Systemic Lupus Erythematosus in the Arctic Region of Norway

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ABSTRACT. ***Objective.*** The marked regional variation in the incidence, prevalence, and presentation of systemic lupus erythematosus (SLE) is possibly related to differing spectra of local environmental factors. The aim of this study was to describe such features in a homogenous Caucasian population exposed to an Arctic climate.

Methods. The study area consisted of the 2 northernmost counties of Norway (middle population 222,403) where 4 hospitals (containing only one rheumatology service) provide specialized health care. Retrieval sources were (1) hospital inpatient discharge registries; (2) hospital outpatient registries; (3) mortality database of the National Office for Statistics. Databases were searched with codes for SLE, Sjögren's syndrome, unclassified connective tissue disease, and discoid lupus for the period 1978–96. Only patients meeting 1982 American College of Rheumatology criteria for SLE were included in the analysis. Annual incidence rate (AIR), point prevalence (PP), and mortality rates were estimated per 100,000 at risk.

Results. Eighty-three incident cases of adult SLE (87% female, mean age 40.6 yrs at diagnosis) were encountered. Crude AIR of SLE in the whole study period was 2.6 (95% CI 1.9–2.9) for adults. Sex-specific AIR was 4.6 for adult women and 0.6 for adult men. AIR in the first (2.4) and second 9-year period (2.7) was similar ($p > 0.2$). The crude overall PP for SLE at January 1, 1996, was 44.9 and was highest in women aged 31–49 (PP 102.5). Mortality in incident cases was 9.6% (after a mean followup of 99 mo) with overall 10-year survival estimated at 75%.

Conclusion. In a Caucasian population exposed to the Arctic climate incidence of SLE is rather low and stable. Course and presentation of SLE in the Arctic is not different from similar populations in the Western world. Improved outcome now makes SLE a disease present in 1 per 1000 Norwegian women aged > 30 years. (J Rheumatol 2001;28:539–46)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS INCIDENCE PREVALENCE
MORTALITY ARCTIC REGION NORWAY

Systemic lupus erythematosus (SLE) is a disease of unknown origin in which a combination of genetic and environmental features causes a loss of self-tolerance that may result in a myriad of autoantibody mediated, often inflammatory lesions[1]. Considerable differences in frequency and severity of the disease have been described from all continents, and although methodological differences can explain part of those discrepancies, local-regional influences are considered important in the expression of the disease[2,3]. Other Nordic areas have reported annual incidence rates of 1.9–3.1 in Denmark[4] and 4.8 in southern Sweden[5]. The most northern part of Norway lies 2000 kilometers north of those areas. Living well above the Arctic Circle its predominantly Caucasian population is subjected to the Arctic climate, with a longlasting winter that sees 168 days of frost and a 2 month period of darkness when sunlight is absent. This is followed by a rapid increase in the number of sunlight hours culminating in a 2 month summer period with 24 hours of sunlight (the "Midnight Sun"). There is evidence suggesting that such extreme light and dark cycles as well as long periods in a cold harsh environment are related to seasonal disorders with concomitant changes in levels of cerebral neurochemical substrates and endocrine and immune functions. These changes are most pronounced among women of reproductive age[6,7]. Its peculiar regional characteristics in combination with the free, but strictly hierarchical Norwegian public health care system made this area an interesting and fitting target for a study into the incidence, prevalence, and seasonal variations of SLE in the 2 northernmost counties of Norway over an 18 year period.

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MATERIALS AND METHODS

Study area. The study area consisted of the 2 northernmost counties in Norway, Finnmark and Troms. They border the Polar Sea and span an area of almost 75,000 km^2 in which 224,500 people live (5.1 % of the Norwegian population at January 1, 1996). The area is mainly rural, without heavy industries, and the majority of its population live along the coast where fishing provides a major source of income. Its population

consists of mainly Caucasians (> 96%); in addition, about 10,000 Samic people (Lapps) live and roam in a tri-country border area. The area had a mean annual migratory rate of –0.12% between 1980 and 1995, with little change in population characteristics during the study period; the percentage of children decreased from 21.2% in 1986 to 20.3% in 1996, while the adult male to female ratio decreased from 1.03 to 1.02[8].

