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LUPUS AROUND THE WORLD

Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden

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Systemic lupus erythematosus (SLE) is a disease of multifactorial etiology. Quantifying the burden of SLE across different countries can clarify the role of genetic, environmental and other causative factors in the natural history of the disease, and to understand its clinical and societal consequences. The aim of this study is to summarize data on SLE incidence and prevalence in the USA, Europe, Asia, and Australia. An extensive review of electronic resources (PubMed and MedLine) and medical journals was conducted to identify published studies on SLE incidence and prevalence over the period of 1950–early 2006. Researchers in the countries of interest provided additional information on the epidemiology of SLE. The incidence and prevalence of SLE varies considerably across the countries. The burden of the disease is considerably elevated among non-white racial groups. There is a trend towards higher incidence and prevalence of SLE in Europe and Australia compared to the USA. In Europe, the highest prevalence was reported in Sweden, Iceland and Spain. There are marked disparities in SLE rates worldwide. This variability may reflect true differences across populations, or result from methodological differences of studies. The true geographic, racial, and temporal differences in SLE incidence and prevalence may yield important clues to the etiology of disease. *Lupus* (2006) **15**, 308–318.

Key words: epidemiology; incidence; lupus; prevalence

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with variable manifestations, with etiology that has not yet been fully described but believed to be multifactorial. Epidemiological studies on SLE show marked gender, age, racial, temporal and regional variations, indicating hormonal, genetic and environmental disease triggers.

There are striking gender disparities in SLE burden, with higher disease prevalence in women compared to men. Based on clinical experiences alone, it was established that the disease generally affected females in 80–90% of the cases.[1] In a more recent review, the female-to-male ratio in the childbearing years was reported to be about 12 : 1.[2] These observations suggest that hormonal factors play important role in SLE pathogenesis.

Age distribution of SLE cases is usually broad, ranging from children as young as two years old to adults 80 years of age and older. However, in females, incidence of the disease is usually highest at 15–44 years of age, while its prevalence maximal at 45–64 years.[1] Females' highest risk for SLE during childbearing age also suggests a key role of hormones in SLE etiology.

Studies of racial tendencies showed that SLE more frequently affected non-Caucasian individuals. For instance, in the USA, SLE is more frequent in African-Americans, Hispanics and Asians than in Caucasians. SLE occurrence is three to four times higher among African-American women compared to Caucasian women.[2] This suggests an importance of genetic predisposition to SLE, although differences in exposure to environmental factors may also explain excess morbidity from SLE in non-Caucasians.[3]

Temporal increase in SLE burden has been reported by a number of researchers. For instance, only for a period from 1955 to 1974, the incidence of SLE in the USA increased from 1.0 to 7.6.[4,5] Temporal increase in SLE burden may be associated with changes in environmental factors, although increased recognition of the disease and improved diagnostic methods may cause artifactual changes in SLE frequency.

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Regional variations, and in particular, differences in SLE incidence and prevalence in similar racial groups living in different parts of the world, could further shed the light on role of genetic, environmental and other causative factors in etiology and natural history of the disease. However, the differences in SLE burden across the countries and continents are not fully described. Although some published studies included findings on various countries, the available data concerning the incidence and prevalence of SLE are limited and conflicting, partially due to differences in study methodology. In addition, the full worldwide review of the available data has not been performed. The present study was undertaken to summarize the available data on SLE incidence and prevalence in the USA, Canada, several European countries (UK, France, Germany, Italy, Spain, Sweden and Iceland), Australia, Japan, and Martinique, to give an estimation of disease burden in these countries.

Methods

To identify relevant studies, the computerized bibliographic database of the National Library of Medicine (Medline 1966 to January 2006) was searched using Ovid and PubMed. The references from all retrieved articles and selected review papers and books were also reviewed to ensure that all potentially eligible articles were identified for evaluation. From the articles identified, we selected all those that reported data on incidence and/or prevalence of systemic lupus in the countries of interest, with or without stratification by race and gender.

From each article we abstracted information on author(s), journal, year of publication, country/geographical area studied, case source(s) (eg, hospital records, physians interviews, or population surveys), timeframe over which incidence and/or prevalence of SLE were assessed, actual number of cases identified, and incidence and/or prevalence estimates reported. It was also recorded whether capture–recapture technique was used for more accurate estimation of incidence and prevalence by formally calculating ascertainment-corrected rates.[6]

We reported incidence as a number of new cases per 100 000 of the population per year and prevalence as a cross-sectional estimate of the number of cases per 100 000 of the population per year, as per figures presented in the Results. We summarized incidence and/or prevalence by race and/or gender whenever the data were available. If only gender-specific estimates were provided, the overall number was calculated as an average between male and female estimates, adjusting for a male to female ratio in a population of interest assessed from country-specific census data. We also recorded whether the estimates were adjusted by age.

