Incidence of Systemic Lupus Erythematosus and Lupus Nephritis in Denmark: A Nationwide Cohort Study

Marie-Louise F. Hermansen, Jesper Lindhardsen, Christian Torp-Pedersen, Mikkel Faurschou, and Søren Jacobsen

ABSTRACT. ***Objective.*** To determine the incidence of systemic lupus erythematosus (SLE) and SLE with concomitant or subsequent lupus nephritis (LN) in Denmark during 1995–2011, using data from the Danish National Patient Registry (NPR).

Methods. To assess the incidence of SLE, we identified all persons aged ≥ 18 years in the NPR with at least 1 International Classification of Diseases, 10th ed (ICD-10) code of SLE and at least 365 days of followup under this diagnosis. Identification of LN cases was based on fulfillment of these criteria and ≥ 1 registration under an ICD-10 code of nephritis concomitantly with or after first SLE registration.

Results. The overall annual incidence rate per 100,000 for SLE was 2.35 (95% CI 2.24–2.49); 0.69 (95% CI 0.60–0.78) for men and 3.96 (95% CI 3.75–4.17) for women. For LN, the mean annual incidence rate per 100,000 was estimated to be 0.45 (95% CI 0.38–0.53); 0.20 (95% CI 0.13–0.28) for men and 0.69 (95% CI 0.57–0.83) for women. The differences in SLE incidence rates between sexes decreased by age, and the incidence did not differ between men and women after the age of 60 years for LN. The estimated incidences showed no trends by calendar time. Estimated overall point prevalence (December 31, 2011) per 100,000 was 45.2 (95% CI 43.3–47.4) and 6.4 (95% CI 5.7–7.2) for SLE and LN, respectively.

Conclusion. Our Danish population-based data showed a stable incidence of SLE and LN. As expected, we found higher incidence rates among women than among men, particularly in younger persons. (J Rheumatol First Release May 1 2016; doi:10.3899/jrheum.151221)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
LUPUS NEPHRITIS
EPIDEMIOLOGY
INCIDENCE

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by fluctuating disease activity and variable involvement of multiple organs. Involvement of the kidneys, i.e., lupus nephritis (LN), occurs in a significant proportion of patients with SLE. Patients with SLE with LN formed about one-third of a Danish population-based SLE cohort[1] and 45% of a Danish hospital-based cohort[2]. In the latter cohort, 8.9% of all patients with LN developed chronic renal insufficiency or endstage renal disease per year[3]. Patients with LN often have a more severe disease course than patients with SLE without nephritis[4], and it is therefore of interest to study the epidemiology of SLE and LN separately.

Epidemiological studies worldwide have revealed considerable variations in the incidence and prevalence of SLE, probably reflecting both differences in risk of SLE development related to ethnic/genetic factors and differences in study methodology[5]. Few studies exist on the epidemiology of LN[6,7,8,9].

In Denmark, the incidence and prevalence of SLE has not been investigated on a national level. However, Laustrup, *et al*[10] examined a population-based cohort from a restricted area of Denmark and found a median annual incidence of SLE of 1.04 per 100,000 during an 8-year observation period (1995–2002) and a point prevalence of 28.3 per 100,000 in 2002. To our knowledge, the epidemiology of LN in Denmark has not been studied.

From the Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet; Department of Cardiology, Copenhagen University Hospital, Gentofte Hospital, Copenhagen; Department of Health Science and Technology, Aalborg University, Aalborg, Denmark.

Supported by The Danish Rheumatism Association.

M.L. Hermansen, MD, Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet; J. Lindhardsen, MD, PhD, Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet, and Department of Cardiology, Copenhagen University Hospital, Gentofte Hospital; C. Torp-Pedersen, MD, DMSc, Professor of Cardiology, Department of Health Science and Technology, Aalborg University; M. Faurschou, MD, PhD, Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet; S. Jacobsen, MD, DMSc, Professor of Rheumatology, Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet.

Address correspondence to Dr. M.L. Hermansen, Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet, Section 4242, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
E-mail: Marie-Louise.From.Hermansen@regionh.dk

Accepted for publication March 10, 2016.

