



Trend of prevalence and incidence of systemic lupus erythematosus in South Korea, 2005 to 2015: a nationwide population-based study

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Background/Aims: The aim of this study was to evaluate the trend of incidence and prevalence of systemic lupus erythematosus (SLE) in South Korea from 2005 to 2015.

Methods: From 2005 to 2015, individuals with SLE were identified from the National Health Insurance database, which records information on almost all Koreans. SLE was defined according to the International Classification of Diseases, 10th revision (ICD-10), code M32. The incidence was calculated per 100,000 person-years. The prevalence was calculated per 100,000 people and stratified by year, age group, sex, region, and income.

Results: The annual prevalence of SLE increased slightly from 21.25/100,000 people in 2005 to 35.45/100,000 people in 2015. In contrast, the annual incidence of SLE decreased slightly from 5.42/100,000 person-years in 2005 to 3.6/100,000 person-years in 2015. The prevalence and incidence of SLE were 10- and 6-fold higher in women than in men, respectively. The peak age of prevalence and incidence was 30 to 39 years in 2005; in 2015, the peak age of prevalence was 30 to 49 years and of incidence was 20 to 49 years. Regional variation was observed in both incidence and prevalence of SLE. Jeju province showed the highest prevalence of SLE (44.54/100,000 person-years), and Gwangju province showed the highest incidence of SLE (6.98/100,000 person-years) in 2015. The income status did not affect the prevalence or incidence of SLE except in patients without income who received medical aid.

Conclusions: The incidence of SLE has declined, but the prevalence has increased in Korea in recent years. Peak age of SLE trend to right shift in Korea.

Keywords: Lupus erythematosus, systemic; Prevalence; Incidence; Database; Korea

INTRODUCTION

Systemic lupus erythematosus (SLE) is a rare, chronic autoimmune disease that can vary in severity from mild to potentially life-threatening. To improve its

management, it is important to know the prevalence of the disease, including the clinical and socioeconomic characteristics of the affected population [1-3]. Both the magnitude and severity of SLE differ markedly with respect to sex, age, race, and region [4]. The prevalence and

incidence of SLE are 100 to 150/100,000 and > 5/100,000 person-years, respectively [5-9]. A recent review of the epidemiology of SLE in the Asia-Pacific region showed that the prevalence and incidence were in the range of 4.3 to 45.3/100,000 and 0.9 to 3.1/100,000 person-years, respectively [10].

The majority of the epidemiologic data on SLE available in the literature is from single-center or cohort studies, but such studies are costly and time-consuming [11,12]. In contrast, the use of population-based data is more convenient and precise; one such database is the National Health Insurance (NHI) in Korea, which records extensive data of almost all Koreans. Previous epidemiologic studies on SLE in South Korea have focused on identifying a way to precisely estimate the prevalence and incidence of SLE using population-based surveillance systems [13,14].

The trend of peak age of the prevalence and incidence of SLE, sex, region, and socioeconomic status has not been reported thus far in Korea. Therefore, the present study aimed to determine the prevalence and incidence of SLE in South Korea, including temporal trends and variations in age, sex, region, and income from 2005 to 2015 by using the Korean NHI database.

METHODS

Study design and database

We conducted a nationwide cross-sectional study using the Korean NHI database of the Health Insurance Review Agency from 2005 to 2015. This database includes all claims data provided by the NHI and the Medical Aid programs [15]. The Korean NHI program is a compulsory social insurance scheme that covers approximately 97% of the Korean population; the remaining 3% are protected under the Medical Aid program [16]. The database consists of anonymized data that can be used for research purposes and reports the service code (admission or outpatient clinic), year (billing year), age (year old), region (province), sex (male or female), hospital (private clinic, hospital, or university hospital), department (internal medicine, dermatology, etc.), admission (admission or no admission), and billing number included all claimed national insurance data. The NHI database is credible and well-grounded for its use in managing the

national statistical resources.

This study was approved by the Institutional Review Board of the National Institute for Bioethics Policy (NHIS-2018-1-109) and the Chonnam National University Hospital (CHUN-EXP-2017-235) in South Korea, and it was conducted according to the principles of the Declaration of Helsinki. Anonymized and de-identified information was used for analyses, and therefore informed consent was not required.