SLE researchers in the countries of interest were asked to provide any additional available reports on epidemiology of SLE, or to confirm unavailability of such information.

Results were arrayed by outcome (incidence and prevalence), countries of interest and date of publication. The results across studies for a same outcome, country, and racial group were pooled to report a median estimate and a range (presented in the figures). No statistical testing of differences in SLE burden across the countries has been performed.

We identified approximately 60 studies that mentioned incidence and/or prevalence of systemic lupus erythematosus in the countries of interest. The present review is focused on 32 studies reported quantitative assessment of SLE burden in adults aged 16 years or older; other reports were excluded either due to focus on children aged <16 years, or due to lack of clear definition of the target population or methods used for case identification. Of the 32 selected studies, eight reported the information on the USA, one on Canada, 16 on Europe, three on Australia, three on Japan and one on Martinique.

Results

SLE incidence

USA and Canada. The data for the USA and Canada are summarized in Table 1. Siegel *et al.*[1,4,7] conducted studies in New York and Alabama states. Over the period of 1956–1965 in New York, overall age-adjusted incidence for both genders was reported to be 1.4 among whites, 4.6 among black and 2.3 among Puerto Rican. The incidence in Jefferson County, AL, was at least twice as low as those reported in New York, NY: 0.8 in whites and 1.7 in black.[4] Michet *et al.*[8] found an overall age-adjusted incidence of 1.8, for all races combined, in the Rochester area, MN; no race-specific estimates were reported in this study. A survey conducted by Hochberg *et al.*[9] in Baltimore, MD, showed the age-adjusted incidence of 2.2 and 7.2 in whites and black, respectively. McCarty *et al.*[10] assessed SLE incidence in the Allegheny County, Pennsylvania[6] using capture-recapture technique, and reported the crude incidence of 2.0 in whites and 5.3 in black. The most recent study of Naleway *et al.*[11] showed the age-adjusted incidence of 5.1, for all races combined, in rural Wisconsin area.

The data on incidence of SLE in adult population of Canada are scarce. In a population-based study of Peschken *et al.*,[12] crude annual incidence rates ranged

Table 1 Studies on incidence and prevalence of SLE in the USA and Canada

Author	*Country/ geographical area*	*Race*	*Period*	*Number of patients**	*Incidence*			*Prevalence*			*Age adjustment*	*Capture–recapture technique*
					Females	*Males*	*Overall*	*Females*	*Males*	*Overall*		
Siegel *et al.* (1962)	USA, New York, NY	White	1951–1959	42[I]	1.2	0.14	0.7[a]	ND	ND	ND	Yes	No
		Black		13[I]	3.9	0.8	2.4[a]	ND	ND	ND		
Siegel *et al.* (1973)	USA, New York, NY	White	1956–1965	55	2.5	0.3	1.4[a]	16.8	2.9	9.9[a]	Yes	No
		Black		16	7.9	1.1	4.6[a]	55.8	3.3	29.6[a]		
		Puerto Rican		25	4.1	0.3	2.3[a]	33.6	2.3	18.0[a]		
Siegel *et al.* (1970)	USA, Jefferson County, AL	White	1956–1965	18	1.1	0.4	0.8[a]	7.7	1.8	4.8[a]	Yes	No
		Black		19	3.0	0.3	1.7[a]	18.5	0	9.3[a]		
Michet *et al.* (1985)	USA, Rochester, MN	All races	1950–1979	25[I]	2.5	0.9	1.8	53.8	19.0	40.0	Yes	No
Hochberg *et al.* (1985)	USA, Baltimore, MD	White	1970–1977	79[I]	3.9	0.4	2.2[a]	ND	ND	ND	Yes	No
		Black		223[I]	11.4	2.5	7.2[a]					
McCarty *et al.* (1995)	USA, Pittsburgh, PA	White	1985–1990	141[I]	3.5	0.4	2.0	ND	ND	ND	No[c]	Yes
		Black		48[I]	9.2	0.7	5.3					
Ward *et al.* (2004)	USA, Nationwide	All races	1988–1994	40	ND	ND	ND	100.0	3.4	53.6	No	No
Naleway *et al.* (2005)	USA, rural Wisconsin area	All races	1991–2001	117	8.2	1.9	5.1	131.5	24.8	78.5	Yes	No
Peschken *et al.* (2000)	Canada, Province of Manitoba	North American Indians	1980–1996	49	ND	ND	2.0–7.4[b]	ND	ND	42.3	Yes	No
		White		208	ND	ND	0.9–2.3[b]	ND	ND	20.6		

*Prevalent cases if not otherwise indicated; "I" superscript = incident estimate.

