176	515	0.96	0.91–1.00	289	876	0.98	0.95–1.02
Basedow disease/Graves disease/hyperthyroidism	41	151	0.89	0.80–0.98	30	131	0.64	0.57–0.72	71	282	0.81	0.66–1.00
Autoimmune thyroiditis/Hashimoto thyroiditis	2	3	2.92	1.79–4.76	4	13	1.02	0.74–1.38	6	16	1.32	0.71–2.44
Cardiometabolic conditions												
Diabetes mellitus, type 2	260	1,033	0.91	0.87–0.94	429	2,098	0.60	0.58–0.61	689	3,131	0.83	0.79–0.87
Metabolic syndrome	18	66	0.98	0.84–1.14	16	56	0.83	0.71–0.98	34	122	0.86	0.77–0.96
Obesity	31	104	1.04	0.92–1.16	34	92	1.07	0.96–1.20	65	196	1.02	0.94–1.11
Hypercholesterolemia	79	320	0.97	0.90–1.04	120	395	1.15	1.08–1.22	199	715	1.06	1.01–1.10
Hypertensive disorders	537	2,353	0.74	0.72–0.76	810	4,075	0.52	0.51–0.53	1,347	6,428	0.63	0.61–0.65
Myocardial infarction	32	246	0.58	0.53–0.63	67	457	0.66	0.63–0.69	99	703	0.62	0.60–0.64
Coronary artery disease	88	476	0.43	0.38–0.48	225	1,041	0.39	0.37–0.43	313	1,517	0.41	0.38–0.43
Incontinence												
Stress incontinence	81	213	1.26	1.18–1.36	117	249	1.31	1.24–1.40	198	462	1.28	1.22–1.35
Urge incontinence	108	178	2.02	1.90–2.16	132	226	1.65	1.55–1.75	240	404	1.79	1.71–1.87
Pain syndromes												
Irritable bowel syndrome	20	67	1.01	0.88–1.17	30	84	0.99	0.88–1.12	50	151	1.00	0.91–1.09
Fibromyalgia	5	18	1.02	0.79–1.35	7	24	0.73	0.56–0.94	12	42	0.85	0.61–1.18
Interstitial cystitis	48	66	2.38	2.14–2.64	21	72	0.84	0.74–0.97	69	138	1.50	1.38–1.62

of the socioeconomic status and found strong evidence that there is no SES variation in the risk of LS. Because our SES categories strongly correlate with education, our results clearly differ from the findings by Virgili et al.<sup>18</sup> The urbanization level of the place of residence did not affect the risk of LS.

Previous research describing comorbidities of LS patients have included only a limited number of patients often recruited from specialized clinics. These studies used control groups of varying quality or no control groups at all. The studies have often been subject to recall bias because of self-reporting of comorbid conditions. We attempted to overcome these difficulties by using population-based and nationwide registry data. The used registries are complete, and their quality has been validated.<sup>23</sup> In Finland, public health care is universally accessible to all, and the cost is mainly covered by municipalities and by a national health insurance. Thus, the generalizability of present results is higher than in most previous studies.

Perhaps the greatest difficulty in previous studies has been an unclear temporal relationship of LS and potential risk factor. We included only comorbid diagnoses that predate the index date. Considering the sometimes long diagnostic delay in LS,<sup>1,2</sup> we additionally stratified the ORs by the temporal distance of the diagnosis of comorbidity and index date. For most comorbid diagnoses, the ORs were similar in both strata. However, the ORs for SLE, Sjögren syndrome, atopic dermatitis, and vitiligo increased with increasing temporal difference, which might be an indication of an association, or even causality, with a lead time of several years.

Some LS diagnoses may be missing from our data. These probably include mild cases diagnosed and treated only in the primary or private health care, not covered by the HILMO. Moreover, the prevalence of some common comorbid diagnoses (e.g., hypertension, type 2 diabetes, and hypothyroidism) was low in the HILMO data because these diseases are usually managed in the

primary care setting. This limitation, however, only decreases the number of events but should not bias the ORs because it applies similarly to both cases and controls.

## CONCLUSION

Our study of 10,692 women with LS and 32,076 controls shows that the risk of LS is highest in women diagnosed with some autoimmune diseases—especially those affecting the skin (morphea, lichen planus, vitiligo, or alopecia), but also others (celiac disease, or Crohn disease). The LS women also had had urinary incontinence more often than the controls. The place of residence and the SES were not associated with LS, whereas having given birth increased the odds of LS. These results indicate that LS may arise from similar pathophysiological processes as other autoimmune diseases with a local irritational or traumatic trigger.

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