All inhabitants have free access to both primary (family physician) and secondary (specialist) health care. The region contains 3 community hospitals and one tertiary care facility, where the only rheumatology service is located. This service periodically provides ambulatory care for rheumatological patients at the 3 community hospitals; no private rheumatology or internal medicine practices were present in the area during the study period. Both counties have administrative and financial responsibility for health care provision for their inhabitants, who can receive free medical care outside their county only after prior evaluation at the referral center. For the same reason, all serological testing for patients with suspected rheumatic diseases (including measuring complement factors) is performed at the Clinical Immunology Laboratory in Tromsø that participates in regular national quality controls. Antinuclear antibody (ANA) testing was performed by immunofluorescence technique from 1978 to 1993 and by automated ELISA (which is more sensitive to anti-SSA antibodies) from 1993 onward; all ANA positive sera were automatically tested for anti-dsDNA antibodies (by *Crithidia lucillae* assay and by ELISA since 1993), as well as for antibodies against SSA/SSB, Sm, and anti-RNP. In case a positive ANA test was accompanied by a positive test for any of these specific autoantibodies, the requesting physician received the test results with a note that such autoantibodies could indicate the presence of SLE or related diseases. In general, such patients are then referred to our Rheumatology Service for evaluation.

Case ascertainment and data collection. All 4 hospitals maintain diagnosis registries, which were automated around 1980. The inpatient database contains all discharge diagnoses relevant to the hospital stay, while the outpatient registry contains codes only for the main disease that leads to the outpatient visit. These 2 registries were the main source of patient retrieval; they were searched for SLE (ICD-9 code 710.0), Sjögren's syndrome (SS) (710.2), unclassified connective tissue disease (710.9), and discoid lupus (695.4) in the period January 1978 to January 1996. In addition, at the start of data collection all general practitioners in the area received a short version of the study protocol and were asked to refer to our service any hitherto unidentified patient with at least one objective finding in the presence of ANA. Finally, data on deceased persons with SLE as the main or contributing cause of death according to the death certificate for the whole region in the study period were obtained from the Health Section of the National Bureau of Statistics (now Norway Statistics).

Records for all patients with a relevant diagnosis were retrieved from hospitals or family physicians and analyzed by one investigator using a predefined data extraction form[9]. Patients fulfilling at least 4 of the 1982 American College of Rheumatology (ACR) classification criteria for SLE[10] were included. The following information was collected: demographic data, date of SLE onset (determined by first objective symptom attributable to SLE), date of SLE diagnosis (defined as the time when 4 ACR criteria were met), type and number of ACR criteria at diagnosis, disease activity at diagnosis according to the SLE Disease Activity Index (SLEDAI), date and cause of death, or date of last followup. Features not described in the record were considered to be not present. Also recorded were laboratory data at diagnosis as recorded by the local hospital laboratories: erythrocyte sedimentation rate, C-reactive protein, complete blood count, serum creatinine, and urine dipstick findings with urine sediment microscopy. Serologic data recorded included results of ANA screening with testing for specific autoantibodies and levels of complement factors (C3, C4, CH50).

Statistics. All population figures were obtained from the National Bureau of Statistics. The adult population was defined as all persons ≥ 16 years of age. Incidence and mortality data for the whole period were calculated using the 1986 population data as the middle population; this year was also chosen as the point of division for the study period to study possible changes in epidemiological findings over time. Annual incidence rate (AIR), point prevalence (PP), and mortality rates (MR) are reported per 100,000 at risk. PP rates were estimated per January 1, 1980 (population 224,745), January 1, 1986 (222,403), January 1, 1992 (220,682), and January 1, 1996 (223,370). Ninety-five percent confidence intervals (CI) for rates were calculated with the approximation formula for standard error. Survival estimates were calculated by Kaplan-Meier method and analyzed by log-rank testing.