The primary objective of our present study was to assess the incidence of SLE and SLE with concomitant or subsequent LN, respectively, in the Danish adult population during 1995–2011. Further, we aimed to determine age- and sex-specific incidence estimates.

MATERIALS AND METHODS

Data sources. The Danish National Patient Registry (NPR) is a population-based administrative registry, which has collected data from all Danish hospitals since 1977 with complete nationwide coverage since 1978. By law, local administrative systems are required to submit standardized data from all hospitals to the NPR at least monthly. Data from private practices are not included in the NPR. Information reported to the NPR includes administrative data, diagnoses, treatments, and examinations for each individual contact in an inpatient (from 1977) or outpatient (from 1995) hospital setting in Denmark. For each hospital contact, a person would be registered with 1 primary diagnosis as the main reason for the contact, and if appropriate, 1 or more supplementary diagnoses, e.g., underlying chronic diseases[11].

The diagnoses are coded according to the International Classification of Diseases (ICD) with use of the eighth revision from 1977 to 1994 and the 10th revision (ICD-10) thereafter.

Unique and permanent personal identification of subjects in the NPR is ensured by the Danish Civil Registration System, a national database that keeps track of all demographic changes in Denmark[12]. Data for our present study were made available by Statistics Denmark in anonymized form; however, a small dataset containing unique person identification numbers and ICD codes was obtained from the Danish Health and Medicines Authority for validation purposes.

Validity of SLE diagnoses in the NPR. In the NPR, we identified all patients ≥ 18 years of age registered with at least 1 primary or supplementary ICD-10 code of SLE (DM321, DM328, and DM329; Supplementary Data available from the authors on request). From this dataset, 208 patients were randomly selected from 3 tertiary care centers and 3 local hospitals in different regions of Denmark. In Denmark, patients with SLE are seen only in local hospitals and tertiary care centers, not general or private practices[10]. The medical files of the 208 patients were scrutinized to estimate the positive predictive value (PPV) of the coding of SLE in the NPR.

Two SLE classification systems were used in the validation process: (1) the 1982 classification criteria for SLE defined by the American College of Rheumatology (ACR) including the revision from 1997, and (2) the criteria for delineating clinically defined SLE proposed by Fries and Holman[13,14,15].

Among the 208 patients selected for case validation, 152 (PPV 73%) had clinically defined SLE and 144 (PPV 69%) fulfilled the ACR classification criteria.

To develop a case identification strategy associated with higher validity for SLE, we investigated the influence of followup time and the number of hospital contacts because of SLE in the NPR. To exclude initially misclassified cases, we chose by an iterative process a search algorithm in which the first registration of SLE in the NPR should be followed by (1) 1 year of outpatient followup or (2) consecutive inpatient admissions coded with an SLE diagnosis with < 3-month intervals during the first year of followup. The last criterion catches the proportion of patients with SLE with more severe presentations who are initially followed with regular inpatient admissions.

By applying this strategy on the above-mentioned 208 patients, we identified 146 patients, of whom 130 (PPV 89%) fulfilled the clinical criteria for SLE and 125 (PPV 86%) fulfilled the ACR criteria.

We included patients in our LN cohort if they fulfilled the criteria for SLE defined above and had been registered with a code of nephritis or damage hereof (DN00-DN06, DN082, DN085, DN162, DN164, DN168, DN18, DN19, DN26, M32.1B) concomitantly with or after the first SLE code in the NPR. A diagnosis of LN was confirmed by medical files review if a patient had (1) biopsy-proven LN or (2) persistent proteinuria > 0.5 g/24 h. Among the 208 patients included in the validation studies, 67 met the criteria for LN. In this subgroup, 60 patients (90%) were confirmed to have LN by medical files review. Kidney biopsies had been performed in 70% of the 60 patients with a code of nephritis.