Identification of SLE cases

The NHI statisticians compiled data on all patients from institutes nationwide, who were treated under the International Classification of Diseases, 10th revision (ICD-10), code M32 for 13 years from 2002 to June 2015 (washout period was from 2002 to 2004). The South Korea government has enhanced benefit coverage for four major conditions (cancer, cardiovascular disease, cerebrovascular disease, and rare diseases), and SLE is one of the rare diseases. Within this system, the NHI has established a registration program for rare intractable diseases (code V136). Due to enforced privacy laws, detailed personal information could not be retrieved; instead, each patient was allocated an identification number.

Estimation of prevalence and incidence

For annual prevalence, the year-specific numerator included subjects with prevalent SLE in the specific calendar year, and the denominator included the mid-year population from the Korean National Statistical Office of the year. For annual incidence, the year-specific numerator included subjects with incident SLE in the specific calendar year, and the denominator included the mid-year population from the Korean National Statistical Office of the year. Crude rates, sex- and age-specific rates, standardized rates adjusted for sex and age using the 2015 mid-year population, and their 95% confidence intervals (CIs) were calculated. Incident cases of SLE were defined as those without SLE in a particular year (e.g., 2005) and the preceding 2 years (e.g., 2003 to 2004) that met the algorithm in that year (e.g., 2005) and the following year (e.g., 2006). Subgroup analyses were performed according to age (< 40, 40 to 64, and > 65 years), sex, region, and income. Income was stratified into 20 categories (from P1 [lowest] to P20 [highest]) and a medical aid group (with government-aided medical care).

Table 1. Systemic lupus erythematosus prevalence by year, 2005 to 2015

Year	Total population	No. of prevalent cases	Total crude rate, /100,000 person-years (95% CI)	Male cases	Male crude rate, /100,000 person-years (95% CI)	Female cases	Female crude rate, /100,000 person-years (95% CI)
2005	48,030,635	10,208	21.25 (20.84–21.67)	907	3.76 (3.51–4.00)	9,301	38.94 (38.15–39.73)
2006	48,371,311	11,060	22.86 (22.44–23.29)	1,055	4.34 (4.08–4.61)	1,0005	41.55 (40.74–42.36)
2007	48,603,519	12,003	24.70 (24.25–25.14)	1,126	4.62 (4.35–4.88)	10,877	44.93 (44.09–45.78)
2008	49,560,378	12,981	26.19 (25.74–26.64)	1,202	4.83 (4.56–5.11)	11,779	47.69 (46.83–48.55)
2009	49,884,458	13,914	27.89 (27.43–28.36)	1,272	5.08 (4.81–5.36)	12,642	50.84 (49.95–51.72)
2010	50,166,793	13,270	26.45 (26.00–26.90)	1,151	4.58 (4.31–4.84)	12,119	48.45 (47.58–49.31)
2011	50,445,164	14,216	28.18 (27.72–28.64)	1,270	5.02 (4.75–5.30)	12,946	51.45 (50.56–52.34)
2012	50,763,154	15,130	29.81 (29.33–30.28)	1,377	5.41 (5.13–5.70)	13,753	54.3 (53.39–55.21)
2013	51,013,675	16,152	31.66 (31.17–32.15)	1,517	5.94 (5.64–6.24)	14,635	57.45 (56.52–58.38)
2014	51,281,917	17,324	33.78 (33.28–34.28)	1,621	6.32 (6.01–6.62)	15,703	61.30 (60.35–62.26)
2015	51,574,044	18,282	35.45 (34.93–35.96)	1,771	6.86 (6.54–7.18)	16,511	64.09 (63.12–65.07)

CI, confidence interval.

Statistical analyses

Continuous variables are presented as mean and standard deviation, and categorical variables are presented as number and percentage. To compare the characteristics between the cohorts, the Student’s *t* test was used for continuous variables and the chi-square test was used for binary and categorical variables. All statistical tests were two-tailed, and the significance level was set at *p* < 0.05. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) software program.

RESULTS

Prevalence

From 2005 to 2015, the average number of prevalent cases of SLE was 14,049 (crude rate, 28.02; 95% CI, 20.84 to 32.15), of which 12,752 (90.8%; crude rate, 51; 95% CI, 38.15 to 58.38) were women (Table 1).

Trend in prevalence by year

There was a linear increasing annual trend in the prevalence of SLE, from 21.25/100,000 person-years in 2005 to 35.45/100,000 person-years in 2015 (Table 1, Fig. 1A). After adjusting for length of follow-up, age, and sex, there was still an increasing linear trend in the prevalence, from

20.99/100,000 person-years in 2005 to 35.45/100,000 person-years in 2015.