Standardized mortality ratios were derived by the indirect method. Mann-Whitney U test and chi-square test with Yates' correction were used to determine the significance of differences in continuous and categorical data. All resulting p values < 0.05 were considered to indicate statistical significance.

RESULTS

Patient retrieval. A total of 234 patient records were screened in the search for incident cases of SLE. The resulting diagnoses are summarized in Figure 1. Other diseases were primary SS (n = 31), lupus-like disease (fulfilling < 4 ACR criteria; n = 13), unclassified and mixed connective tissue disease (n = 9), discoid lupus (n = 9), drug induced lupus (n = 5), primary antiphospholipid syndrome (n = 2), and a group of miscellaneous diseases (n = 43) that included biliary cirrhosis, autoimmune hepatitis, pulmonary fibrosis, inflammatory and osteoarthritis, vasculitis, and malignancy. Nine patients were ANA positive without symptoms attributable to a specific disease. All 89 new SLE patients were retrieved through the hospital registries; 12% had been seen on an outpatient basis only and the remaining 88% were found in both out- and inpatient registries. Seven of the 8 (85%) nonsurviving patients from the cohort had SLE registered as a main or contributing cause of death. Figure 2 depicts the numbers and overlap of case retrieval for the various data sources.

Demographics. One hundred eleven patients fulfilled the ACR classification criteria during the study period, of which 89 were true incident cases. Four were children at diagnosis (mean age 12.4 years, range 9–14) and 2 patients were refugees from other countries; all 6 were excluded from this analysis, which thus comprised a cohort of 83 adult patients. Based on the current definition (residing in a Samic designated area and speaking Samic), 3 patients (3.7%) were considered to be of Samic descent. Median age at diagnosis was 39.8 years (range 16–80) and was somewhat higher in men (47.3 yrs, n = 10) than in women (39.2 yrs, n = 73), although not significant (p = 0.14). The time of onset of lupus related symptoms could be traced in 76 patients and median time elapsed until SLE was diagnosed was 23.7 months (range 0–283). Disease manifestations in this cohort at diagnosis and cumulatively during a mean followup of 99 months are shown in Figure 3. Two female patients remained ANA negative throughout their disease course, which was characterized by nonerosive arthritis, thrombo- and leukocytopenia, oral ulcers, and presence of LE cells in one, and by discoid lesions, photosensitivity, serositis,

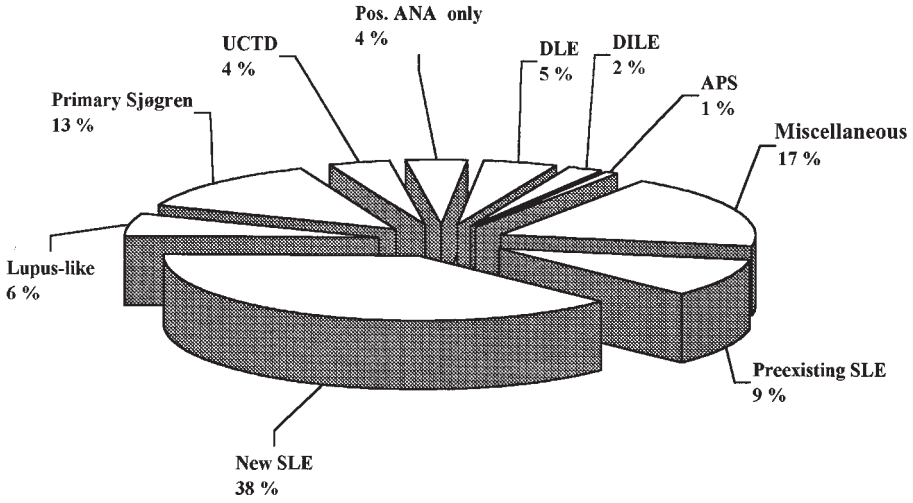

Figure 1. Distribution of diagnoses resulting from the screening of 238 records. Lupus-like: < 4 ACR criteria for SLE; UCTD: undifferentiated connective tissue disease; DLE: discoid lupus; DILE: drug induced lupus; APS: antiphospholipid antibody syndrome.