Case definition. Based on our validation results, we defined SLE cases as persons aged 18 years or more registered with a first-time diagnosis of SLE during the study period and requirements for followup under this diagnosis as described above. Identification of incident LN cases was based on fulfilling the case definition for SLE and a first-time diagnosis of nephritis concomitantly with or after the first SLE code in the NPR. Study index date was defined as 1 year after first NPR registration as a consequence of our search algorithm.

Statistical analysis. Incidence rates were calculated as new cases per 100,000 person-years. The denominator was estimated by determining all Danes alive and aged 18 years or more each calendar year for the subgroup in question. Incidence rates and gender incidence rate ratios (GIRR) with 95% CI were calculated under the assumption that the number of observed cases followed the Poisson distribution. Stata 11.2 was used for all statistical analyses.

Ethics. The study was approved by the Danish Data Protection Agency (2007-58-0015) and the Danish Health and Medicines Authority (3-3013-191/1/KWH).

RESULTS

We identified 1644 incident SLE cases during 1995–2011. Among these, 233 incident cases with LN were identified. Demographic characteristics are presented in Table 1.

In 135 of the 233 patients with LN (58%), the diagnoses of SLE and nephritis were registered simultaneously.

Incidence by calendar time. As illustrated in Figure 1, annual SLE incidence rates between 1.65 per 100,000 (1.42–1.89) and 2.91 per 100,000 (2.61–3.23) were observed across the period of study. The overall annual incidence rate of SLE was 2.35 per 100,000 (2.24–2.49). For women and men, the overall annual incidence rates of SLE were 3.96 per 100,000 (3.75–4.17) and 0.69 per 100,000 (0.60–0.78), respectively.

We observed an increasing incidence of LN during the first half of the study period (data not shown). This increase, however, was expected because of our methodological approach excluding incident SLE cases prior to 1995 and the fact that LN is often developed after SLE presentation. During 2004–2011, the mean annual incidence rate was 0.45 per 100,000 (0.38–0.53) with no major differences observed across calendar years (range 0.29–0.63 per 100,000). Mean annual incidence rates of LN for women and men during 2004–2011 were 0.69 per 100,000 (0.57–0.83) and 0.20 per 100,000 (0.13–0.28), respectively.

Table 1. Demographic characteristics of a Danish SLE case cohort. Values are median (interquartile range) unless otherwise specified.

Characteristics	SLE	SLE with Concomitant or Subsequent Lupus Nephritis
Total, n (%)	1644 (100)	233 (14)
Female, n (%)	1409 (86)	177 (76)
Age, all, yrs	47 (35–58)	42 (31–56)
Age, females, yrs	46 (34–57)	41 (30–51)
Age, males, yrs	54 (42–65)	51 (35–67)
Non-ethnic Danes, n (%)	99 (6)	26 (11)

SLE: systemic lupus erythematosus.

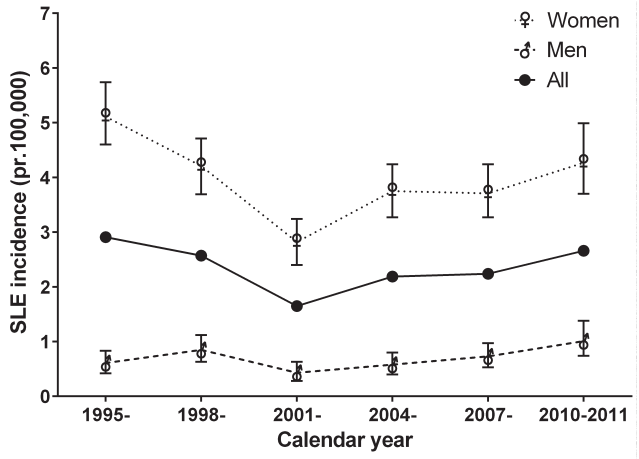

Figure 1. Sex-specific incidence rates (per 100,000 person-yrs) by calendar year with 95% CI for SLE. SLE: systemic lupus erythematosus.