[a]Calculated as an average between male and female estimates, adjusting for a male to female ratio in overall population.

[b]Reported estimates are not age-adjusted.

[c]Only crude overall estimates reported (although age-specific rates were also estimated).

2.0–7.4 for North American Indians and 0.9–2.3 for the remaining population between 1980 and 1996 (Table 1).

European countries. The incidence. of SLE in France, Iceland, Spain, Sweden and the UK are summarized in Table 2.

In France, in 1982, Amor *et al.*[13] conducted a nationwide survey among rheumatologists belonging to the French Rheumatology Society and reported the overall crude incidence of 1.0 per 1 000 000. Based on the recent National Public Insurance survey, Piette *et al.* reported the overall nationwide incidence of 5.0.[14]

In Iceland, a nationwide retrospective study by Gudmundsson *et al.*[15] found that the overall age-adjusted incidence was 3.3.

In Spain, Lopez *et al.*[16] conducted a hospital-based study in the Caucasian population of from the North of the country and reported the overall crude incidence of 2.2.

In Sweden, Nived *et al.*[17] conducted a hospital-based study in Southern part of the country during 1981 and 1982 and reported the overall incidence of 4.8. Jonsson *et al.*[18] conducted a study within the same geographical area during 1981–1986, and found the overall incidence of 4.0. Stahl-Hallengren *et al.*[19] studied incidence of SLE in the same region during 1987–1991, and reported overall age-adjusted incidence of 4.8 and 4.5 in 1986 and 1991, respectively.

In the UK, a hospital- and clinic-based study of Hopkinson *et al.*[20] showed that the overall age-adjusted incidence in Nottingham was 4.0. Using population estimates from 1991 National Census, they later reported race-specific incidence rates of 31.9 in Afro-Caribbean, 4.1 in Asian and 3.4 in Caucasian.[21] Johnson *et al.*[22] conducted a study in Birmingham, UK, and reported the age-adjusted incidence of 11.9 in Afro-Caribbean, 15.2 in Asian, and 2.5 in Caucasian. The most recent nationwide study of Nightingale *et al.*[23] based on the population of the General Practice Research Database (GPRD) showed the overall crude incidence of 3.0.

Other countries. The summary of incidence data in some selected countries is given in Table 2.

In Australia, a hospital-based study of Australian aborigines[24] showed the overall crude incidence of 11.0. In Japan, Iseki *et al.*[25] conducted a hospital- and clinic-based study on the population of Okinawa, and reported that over the period from 1972 to 1991, the overall crude incidence increased from 0.9 to 2.9. Deligny *et al.*[26] conducted an extensive population-based study in Martinique and reported the overall incidence of 4.7.

SLE incidence in the countries of interest is summarized in Figure 1. The figure reflects remarkably higher SLE incidence among non-whites compared to whites. The lowest overall incidence estimates were reported in Iceland and Japan, and highest in the USA and France.

SLE prevalence

USA and Canada. The prevalence data for the USA are summarized in Table 1. In New York, NY, Siegel *et al.*[1,4,7] reported the age-adjusted prevalence of 9.9 in whites, 29.6 in black, and 18.0 in Puerto Rican.[1] In Jefferson County, Alabama, they found the prevalence at least two-fold lower that in the New York area: of 4.8 in whites and 9.3 in black.[4] Michet *et al.*[8] reported the overall age-adjusted prevalence of 40.0 in the Rochester area, MN. In the nationwide study of Ward *et al.*,[27] the overall crude prevalence was 53.6. Naleway *et al.*[11] recently found that over 1991–2001, the overall age-adjusted prevalence in rural Wisconsin area was 78.5.

In Canada, Peschken *et al.*[12] showed a two-fold higher prevalence of SLE in North American Indians (42.3) compared to non-Indians (20.6).