Sex and age

Every year, women showed a significantly higher prevalence of SLE than men. In addition, from 2005 to 2015, an increasing trend was observed in both sexes, which was more marked in women (Fig. 1A). The overall peak age of prevalence was 30 to 39 years in 2005, but the peak age was higher (40 to 49 years) in 2015. From 2005 to 2015, the peak age of SLE prevalence among men was not different in all ages > 20 years. However, the peak age of prevalence among women was similar to the overall prevalence graph (30 to 39 years of age in 2005 and 30 to 49 years of age in 2015) (Fig. 2A).

Region

In 2005, Jeju province had the highest prevalence of SLE (25.09/100,000 person-years), and Jeonnam province had the lowest prevalence of SLE (13.73/100,000 person-years). In 2015, Gyeongnam province had the lowest prevalence of SLE (27.32/100,000 person-years), and Jeju province had the highest prevalence of SLE (44.54/100,000 person-years) (Fig. 3A).

Income

In 2015, the prevalence of SLE was not significantly dif-

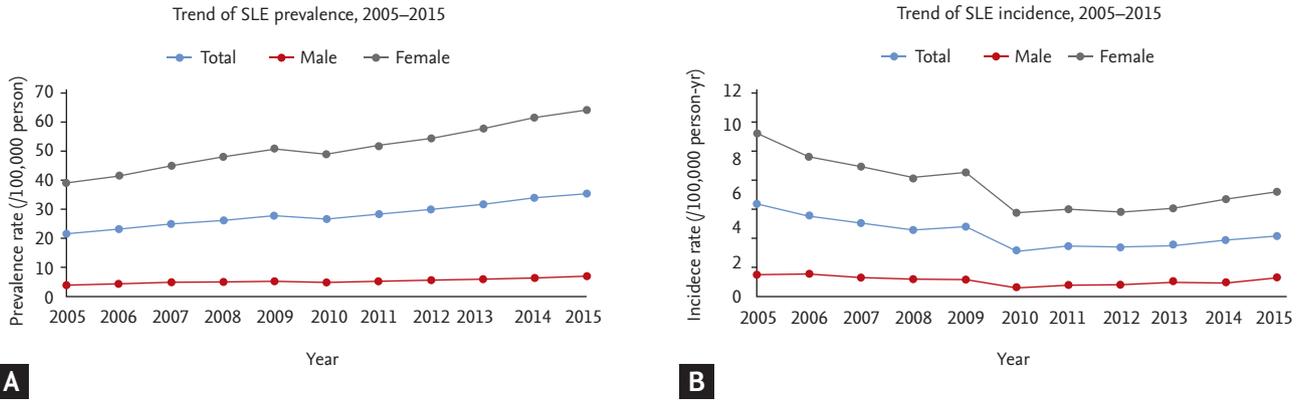


Figure 1. (A) Trend of systemic lupus erythematosus (SLE) prevalence from 2005 to 2015 and (B) trend of SLE incidence from 2005 to 2015.