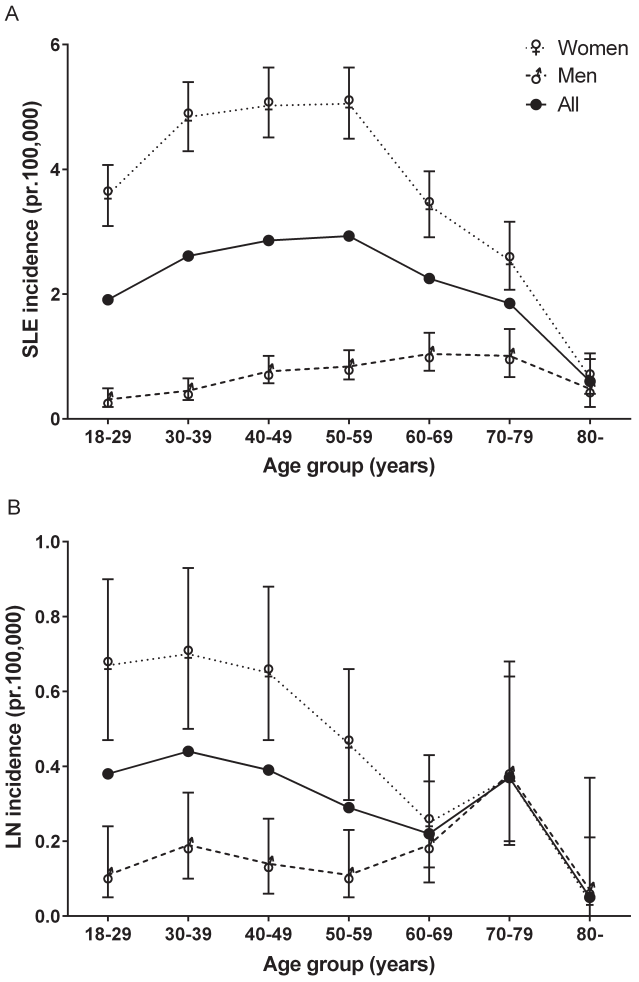

Figure 2. Age- and sex-specific incidence rates (per 100,000 person-yrs) with 95% CI for (A) SLE and (B) SLE with concomitant or subsequent LN. SLE: systemic lupus erythematosus; LN: lupus nephritis.

Incidence by age. Age- and sex-specific incidence rates are shown in Figure 2. The SLE incidence varied considerably between women and men in the 30–59 years age groups with incidence rates up to 10 times higher for women than for men in the age group 30–39 years (4.84 per 100,000, 4.29–5.40 vs 0.45 per 100,000, 0.30–0.65; Figure 2A). The incidence rate of SLE for women was highest in the age groups 30–59. After the age of 60 years, the incidence rates for women dropped toward the incidence rates observed among men. In contrast, incidence rates for men increased slightly with age, and the highest incidence rates were observed in the age groups 60–79 years (Figure 2A). As displayed in Figure 2B, the highest incidence rates of LN were observed among women younger than 50 years of age. Among older women, the incidence rates of LN were comparable to those observed among men.

Incidence rate ratios specific for sex. GIRR for women versus men are shown in Figure 3. The overall GIRR for SLE and LN were 5.77 (5.03–6.62) and 3.04 (2.25–4.11), respectively. GIRR for SLE decreased with age. Thus, GIRR for the age groups 18–30 years and > 80 years were 11.57 (7.24–18.50) and 1.37 (0.57–3.27), respectively (Figure 3A).