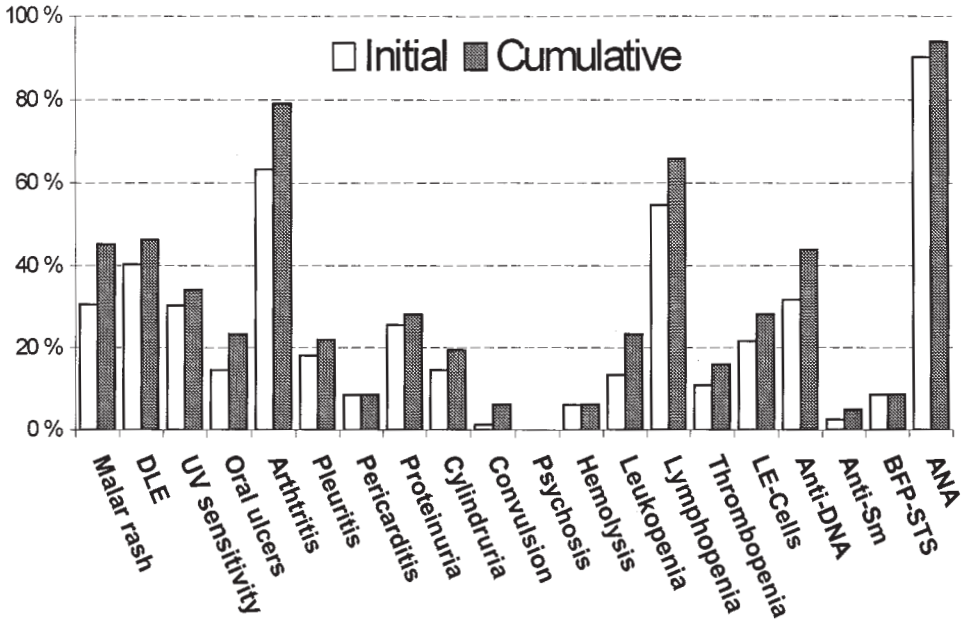

Figure 2. Case retrieval and overlap from the various data sources.

lymphopenia, and spontaneous abortions in the other. Age (44.2 vs 39.8 yrs), sex distribution, SLEDAI at diagnosis (9.2 vs 8.2), and number of ACR criteria fulfilled (4.7 vs 5.1; p = 0.2) in incident cases were similar in both study periods. The frequency of the various clinical criteria at presentation was also similar; however, the number of patients with positive LE cell preparations decreased (from 31 to 14%; p = 0.06), while the number with positive anti-dsDNA increased (from 21 to 42%; p = 0.03). The seasonal distribution by month of diagnosis for the whole study period is shown in Figure 4. There was no difference in the number of patients diagnosed during summer periods (May to September, 45.8%) versus the rest of the year (October to May, 54.2%), while the peak of incident cases in the month of June was not significant (odds ratio 7.7 versus the rest of the year, CI 0.7–6.5). Using the self-reported time of onset of SLE symptoms the data were 52% for summer and 48% for the rest of the year, while onset of symptoms was reported more often in June than in other months (odds ratio 7.1, CI 2.4–19.5).