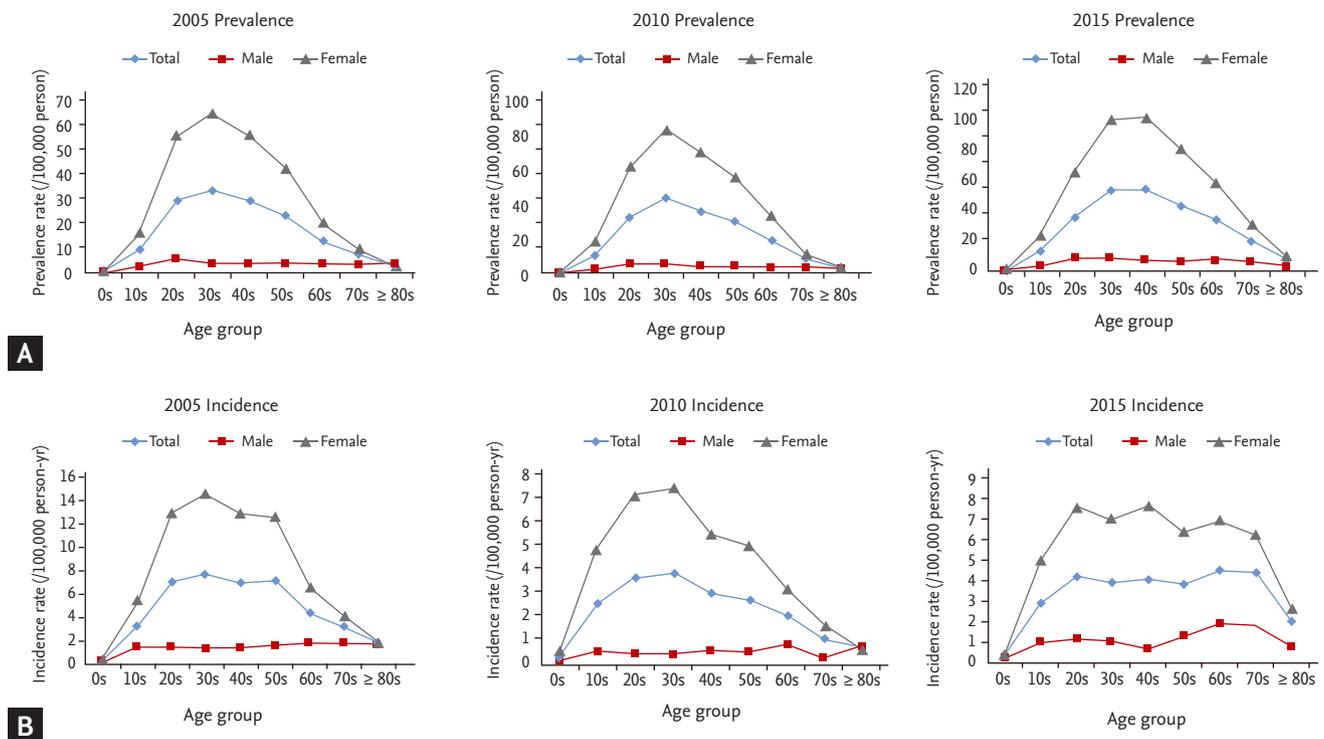


Figure 2. Peak age of (A) prevalence and (B) incidence in 2005, 2010, and 2015.

ferent among all income groups, but the medical aid group showed higher prevalence and incidence than all other income groups (Fig. 4).

Incidence

From 2005 to 2015, the number of incident cases of SLE was 1,849 patients (crude rate, 3.72; 95% CI, 2.55 to 5.63)

of which 1,617 (87.58%) (crude rate, 6.52; 95% CI, 4.62 to 10.01) were women (Table 2).

Trend in incidence by year

Fig. 1B shows the trend in incidence by year. There was an annual decrease in the incidence of SLE from 2005 to 2010, with a peak incidence in 2005 (5.42/100,000

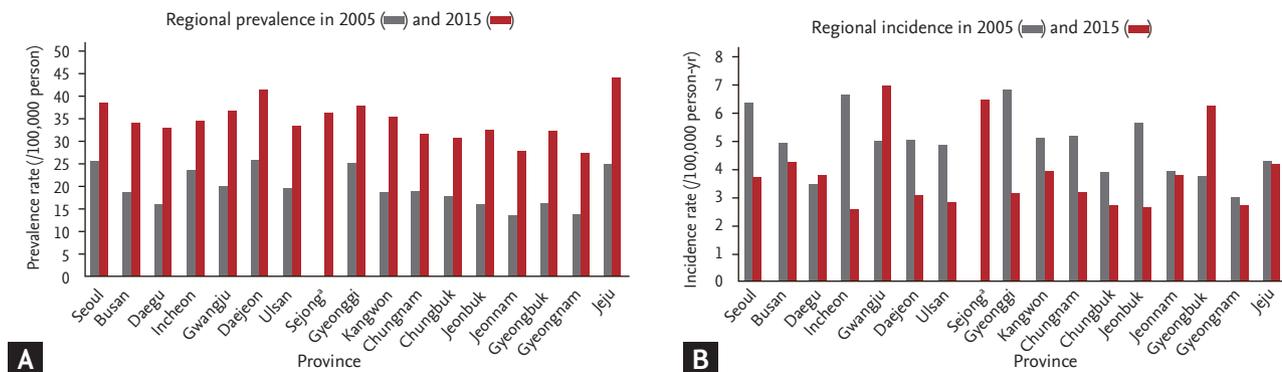


Figure 3. Regional (A) prevalence and (B) incidence in 2005 and 2015. ^aSejong city has been built since 2012.