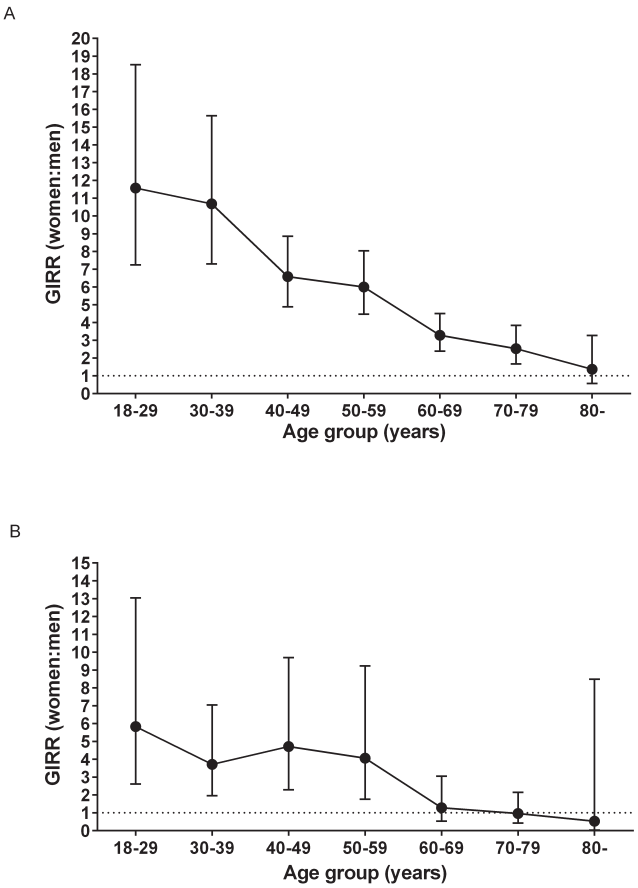

Figure 3. Age-specific GIRR for women versus men shown with 95% CI for (A) SLE and (B) SLE with concomitant or subsequent LN. GIRR: gender incidence rate ratios; SLE: systemic lupus erythematosus; LN: lupus nephritis.

For LN, GIRR (Figure 3B) revealed significantly higher risks for women as compared with men in the age groups below 60 years, with the highest GIRR observed in the age group 18–30 (GIRR 5.83, 2.61–13.04). In the age groups ≥ 60 years, no differences in incidence rates were found between sexes.

Prevalence. To estimate the point prevalence in 2011, we summed all identified cases from the start of followup to the end of 2011 and subtracted patients who died during this period. A total of 1887 persons (1680 women and 207 men) identified with SLE were living in Denmark by December 31, 2011, which translated into a point prevalence per 100,000 persons of 45.2 (43.3–47.4); 79.6 (75.9–83.5) for women and 10.1 (8.8–11.5) for men.

Of these 1887 patients, 267 had LN (223 women and 44 men), corresponding to a point prevalence of LN per 100,000 persons of 6.4 (5.7–7.2); 10.6 (9.2–12.1) for women and 2.1 (1.6–2.9) for men.

DISCUSSION

In our present population-based study, we used register-based data to investigate the epidemiology of SLE and of LN in Denmark during 1995–2011.

We found an overall annual incidence rate for SLE of 2.35 per 100,000 (2.24–2.49). In a population-based cohort study, Laustrup, *et al*[10] assessed the epidemiology of SLE in a smaller area of Denmark and found a median annual incidence of SLE of 1.04 per 100,000 during 1995–2002. Comparing our data to those reported by Laustrup, *et al*, it seems likely that our register-based study does not underestimate the incidence of SLE in Denmark. Slightly higher incidence rates for SLE were obtained in a large-scale epidemiological study from Sweden[16], while a mean annual incidence rate of 3.0 per 100,000 was reported in a community-based study from the capital region of Oslo, Norway[17]. The authors of a Finnish study[18] reported a mean annual incidence of 1.69 per 100,000. This is lower than the national incidence estimates in most other Scandinavian countries. However, the Finnish results were based on data from an insurance institution, and so may not be representative of the general Finnish population.

In 2 studies from the United Kingdom, studies based on a national register (General Practice Research Database; GPRD), the authors found higher overall incidence rates than we did[19,20]. Somers, *et al*[19] reported an overall age-standardized incidence of 4.71 per 100,000 during 1990–1999, while Rees, *et al*[20] found an overall incidence of 4.91 per 100,000 during 1999–2012. It could be speculated that the higher incidence rates observed in the British studies reflect risk factors for SLE related to ethnicity and/or environmental exposures. As in our study, the cases included in the 2 UK studies were register-derived, but the specific validity of the SLE coding in the GPRD was not examined.

In our present investigation, stable annual incidence rates were observed across the calendar period of study. Stable incidence rates were also reported from Sweden during 1981–1991[16], Norway during 1999–2008[17], and the United Kingdom during 1990–1999[19].