Epidemiology, incidence, prevalence, and mortality. The 83 incident cases of adult SLE resulted in a crude overall

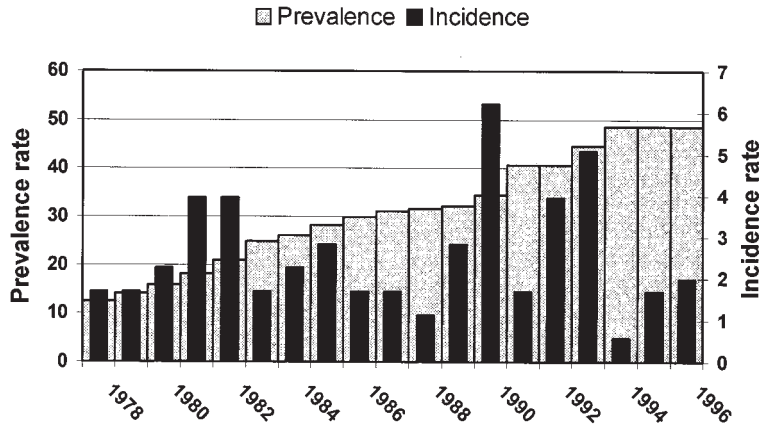

Figure 3. Disease manifestations in 83 new patients diagnosed with SLE between 1978 and 1996 in northern Norway.

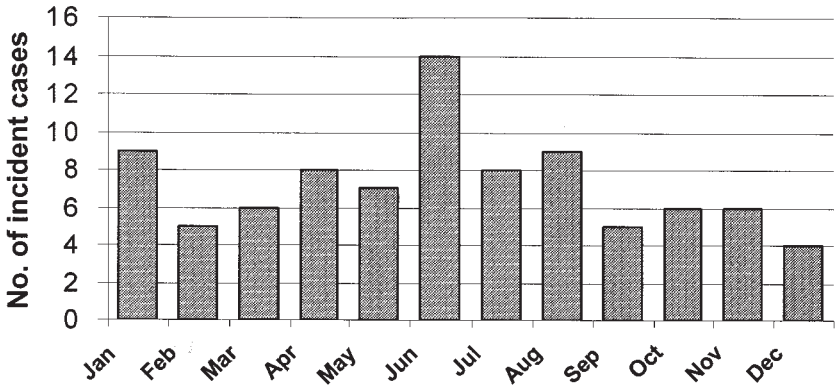

Figure 4. Seasonal distribution of incident cases of SLE in northern Norway by month of diagnosis.

annual incidence rate (AIR) of 2.6 (CI 2.1–3.2) for the adult population. Crude age- and sex-specific AIR are summarized in Table 1; a low AIR was found in children and adult men (0.5 and 0.6, respectively), with a peak incidence of 5.6 (CI 3.8–7.8) in women aged 30–49. Overall incidence was slightly higher in the second half of the study period (2.4 vs 2.7) and a trend to increased AIR was observed in most groups, except in women aged > 50 years. Age standardized AIR was 2.9 (CI 2.4–3.3) overall, 0.7 (CI 0.6–0.8) for men and 5.1 (CI 3.2–7.0) for women.

In 1978, 22 patients (3 men) were known with a previous diagnosis of SLE and are included in the prevalence figures. One adult patient with incident SLE emigrated and 3 pediatric patients that reached adulthood were included from the date they reached 16 years of age, leading to a total of 89 patients with SLE at the end of this study period per January 1, 1996, and a crude point prevalence of 49.5. Age standardized rates at that time were 49.7 (CI 44.3–55) overall, 9.7 (CI 6.9–12.6) for men and 89.3 (CI 78.9–100.2) for women. There was a gradual increase in disease prevalence during the whole observation period in all sex and age groups (data not shown), with SLE prevalence in 1996 being highest in women aged > 30 years (PP 101.5), indicating 1 per 1000 women in that age group had SLE.