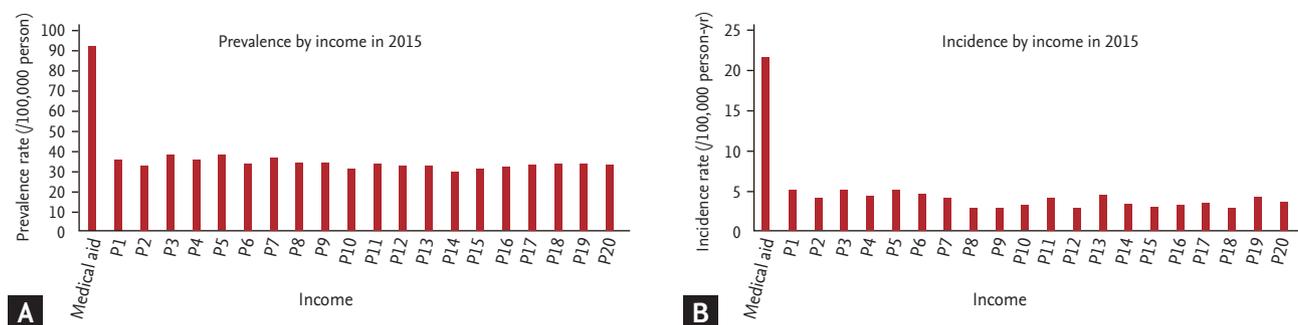


Figure 4. (A) Prevalence and (B) incidence rate by income in 2005.

Table 2. Systemic lupus erythematosus incidence by year, 2005 to 2015

Year	Total population	No. of incident cases	Total crude rate, /100,000 person-years (95% CI)	Male cases	Male crude rate, /100,000 person-years (95% CI)	Female cases	Female crude rate, /100,000 person-years (95% CI)
2005	48,020,871	2,602	5.42 (5.21–5.63)	306	1.27 (1.13–1.41)	2,296	9.62 (9.22–10.01)
2006	48,359,044	2,298	4.75 (4.56–4.95)	317	1.31 (1.16–1.45)	1,981	8.23 (7.87–8.59)
2007	48,588,945	2,106	4.33 (4.15–4.52)	265	1.09 (0.96–1.22)	1,841	7.61 (7.26–7.96)
2008	49,543,570	1,967	3.97 (3.79–4.15)	248	1.00 (0.87–1.12)	1,917	6.96 (6.63–7.29)
2009	49,865,845	2,046	4.10 (3.93–4.28)	229	0.92 (0.80–1.03)	1,817	7.31 (6.98–7.65)
2010	50,146,319	1,350	2.69 (2.55–2.84)	127	0.50 (0.42–0.59)	1,223	4.89 (4.62–5.17)
2011	50,423,558	1,460	2.90 (2.75–3.04)	172	0.68 (0.58–0.78)	1,288	5.12 (4.84–5.40)
2012	50,740,294	1,434	2.83 (2.68–2.97)	175	0.69 (0.59–0.79)	1,259	4.97 (4.70–5.25)
2013	50,989,598	1,545	3.03 (2.88–3.18)	225	0.88 (0.77–1.00)	1,320	5.19 (4.91–5.47)
2014	51,256,546	1,678	3.27 (3.12–3.43)	212	0.83 (0.71–0.94)	1,466	5.73 (5.44–6.02)
2015	51,547,020	1,854	3.60 (3.43–3.76)	276	1.07 (0.94–1.20)	1,578	6.13 (5.83–6.43)

CI, confidence interval.

Table 3. Death rate of systemic lupus erythematosus patients during follow-up

Age group ^a	Total			Male			Female		
	Number	Death	Death rate ^a	Number	Death	Death rate ^a	Number	Death	Death rate ^b
< 10	200	7	5.60	67	1	2.23	133	6	7.49
10s	2,102	59	5.02	353	10	4.81	1,749	49	5.06
20s	3,839	118	5.00	441	8	3.00	3,398	110	5.25
30s	4,756	148	5.01	457	24	8.82	4,299	124	4.63
40s	4,181	194	7.82	422	35	14.36	3,759	159	7.10
50s	2,937	211	13.33	345	43	25.61	2,592	168	11.87
60s	1,493	252	35.48	290	80	66.50	1,203	172	29.16
70s	716	211	87.55	148	66	150.94	568	145	73.50
≥ 80	116	61	225.31	29	19	274.01	87	42	208.54
Total	20,340	1,261	10.82	2,552	286	20.81	17,788	975	9.48

^aAge group at diagnosis.^bPer 1,000 person.

person-years). The lowest incidence was noted in 2010 (2.69/100,000 person-years); thereafter, the incidence increased slightly every year until 2015 (3.6/100,000 person-years). After adjusting for the length of follow-up, age, and sex, the trend was still similar (5.47/100,000 person-years in 2005, 2.69/100,000 person-years in 2010, and 3.59/100,000 person-years in 2015).