European countries. The prevalence of SLE in Finland, France, Germany, Iceland, Italy, Northern Ireland, Spain, Sweden and the UK are summarized in Table 2.

In Finland, Helve *et al.*[28] conducted a nationwide study based on hospital discharge records and cause of death statistics of 1976–1978, and reported the overall crude prevalence of 28.0. In France, Piette *et al.*[14] reported the nationwide overall prevalence of 40.0 based on the National Public Insurance survey. In Germany, Zink *et al.*[29] described the case mix of the German rheumatologic database in 1998. They found 1211 prevalent cases of SLE, but have not reported the formal prevalence estimate. In Iceland, a nationwide retrospective study by Gudmundsson *et al.*[15] showed the overall age-adjusted prevalence of 35.9. In Italy, Benucci *et al.*[30] recently studied prevalence of SLE in the population of Scandicci-Le Signe area of Florence using the Lupus Screening Questionnaire (LQS). They reported the overall crude prevalence of 71.0. In Northern Ireland,[6] Gourley *et al.*[31] found that the overall crude prevalence of SLE was 25.4. In Spain, the EPISER nationwide survey[32] conducted by rheumatologists on randomly selected residents showed the overall prevalence of SLE of 91.0. In the hospital-based study of Lopez *et al.*[16] conducted in the Caucasian population of from the north of the country, the overall crude prevalence was 34.1. In Sweden, in the hospital-based study of Nived *et al.*, the overall prevalence in the Southern region of the country was found to

Table 2 Studies on incidence and prevalence of SLE in other countries

Author	Country/ geographical area		Case source(s)	Period	Number of patients*	Incidence			Prevalence			Age adjustment	Capture–recapture technique
						Females	Males	Overall	Females	Males	Overall		
Helve *et al.* (1985)	Finland	All races	Hospital records and cause of death registers	1976–1978	1427	ND	ND	ND	ND	ND	28.0	No	No
Amor *et al.* (1983)	France	All races	Physicians survey	1982	64	ND	ND	1 per 1 000 000	ND	ND	ND	No	No
Piette *et al.* (2004)	France	All races	National public insurance survey	2004	NS	ND	ND	5.0	ND	ND	40.0	NS	No
Zink (2001)	Germany	All races	Clinical, hospital records	1993–1998	1211	ND	ND	ND	ND	ND	1211 cases	NS	No
Gudmundsson *et al.* (1990)	Iceland	All races	Clinical, hospital records; physicians survey	1975–1984	76	5.8	0.8	3.3	62.0	7.2	35.9	Yes	No
Benucci *et al.* (2003)	Italy, Florence	All races	Clinical records, patients evaluation	2002	23	ND	ND	ND	ND	ND	71.0	No	No
Gourley *et al.* (1997)	Northern Ireland	All races	Clinical records; physians, patients survey; patients	1992–1993	415	ND	ND	ND	46.5	4.3	25.4	No[b]	Yes
EPISER study (2001)	Spain including islands	All races	Population survey, patients evaluation	1998–1999	9	ND	ND	ND	130.0	52.0	91.0	NS	No
Lopez *et al.* (2003)	Spain, North	White	Clinical, hospital records	1992–2002	367	3.6	0.5	2.2	57.9	8.3	34.1	No	No
Nived *et al.* (1985)	Sweden, South	All races	Clinical, hospital records	1981–1982	65	7.6	2.0	4.8	64.8	11.7	38.9	NS	No
Jonsson *et al.* (1990)	Sweden, South	All races	Clinical, hospital records; physicians survey	1981–1986	39[I]	5.4	1.0	4.0	ND	ND	ND	NS	No