Eighteen patients (11 true incident cases, 7 with preexisting disease) died during the study period for an overall case fatality rate of 16.2%. Median disease duration and age at death were 110 months (range 3–222) and 59.2 years (range 30–83), respectively, and did not differ between male (n = 3) and female nonsurvivors (p > 0.3). Eleven patients (61%) died while in remission of their disease (SLEDAI = 0), 2 patients (11%) died with continued low disease activity (SLEDAI scores were 2 and 3, respectively), while lupus flares were present at death in 5 patients (27%) with a mean SLEDAI score of 9.6 (range 4–16). Main causes of death in the 13 patients with low to moderate disease activity were cardiovascular (including sudden death) in 5, cerebrovascular accidents in 2, infections in 3, perforated ulcus in one,

Table 1. Mean annual incidence rates (95% CI) for SLE per 100,000 at risk by age and sex.

	Total No. in Population	No. of Cases	Whole Study Period (CI)	1978–86 (No. of Cases)	1987–95 (No. of Cases)
Children ≤ 15 yrs	45,370	4	0.5 (0.3–1.12)	0.47 (2)	0.49 (2)
All adults	177,033	83	2.6 (2.1–3.2)	2.4 (39)	2.7 (44)
Men > 15 yrs	89,402	10	0.6 (0.3–1.3)	0.37 (3)	0.85 (7)
Women > 15 yrs	87,631	73	4.6 (3.6–5.8)	4.66 (36)	4.58 (37)
16–29	22,325	21	5.2 (3.2–7.7)	4.47 (8)	5.96 (9)
30–49	32,770	33	5.6 (3.8–7.8)	4.89 (14)	6.64 (22)
≥ 50	32,536	19	3.2 (2.0–5.1)	4.5 (14)	2.1 (6)

Table 2. Age and sex-specific mean annual mortality rates for patients with SLE per 100,000 at risk.

	No. of Deaths	Crude Annual Mortality Rate (CI)	Standardized Mortality Ratios (CI)
Children ≤ 15 yrs	0	—	—
Adults > 15	18	0.46 (0.34–0.9)	2.2 (1.4–3.1)
Men > 15	3	0.18 (0.04–0.6)	1.8 (1.2–2.4)
Women > 15	15	0.95 (0.53–1.57)	1.3 (1.0–1.6)
16–29	0	—	—
30–49	4	0.68 (0.19–1.74)	1.7 (1.2–2.2)
≥ 50	11	1.88 (0.9–3.3)	3.9 (2.1–5.6)

suicide in one, and unknown in one. Crude annual mortality rate was 0.4 per 100,000 population. Age and sex-specific mortality rates as well as standardized mortality ratios are shown in Table 2 and indicate an overall 2-fold higher risk of death after SLE has been established. Five and 10 year survival estimates for the true incident cases with followup extending to January 1, 1999, were 92 and 75%, respectively (Figure 5). No prognostic value was found for any of the ACR criteria at diagnosis or diagnosis before or after 1986; a history of any kind of thrombosis at diagnosis, however, was strongly associated with poorer survival ($p < 0.0001$).