Sex and age

From 2005 to 2015, the incidence of SLE among women was 6- to 8-fold higher than that among men. In addition, women were significantly younger than men at diagnosis. At all ages, the incidence of SLE was higher among women than among men. The peak age of incidence for women (30 to 39 years) was lower than that for men (60 to 79 years) in 2005. However, in 2015, there were two peak ages of incidence (20 to 29 years and 40 to 49 years). The peak age of incidence for men was similar in the entire age group over 20 years in 2005, but there was a peak age in 2015 (60 to 79 years) (Fig. 2B).

Region

There was geographic variation in the incidence of SLE from 2005 to 2015. In 2015, the lowest incidence occurred in Incheon province (3.87/100,000 person-years) and the highest incidence occurred in Gwangju province (6.98/100,000 person-years) (Fig. 3B). However, in 2005, Gyeongnam province showed the lowest inci-

dence (3.02/100,000 person-years) and Gyeonggi province showed the highest incidence of SLE (6.82/100,000 person-years) (Fig. 3B).

Death rate

Table 3 shows the death rate of the total, male, and female patients with SLE. Men showed a higher death rate than women, and this difference was prominent in patients over the age of 30 years.

DISCUSSION

In this study, we determined the nationwide prevalence and incidence of SLE in South Korea by using the NHI claims data that covered almost all Koreans. Our main finding was that the incidence of SLE in South Korea decreased, whereas the prevalence of SLE increased in the last decade.

In our study, the average prevalence of SLE in South Korea was 28.02/100,000 person-years from 2005 to 2015. Overall, the prevalence of SLE is 30 to 50/100,000 people across Asian countries (except Taiwan [97.5/100,000 person-years]) [17-21] and 20 to 70/100,000 people in Europe [22-29]. The prevalence of SLE in Korea reported in our study was lower than that reported in both China (31.1 to 46.5/100,000 person-years) and Japan (7.0/100,000 men, 68.4/100,000 women) [30]. Similarly, our reported preva-

lence was lower than that reported in America; the prevalence of SLE is highest in America (100 to 150/100,000 people), including USA [5-9,31,32], Canada [33,34], and Puerto Rico [35], compared to all other countries worldwide [30].

The prevalence of SLE in South Korea and Taiwan was highest in the age group of 30 to 39 years. In contrast, the prevalence of SLE in the UK and Norway was highest in the age groups of 50 to 59 years and 60 to 69 years, respectively [20,24,36]. In addition, we confirmed female predominance in the prevalence of SLE, with approximately 10-fold higher prevalence in women than in men. The female-to-male ratio of patients with SLE was similar to that reported previously (~5:1 to ~10:1) [7,8,21,24,26,29,30,37]. Studies have reported that this ratio tends to increase with age and peaks during the child-bearing ages, declining slowly thereafter [20,24,29,36].

In this study, we observed regional variation in the prevalence of SLE, with the highest prevalence in Jeju province, highest incidence in Gwangju province, lowest prevalence in Gyeongnam province, and lowest incidence in Incheon province. The incidence rate of most provinces decreased, except Gwangju and Gyeongbuk provinces. Consistent with our findings, the UK has reported regional variations in SLE prevalence and incidence [30]. Such geographical variation could reflect differences in the genetic mixture of the population or variation in environmental exposure. For example, countries near the equator are more exposed to ultraviolet radiation than those located further away from the equator, which may be an environmental trigger for SLE [38]. Korea has a relatively small geographical area and a homogenous race. Although regional variation has not been previously noted in Korea, the present study suggests that there is regional variation in even small areas and within a single race. One of possibility of this regional variation may be distribution of SLE specialists or hometowns of the principle investigators of national SLE cohort studies.