continued

Table 2 *continued*

Stahl-Hallengren *et al.* (2000)	Sweden, South	All races	Clinical, hospital records, patients evaluation	1986	121	ND	ND	4.8	ND	ND	42.0	Yes	No
				1991	379	ND	ND	4.5	ND	ND	68.0		
Hopkinson *et al.* (1993)	UK, Nottingham	All races	Clinical, hospital records; physicians survey	1989–1990	147	6.5	1.5	4.0	45.4	3.7	24.6	Yes	No
Hopkinson *et al.* (1994)	UK, Nottingham	Afro-Caribbean	Clinical, hospital records; physicians survey; population estimates: National Census 1991	1989–1990	21	ND	ND	31.9	ND	ND	207.0	Yes	No
		Asian			7	ND	ND	4.1	ND	ND	48.8		
		Chinese			2	ND	ND	ND	ND	ND	92.9		
		White			117	ND	ND	3.4	ND	ND	20.3		
Johnson *et al.* (1995)	UK, Birmingham	Afro-Caribbean	Clinical, hospital records; physicians survey	1991	50	22.8	0.5	11.9	197.2	6.4	111.8	Yes	Yes
		Asian			36	29.2		15.2	96.5	4.3	46.7		
		White			155	4.5		2.5	36.3	3.4	20.7		
		All races			241	6.8[i]	2[a]	3.8[i]	49.6[a]	3.6[a]	27.7[a]		
Nightingale *et al.* (2006)	UK, Nationwide	All races	Clinical, hospital, prescription records	1992–1998	390[l]	5.3	0.7	3.0	ND	ND	ND	No[b]	No
Anstey *et al.* (1993)	Australia, Darwin, Katherine and East Arnhem	Aborigines	Clinical, hospital records; physicians survey	1993	22	ND	ND	11.0	100.0	5.2	52.6	No	No
Grennan *et al.* (1995)	Australia, Northern Queensland	Aborigines	Clinical, hospital records; physicians survey	1993–1994	20	ND	ND	ND	ND	ND	89.3	No	No
	Australia, Sydney	Aborigines			3	ND	ND	ND	ND	ND	13.4		
Segasothy *et al.* (2001)	Australia, Central	Aborigines	Hospital records; physicians survey	July–Dec 1999	14	ND	ND	ND	122.5	24.5	73.5	No	No
		White			6	ND	ND	ND	32.2	6.4	19.3		
Fukase *et al.* (1980)	Japan, except Okinawa	All races	Clinical, hospital survey	1972	1177	ND	ND	ND	9.1	0.8	5.0	No	No
Nakae *et al.* (1984)	Japan	All races	Clinical, hospital survey	1984	22856	ND	ND	ND	36.8	3.6	19.1	No	NS

continued

Table 2 *continued*

Author	Country/ geographical area	Race	Case source(s)	Period	Number of patients*	Incidence			Prevalence			Age adjustment	Capture–recapture technique
						Females	Males	Overall	Females	Males	Overall		
Iseki *et al.* (1994)	Japan, Okinawa	All races	Clinical, hospital records	1972	566	1.6	0.4	0.9	6.6	0.8	3.7	No	No
				1991		4.7	0.8	2.9	68.4	7.0	37.7		
Deligny *et al.* (2002)	Martinique	All races	Hospital records, physicians survey, death registry	1990–1999	286	8.5	0.7	4.7	115	9.2	64.2	NS	No

NS = not specified.
*Prevalent cases if not otherwise indicated; I superscript = incident estimate.
[a]Estimates reported are not age-adjusted.
[b]Only crude overall incidence estimates were reported (although age-specific incidence rates were also reported).

be 38.9. In the study of Stahl-Hallengren *et al.*[19] conducted within the same geographical area, the overall age-adjusted prevalence was 42.0 in 1986, and 68.0 in 1991.

In the UK, Hopkinson *et al.*[20] reported the overall age-adjusted prevalence of 24.6 in the Nottingham area. Racial breakdown based on 1991 National Census further showed the prevalence of 207.0 in Afro-Caribbean, 48.8 in Asian, 92.9 in Chinese and 20.3 in Caucasian, respectively.[21] Johnson *et al.* reported the age-adjusted prevalence of 111.8, 46.7 and 20.7 in Afro-Caribbean, Asian and Caucasian, respectively, in the population of Birmingham, UK.[22]

Other countries. The summary of prevalence data in some other countries of the world are presented in Table 2. In the study of Australian aborigines[24] in the defined geographical area of Darwin, Katherine and East Arnhem, the overall crude prevalence reported to be 52.6. Grennan *et al.*[33] reported the crude SLE prevalence of 89.3 in Australian Aborigines located in Northern Queensland in the Cape York Peninsula and 13.4 in metropolitan Sydney. Segasothy *et al.*[34] compared the prevalence of SLE among Aborigines and Caucasians in Central Australia, and reported the crude prevalence of 73.5 in Aborigines and 19.3 in Caucasians.