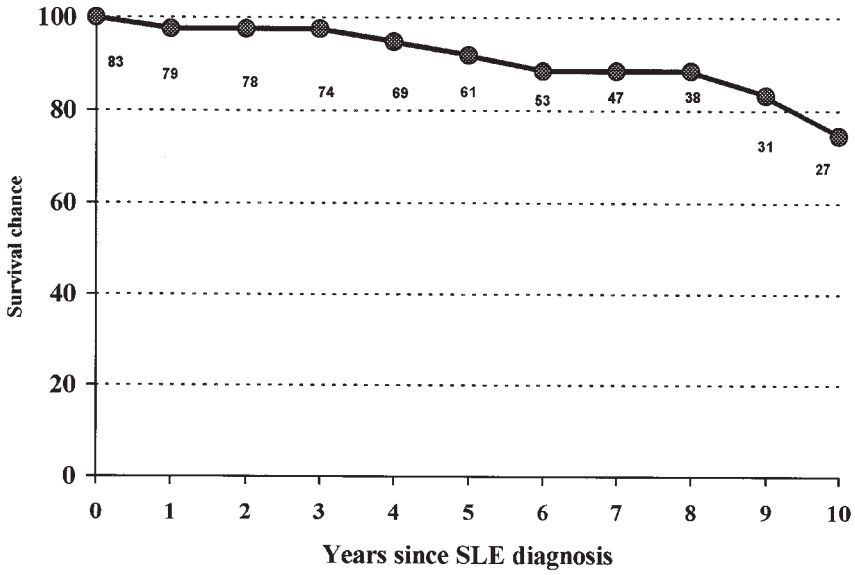

Figure 5. Survival curve for incident cases of SLE in the period 1978–1995. Numbers under the curve refer to the number of patients still in study.

DISCUSSION

There is substantial variation in the frequency and severity of SLE on different continents[3,11]. Aside from methodological considerations these discrepancies may be due to genetic makeup of the study population, environmental influences they are exposed to, or a combination of both. To unravel this puzzle it is important that homogenous populations are studied in different environments with the use of reproducible and validated methods. This study reports results on SLE incidence, prevalence, and mortality in a homogenous Caucasian population, exposed to the harsh Arctic climate that may contribute to SLE in various ways. It brings longlasting winters, when inland temperatures as low as –30°C are not uncommon. Extended cold exposure has been associated with such diverse pathophysiological processes as complement activation, presence of IgM antilymphocyte antibodies, and the induction of apoptosis[12-14], while clinically, cold exposure has been related to perniosis, urticarial vasculitis, chilblain lupus, and exaggerated Raynaud's phenomenon with resulting cerebral and myocardial ischemia, as well as thrombophilia due to increased levels of von Willebrand factor, endothelin-1, and cryofibrinogemia[15-19]. In addition to cold exposure the inhabitants are subjected to abnormal dark–light cycles that result in seasonal changes in immune function, which are at least partly hormone mediated (by melatonin, prolactin, and adrenal steroids) and occur most often in fertile women[6,7]. Despite these considerations, the findings in this study do not point to a significant influence of the Arctic climate on SLE frequency or severity in this Caucasian population. The AIR of 2.6/100,000 adults is similar to the rates observed in comparable populations residing at lower latitudes such as Denmark (AIR between 1.5 and 3.1), Nottingham, UK (AIR 2.4), and Rochester (AIR 3.1) and Pennsylvania (AIR 2.8) in the USA[4,20-22]. Iceland, intermediately positioned just below the Arctic Circle, has reported an AIR of SLE of 3.3[23]. In southern Sweden, median AIR in adult Caucasians was 4.5 between 1981 and 1986 and 4.8 in 1987–1991 (while mean AIR with ACR criteria as recalculated from their data was then 3.5). The lack of access to an ANA registry (privacy laws prohibit such a register, such as that used by Stahl-Hallengren, *et al*[5]) and the differing diagnostic criteria and study design seem the most plausible explanations for the remaining difference[24]. SLE incidence throughout the 18 years was as stable as in southern Sweden[5], while SLE incidence increased in Rochester, USA, in the same period; this was mainly due to increased incidence of African-American patients[21]. While not a primary goal, the data also allowed the estimation of AIR for children, on which few data exist; the AIR of 0.5 per 100,000 was comparable to the rates for white children described in Finland (AIR 0.4), Sweden (0.4), and the USA (AIR 0.6)[24-26].

There are some reports on SLE epidemiology in populations with a different genetic background living near or above the Arctic Circle. A high prevalence (112 per 100,000) has been found in Alaskan (Tlingit) Indians, while in Alaskan Eskimos prevalence was estimated to be only 11 per 100,000 (although with a peculiar 1:1 sex ratio)[27,28]. In view of this data and despite the relatively small numbers in the Alaskan studies, one may conclude that climate environment is less important than genetic makeup in SLE susceptibility in Arctic areas. One report found no relation between seasons and lupus disease activity[29].