The annual prevalence of SLE showed an increasing trend and the peak age of prevalence increased from 2005 to 2015, which suggests improved treatment of SLE and decreased mortality rate. This is a common phenomenon in developed countries, and similar trends were observed in the UK [30]. Since Korea is an aging society, many diseases including SLE show a similar trend

(right shift) in the peak age of prevalence.

In this study, the average incidence was 3.72/100,000 person-years from 2005 to 2015. The incidence of SLE was > 5/100,000 in the USA [6,8,9,20] and 3 to 5/100,000 person-years in Europe [22-26,26] and Asian countries [19-21]. Our result was comparable to the incidence of SLE in Hong Kong and Taiwan. In addition, the SLE incidence in the present study was approximately 6- to 8-fold higher in women than in men, which is similar to the reported difference of 5- to 8-fold in previous studies [19,20,24,26,29,36].

Similar to the case in Taiwan [20], the incidence of SLE increased continuously with age until it reached a peak, after which, it declined slowly, as did the prevalence. However, the incidence of SLE among female Norwegians exhibited a bimodal pattern, with the first and second peaks occurring at 16 to 29 years and 50 to 59 years, respectively. This pattern might be related to the use of contraceptive pills during the reproductive age or hormone therapy after menopause [36]. In other European countries, including the UK, Spain, and Denmark, the incidence of SLE increased until the age of 20 to 39 years and remained high thereafter up to the age of 50 to 69 years, although there are some differences in the age at which the incidence peaks [22,26,27]. In USA, the incidence of SLE appears to increase steadily with age [10,11,32]. In the Caucasian population, late-onset SLE is reported to be more prevalent than early onset SLE [39] and the clinical course is considered to be benign [40]. In contrast, in Asians, SLE is known to be more severe and have a higher mortality rate than in other populations [41]. Our study showed higher death rates in aged persons than in young people and in men than in women. These findings may explain the higher peak age in Korea compared to both Europe and USA and the higher incidence among in the elderly population compared to young people.

We observed an increasing trend in the incidence of SLE during the last decade. Several studies reported a significant increase in the incidence of SLE over several decades [6,29]; however, recent studies conducted over a relatively short period showed almost constant trends in the incidence of SLE [27,36]. The increasing trend reported in the present study might be explained by the increase in social awareness of the disease and wide coverage of the copayment beneficiaries program for rare

diseases. In other words, prevalence can be statistically presumed to be a decrease in the number of deaths after diagnosis (prevalence = incidence × disease duration). Therefore, we could cautiously assume SLE management as better than in the past.

This study also showed that the income level did not affect the prevalence and incidence of SLE, except in patients without income who received medical aid. Medical aid group showed that the incidence is 4 to 5 times higher than the upper income, and the prevalence is about 2.5 to 3 times higher than the upper income. As a result, it seems that Korea's excellent medical care system supports treatment of SLE better than in the past.

Despite our important findings, this study had a few limitations. First, some apparent limitations of using the NHI database stem from the lack of accurate diagnosis, because the original purpose of the data was to manage the NHI rather than use in academic evaluation. Second, the administrative claims data analyzed in this study were obtained when subjects visited healthcare institutions. Therefore, no information was available for SLE patients who did not visit a healthcare institution, which could underestimate the SLE burden. However, this may not have had a substantial impact on our findings, as the NHI claims data cover almost all Koreans and the wide coverage of the NHI system has made access to health institutions easy for the Korean population. Nevertheless, the strength of this study was that the trend of the prevalence and incidence of all Korean SLE patients was evaluated using national big database.

In summary, this study showed that the incidence of SLE in South Korea decreased in the last decade, whereas the prevalence increased. This finding of increased prevalence of SLE suggests that this disease is no longer rare and will have implications for future healthcare planning. Age, sex, and region were found to be risk factors for SLE. Our data confirmed the known predilection of SLE in women. The peak age of diagnosis is middle age, contrary to the generally held belief that lupus mainly targets young people. Furthermore, there is regional variation in the prevalence and incidence in different regions of Korea, and income is not a risk factor for SLE prevalence and incidence in Korea.

KEY MESSAGE

1. Incidence of systemic lupus erythematosus (SLE) in South Korea decreased, whereas the prevalence of SLE increased in the last decade.
2. Incidence and prevalence of SLE showed regional variation in even small areas and within a single race (South Korea).
3. The annual prevalence of SLE showed an increasing trend and the peak age of prevalence increased from 2005 to 2015, which suggests improved treatment of SLE and decreased mortality rate.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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