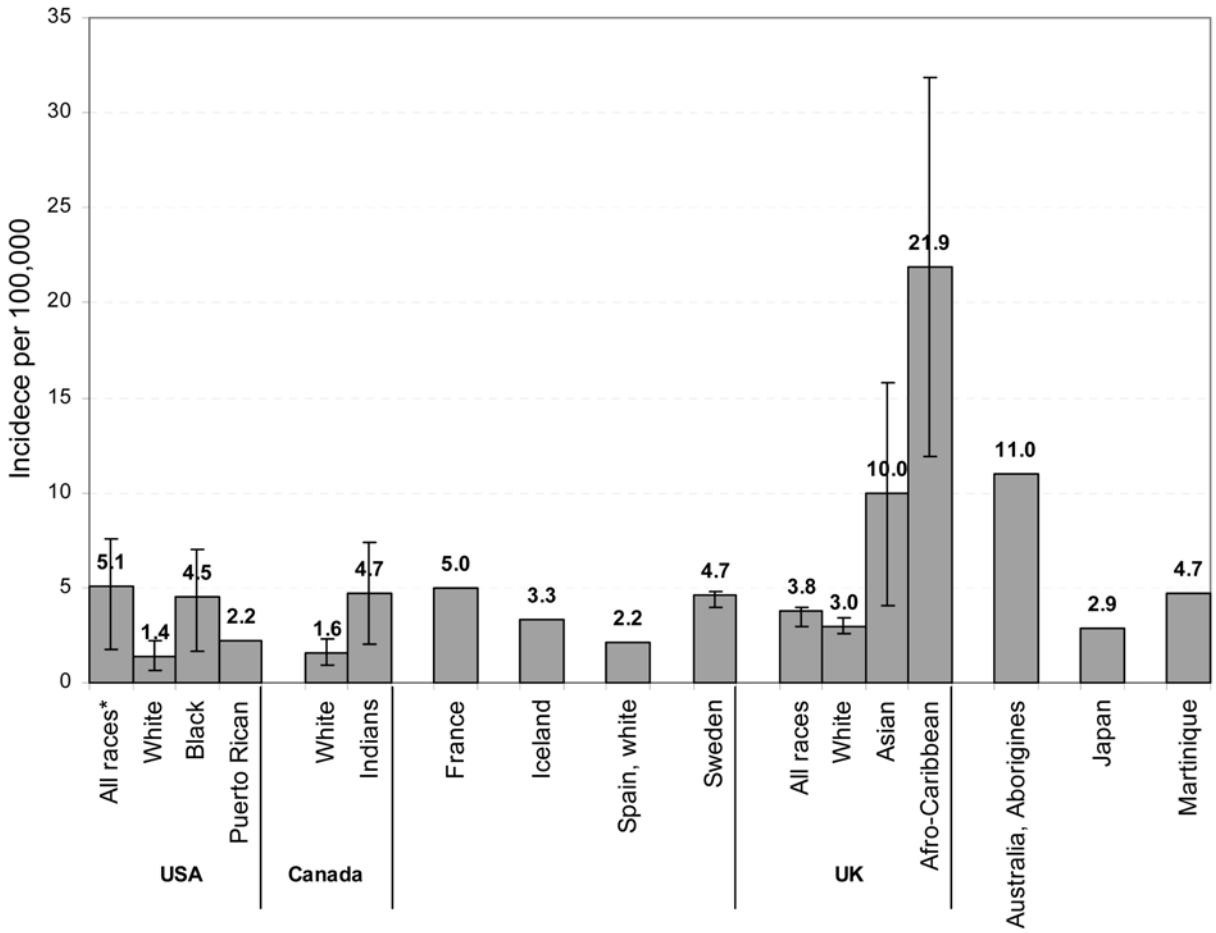
In Japan, an early nationwide study by Fukase *et al.*,[35] showed the overall crude prevalence of 5.0. The authors mention that only 50% of patients diagnosed at hospitals met preliminary ARA criteria (1971). Nakae *et al.*[36] conducted a nationwide epidemiological survey and found that the overall crude prevalence was 19.1. However, the researchers note that the response rate from objected medical institutions was only 43.3%. The hospital- and clinic-based study in Okinawa, Iseki *et al.*[25] reported an increase in prevalence from 1972 to 1991, from approximately 3.7 to 37.7.

In Martinique, Deligny *et al.*[26] estimated the overall prevalence of 64.2.

The summary of SLE prevalence across the countries is presented in Figure 2. It shows remarkably higher SLE prevalence in non-white racial groups compared to whites. The lowest overall prevalence was found in Ireland, the UK and Finland, and highest in Italy, Spain and Martinique.