For LN, we found a mean annual incidence rate during 2004–2011 of 0.45 per 100,000 (0.29–0.38). Other European studies and 1 Australian study have reported remarkably similar results in spite of methodological differences and variations in geography: a register-based study from Norway[6] and 3 studies of biopsy-proven LN from Australia[7], Sweden[8], and the United Kingdom[9], respectively.

Of note, Feldman, *et al*[21] found an average incidence rate of LN of 6.9 per 100,000 person-years among individuals with low income in the United States. The substantial differences between incidence rates for LN observed in North American and European investigations are likely to reflect differences in ethnicity between the populations studied.

It is of interest that incidences of both SLE and LN seem to be related to age.

Our data suggest that SLE, in general, may develop in both pre- and postmenopausal women, whereas LN is a condition that predominantly develops in premenopausal women. Our data also suggest that sex-specific incidence rates of SLE and of LN peak later in life among men than among women.

In 2011, 92% of the Danish population was composed of whites[22]. In a US study on the incidence of SLE, the mean age at diagnosis was found to be lower than in our study[23]. This is at least partly explained by the fact that SLE and LN appears at a younger age in African American women than in white women, and that black patients with SLE have a higher risk of developing LN than white patients with SLE[23].

The point prevalence for SLE in our study was 45.2 (43.3–47.4) per 100,000 persons on December 31, 2011. Laustrup, *et al*[10] reported point prevalence for SLE in 2002 as 28.3 per 100,000. Our higher estimate does not necessarily reflect an increasing prevalence of SLE in Denmark during 2002–2011, but may be ascribed to regional differences and differences in case definitions, which were register-based in our study and criteria-based in the study by Laustrup, *et al*[10].

The prevalence of LN on December 31, 2011, was 6.4 (5.7–7.2) per 100,000 persons and higher for women than for men by a ratio of 5:1. Patel, *et al*[9] found a comparable overall female:male prevalence ratio for LN.

A strength of our study is the use of nationwide register-derived data. Further, we evaluated the validity of SLE registrations in the NPR and defined a search algorithm including both inpatients and outpatients associated with a high PPV for SLE cases identified in the register. Arkema, *et al*[24], examining case definitions in Swedish register data to identify patients with SLE, reported an increased PPV when including both inpatients and outpatients in the search algorithm. Our search algorithm might cause a slight underestimation of the incidence, e.g., if a patient with SLE dies

within the first year from the first registration. The NPR contains data on hospital contacts, but not on visits to private practices. This is, however, not a limitation of our present study because Danish patients with SLE are not likely to be followed exclusively in private practice[10]. The high proportion of whites in our study provides epidemiological data of a relatively homogeneous population concerning ethnicity. On the other hand, our study is low powered regarding subanalyses on ethnicity, and so we have omitted them. A limitation in the case definition by using the NPR is that the register lacks information on clinical and histologic characteristics. Such information could be useful in prognostic studies; however, that was not the aim of our present study. Another weakness is that the LN group for methodological reasons is included in the SLE group.

Our present study provides the first nationwide data on the epidemiology of SLE and LN in Denmark. No major fluctuations in incidence rates of SLE or LN were observed across calendar periods. We observe markedly higher overall incidence rates for SLE and LN among women than among men, particularly in younger and middle-aged persons. Among women, the risk of LN seems to increase earlier in life than nonrenal SLE. Among men, the incidence of both SLE and LN rises later in life than among women. The variations in the incidence of SLE and LN by age and sex are observed because SLE is a disorder with various clinical phenotypes.