Completeness of case ascertainment is a major concern when performing epidemiological studies. This study used 3 different sources to ascertain inclusion of all incident cases, in compliance with recommendations not to rely on a single source of information[2,22,24]. In addition to these different sources (with more than 80% overlap), 2 supportive measures ensured the inclusion of all incident cases. First, a single laboratory performed all tests for autoantibodies and sent physicians a reminder that patients with positive ANA might have SLE; this reduced the chance that SLE cases would not be followed. Second, all primary physicians were notified at the start of the study and invited to refer any case that might have undiagnosed SLE. These methods, in combination with the tightly regulated public health care system, with no private specialist practices in the study area, make it unlikely that a significant number of patients with definite SLE still go undiagnosed in the area. While it may take some years before possible SLE turns definite, especially in elderly patients, as in the Swedish study[5], the longterm followup in this study also reduces the likelihood that such patients were missed. While this analysis ended January 1, 1996, 3 of 21 new incident cases seen in the 4 years since had onset of SLE symptoms in the study period. It has been made clear, however, that only patients fulfilling at least 4 ACR criteria should be included in epidemiological studies to reach maximal specificity and avoid prognostic bias by including less severe cases[2,30]. In addition, SLE no longer is a disease where most patients succumb in the early years, as illustrated by the long interval between diagnosis and time of death in the nonsurviving patients in this and other studies. This makes it unlikely that a large number of patients would have succumbed before receiving a diagnosis of SLE. However, even in cases of apparently exhaustive surveys a formal estimate of the number of missing cases has been recommended[31], and applying the capture-recapture technique on data shown in Figure 2 led to an estimate of 2 missing cases; however, this represents a minimum estimate as sources were heavily dependent[31].

The clinical features of SLE in this Nordic cohort (Figure 2) are largely in agreement with data from similar populations. Of the cold related clinical features, we found urticarial vasculitis in 3.6%, Raynaud's phenomenon in 80.7%, and thrombophilia in 25% of patients. While the high frequency of Raynaud's phenomenon is not unex-

pected, discoid lupus was present in 20% more patients than in other European studies[4,5,20] — despite a lower number with UV sensitivity, indicating that the high total of sunlight hours in the area is less important than the abnormal cycle of sun exposure[29]. Both the Swedish and the Mayo Clinic longterm studies[5,21] reported a reduction in the number of patients with renal disorder over time; both the number presenting with (from 33 to 19%) as well as the cumulative number with clinical signs of nephritis (41 to 27%) decreased in the second half of the present study, but these decreases were not statistically significant ($p > 0.1$). The reduction in number of positive LE cell tests and the increase of positive anti-dsDNA tests reflects the trend where clinical immunology laboratories moved from labor intensive and subjective to automated and easily reproducible testing; such a trend was found by Uramoto, *et al* as well[21]. However, clinical data were collected retrospectively and the findings thus represent minimum figures for these clinical features.

The case fatality rate for incident cases was 9.6% during 99 months of followup, with a 75% ten year survival. The overall annual mortality rate in adults of 4.6 per million persons as well as the sex and age adjusted rates (1.8 in adult men and 9.5 per million in adult women) are in nearly complete agreement with sex-specific rates for Caucasian patients in the USA[2,26,31]. Standardized mortality ratio findings stress that SLE still leads to considerable overmortality that occurs mainly late in the disease course; two-thirds of fatalities occurred in women over age 50 years and remarkably, no fatalities occurred in the age group < 30 years, although it made up a quarter of all incident cases. As incidence rates did not increase significantly over time, the increasing age at death forms the best explanation for the steadily rising prevalence rate of SLE encountered[5]. This development now makes SLE a disease that is present in 1 per 1000 Norwegian women over age 30 years, induces significant morbidity, and follows a chronic course, with mortality mainly occurring in those > 50 years of age.

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