Discussion

The report represents a review of the published data in incidence and prevalence of SLE in the USA, Canada, Western Europe, Australia, Japan and Martinique; it provides the most recent summary of SLE burden



* Total estimates are higher than race-specific since former are estimated by more recent studies.

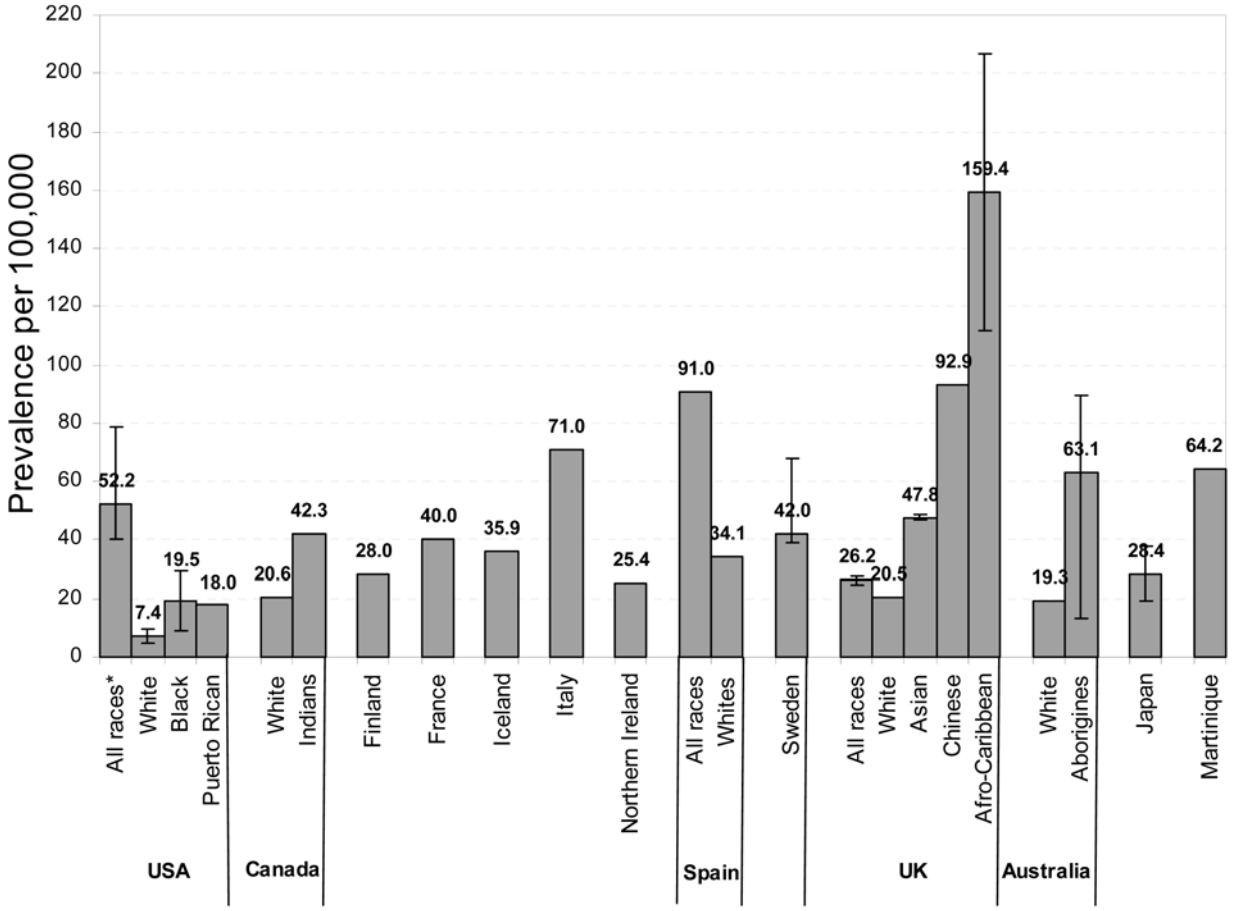
Note: Median value presented if more than one source is available. The error bars show a range of values reported in different studies and/or in different study years within a single study.