REFERENCES

1. Voss A, Green A, Junker P. Systemic lupus erythematosus in Denmark: clinical and epidemiological characterization of a county-based cohort. Scand J Rheumatol 1998;27:98-105.
2. Jacobsen S, Petersen J, Ullman S, Junker P, Voss A, Rasmussen JM, et al. A multicentre study of 513 Danish patients with systemic lupus erythematosus. I. Disease manifestations and analyses of clinical subsets. Clin Rheumatol 1998;17:468-77.
3. Jacobsen S, Starklint H, Petersen J, Ullman S, Junker P, Voss A, et al. Prognostic value of renal biopsy and clinical variables in patients with lupus nephritis and normal serum creatinine. Scand J Rheumatol 1999;28:288-99.
4. Donadio JV Jr, Hart GM, Bergstralh EJ, Holley KE. Prognostic determinants in lupus nephritis: a long-term clinicopathologic study. Lupus 1995;4:109-15.
5. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus 2006;15:308-18.
6. Eilertsen GØ, Fismen S, Hanssen TA, Nossent JC. Decreased incidence of lupus nephritis in northern Norway is linked to increased use of antihypertensive and anticoagulant therapy. Nephrol Dial Transplant 2011;26:620-7.
7. Yong JL, Killingsworth MC, Lai K. Renal biopsy pathology in a cohort of patients from southwest Sydney with clinically diagnosed systemic lupus erythematosus. Int J Nephrol Renovasc Dis 2013;6:15-26.
8. Mohammad AJ, Weiner A, Sjöwall C, Johansson ME, Bengtsson AA, et al. Incidence and disease severity of anti-neutrophil cytoplasmic antibody-associated nephritis are higher than in lupus nephritis in Sweden. Nephrol Dial Transplant 2015;30:i23-30.
9. Patel M, Clarke AM, Bruce IN, Symmons DP. The prevalence and incidence of biopsy-proven lupus nephritis in the UK: evidence of an ethnic gradient. Arthritis Rheum 2006;54:2963-9.
10. Laustrup H, Voss A, Green A, Junker P. Occurrence of systemic lupus erythematosus in a Danish community: an 8-year prospective study. Scand J Rheumatol 2009;38:128-32.
11. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449-90.
12. Westergaard T, Wohlfahrt J, Aaby P, Melbye M. Population based study of rates of multiple pregnancies in Denmark, 1980-94. BMJ 1977;314:775-9.
13. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus (SLE). Arthritis Rheum 1982;25:1271-7.
14. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
15. Fries JF, Holman HR. Systemic lupus erythematosus: a clinical analysis. In: Smith LH Jr, editor. Major problems in internal medicine. Philadelphia: WB Saunders Co; 1975:1-199.
16. Ståhl-Hallengren C, Jönsen A, Nived O, Sturfelt G. Incidence studies of systemic lupus erythematosus in southern Sweden: increasing age, decreasing frequency of renal manifestations and good prognosis. J Rheumatol 2000;27:685-91.
17. Lerang K, Gilboe I, Garen T, Thelle DS, Gran JT. High incidence and prevalence of systemic lupus erythematosus in Norway. Lupus 2012;21:1362-9.
18. Elfving P, Puolakka K, Kautiainen H, Virta LJ, Pohjolainen T, Kaipiainen-Seppänen O. Incidence of systemic lupus erythematosus in Finland, 2000-2007, a nationwide study. Clin Exp Rheumatol 2014;32:953-5.
19. Somers EC, Thomas SL, Smeeth L, Schoonen WM, Hall AJ. Incidence of systemic lupus erythematosus in the United Kingdom, 1990-1999. Arthritis Rheum 2007;57:612-8.
20. Rees F, Doherty M, Grainge M, Davenport G, Lanyon P, Zhang W. The incidence and prevalence of systemic lupus erythematosus in the UK, 1999-2012. Ann Rheum Dis 2016;75:136-41.
21. Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcón GS, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with medicaid coverage, 2000-2004. Arthritis Rheum 2013;65:753-63.
22. Statistics Denmark. [Internet. Accessed March 11, 2016.] Available from: www.dst.dk
23. Somers EC, Marder W, Cagnoli P, Lewis EE, DeGuire P, Gordon C, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis Rheumatol 2014;66:369-78.
24. Arkema EV, Jönsen A, Rönnblom L, Svenungsson E, Sjöwall C, Simard JF. Case definitions in Swedish register data to identify systemic lupus erythematosus. BMJ Open 2016;6: e007769.