Figure 1 SLE incidence in the countries of interest.

worldwide. We found remarkable disparities in SLE burden across the countries. Historically, the rates of SLE in Europe have been lower than in the USA,[22] but recent data from the USA[10,27] makes this tendency less obvious. The lowest overall incidence was found in Iceland and Japan, and highest in the USA and France. The overall prevalence was the lowest in Northern Ireland, the UK and Finland, and the highest in Italy, Spain and Martinique. The burden of SLE was consistently increased in non-white population of the USA, Europe, Canada and Australia. The gender differences are well recognized[1–3,37] and the present review did not intend to emphasize them.

The findings summarized in the present review provide no sufficient evidence to conclude that SLE is less common in some countries compared to others. The variability in incidence and prevalence estimates can be attributable to true disparities across the countries or result from the methodological differences among the studies.

Racial composition and its stability (the level of immigration/emigration) in a population have been recognized as one of the important determinants of true disparities in SLE burden. Higher disease prevalence was reported in non-white racial groups.[1,4,9,10,24,34] Unstable racial composition of a population due to transitory nature of certain groups (eg, European population in Australia) makes it challenging to accurately assess SLE burden. On the contrary, countries with homogeneic and racially stable population (eg, Iceland) are considered well suited for epidemiological studies.



* Total estimates are higher than race-specific since former are estimated by more recent studies.

Note: Median value presented if more than one source is available. The error bars show a range of values reported in different studies and/or in different study years within a single study.

Figure 2 SLE prevalence in the countries of interest.

Environmental triggers, such as infections and ultraviolet light, constitute another important group of factors determining the burden of SLE. Infectious agents may initiate SLE onset by disturbing immunoregulation, causing damage to tissue, which leads to the release of antigens.[2] High prevalence of major bacterial infections in certain regions of Australia is thought to be involved in SLE pathogenesis in local Aborigines populations.[33,34] UV radiation may induce keratinocyte apoptosis with the release of nuclear antigens that may drive an autoimmune response.[38,39] Varying levels of sunlight exposure in different parts of the world may therefore contribute to disparities in SLE burden across the countries, partially explaining elevated prevalence of the disease in the north of Australia and in the south of Europe.

Estrogens account for the higher immune reactivity in females and can also act as a trigger of autoimmune diseases, such as SLE.[2,40] Varying physiological, therapeutic and pathological conditions (eg, menstrual cycle, chronic stress, inflammatory cytokines, use of corticosteroids, oral contraceptives and steroid hormonal replacement) may change serum estrogen level, therefore contributing to true variations in exposure to SLE in different population groups.[41]

Country-specific health care issues can also contribute to true discrepancies in SLE burden. These include accessibility and affordability of health care, determined by health care system of a particular

country and dependent on a geographical area (urban versus rural). Availability of sensitive diagnostic tests influences the number of identified SLE patients, but has a two-fold effect, facilitating detection of milder cases and increasing the number of false positive diagnoses. Physician knowledge and recognition of disease varying over time and across countries and regions can also explain temporal and geographical dissimilarities in the number of diagnosed SLE cases. Finally, better health care is associated with lower mortality rates, explaining discrepancies in SLE prevalence across the countries.[22]

Methodological differences among studies causing additional artifactual variability in SLE burden across the countries are mostly related either to disparities in case identification and data sources or to analytical issues. The former include differences in diagnostic criteria chosen by authors, with American College of Rheumatology (ACR) criteria used most widely, and other options available, such as Lupus Screening Questionnaire (LQS). Different sources of cases (eg, hospital records review, physicians surveys, major population surveys, use of population-based databases and registries) have different strengths and weaknesses, and may contribute to variability in study results. Hospital records interpretation may vary depending on the diagnostic criteria applied, and patients treated without hospitalization are not estimated. Physicians surveys rely on physicians' recall which introduces bias. Major population surveys allow avoiding many potential biases; however, such studies may not be efficient for the evaluation of the rare disease, such as SLE. Population-based databases are unique source of information on large well-defined populations, but their use limits the generalizability of study results and the ability to compare results from analyses of different databases. Analytical issues include adjustment for major demographic characteristics (eg, age) and application of capture-recapture methods whenever multiple case ascertainment sources are used.[6]

Therefore, the variability in incidence and prevalence across the countries can be attributed to a wide variety of true differences among geographical regions and populations, as well as to variations in study designs, including (but not limited to) methodology of case identification and analytical issues.

Conclusion

There are marked disparities in SLE incidence and prevalence worldwide. However, rigorously conducted epidemiologic studies with similar study methodologies and taking into account all potential sources of variation are needed to permit comparisons of SLE burden across the countries.

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