The global burden of SLE: prevalence, health disparities and socioeconomic impact

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Abstract | Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that can potentially lead to serious organ complications and even death. Its global burden — in terms of incidence and prevalence, differential impact on populations, economic costs and capacity to compromise health-related quality of life — remains incompletely understood. The reported worldwide incidence and prevalence of SLE vary considerably; this variation is probably attributable to a variety of factors, including ethnic and geographic differences in the populations being studied, the definition of SLE applied, and the methods of case identification. Despite the heterogeneous nature of the disease, distinct patterns of disease presentation, severity and course can often be related to differences in ethnicity, income level, education, health insurance status, level of social support and medication compliance, as well as environmental and occupational factors. Given the potential for the disease to cause such severe and widespread organ damage, not only are the attendant direct costs high, but these costs are sometimes exceeded by indirect costs owing to loss of economic productivity. As an intangible cost, patients with SLE are, not surprisingly, likely to endure considerably reduced health-related quality of life.

Systemic lupus erythematosus (SLE) is a systemic autoimmune rheumatic disease with a complex pathogenesis. SLE can potentially cause substantial physical and functional disability and its manifestations are tremendously diverse, ranging from relatively mild cutaneous and articular involvement through to debilitating fatigue, significant cognitive impairment, end-stage renal disease and catastrophic thrombosis[1]; hence, it is often called 'the disease of a thousand faces'. SLE is much more common in women than men, and some women with SLE have difficulty conceiving; many women with SLE — particularly those whose disease is active at the time of conception — also experience numerous complications, both maternal and fetal, during pregnancy[2]. Both men and women with SLE have a higher risk of developing cardiovascular and cerebrovascular disease and malignancy than individuals without SLE, as a consequence of both the disease and its treatments[3,4]. The treatment options for patients with SLE remain limited compared to those for other rheumatic diseases, such as rheumatoid arthritis, and existing therapies are ineffective or poorly tolerated in a sizeable proportion of patients. Unfortunately, almost all large-scale randomized trials of biologic therapies (with only one exception, belimumab) have failed to demonstrate efficacy in patients with SLE[5]. Consequently, progress in the treatment of SLE has been modest, with belimumab being the only new therapy approved in the last 50 years[5].

As SLE is a relatively rare and complex disease, its global burden — in terms of incidence and prevalence, differential impact on populations, economic costs and capacity to compromise health-related quality of life — remains underappreciated and poorly understood. In this article, we first provide an overview of the worldwide incidence and prevalence of SLE, and discuss the factors that contribute to the considerable variation seen in these parameters. We then outline the factors known to contribute to health disparities relating to disease prevalence, development, manifestations and severity of SLE. Finally, we will examine the socioeconomic impact of SLE by detailing estimates and disease-related determinants of direct and indirect costs, and discussing the intangible costs reflected by impairments in health-related quality of life (HRQoL). By enhancing our understanding of the global burden of SLE and its determinants, this Review aims to inform future efforts to reduce health disparities and improve patient outcomes while optimizing resource allocation and decreasing associated health care costs.

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Key points

- Worldwide incidence and prevalence estimates of systemic lupus erythematosus (SLE) vary substantially and are influenced by ethnic and geographic differences, study design and environmental exposures
- Disease severity is greater in African American populations than in white populations
- Poverty, low educational attainment, lack of health insurance, poor social support and poor treatment compliance are all associated with unfavourable disease outcomes, both independent of, and in combination with, ethnic influences
- The treatment of SLE incurs high direct costs, and sometimes even higher indirect costs; costs are influenced by disease severity and organ manifestations
- Health-related quality of life is greatly compromised in patients with SLE

The incidence and prevalence of SLE

Studies in the USA conducted between 1950 and 1992 reported an increasing incidence of SLE[6]. This increase was probably partially attributable to enhanced diagnostic capabilities — through technological advances in immunologic testing, increased awareness of SLE, the development of standardized classification criteria and greater access to specialty care — which enabled the identification of patients with mild SLE, in whom the diagnosis might previously have been missed[7]. Since these studies, some countries, such as Denmark and Norway, have reported a stable disease incidence[8–10], whereas others, such as the UK and Greece, continue to report an increase[7,11–14].

Reported values for the incidence and prevalence of SLE vary considerably worldwide (BOX 1, FIGS 1–3, TABLE 1, Supplementary information S1 (table)), with the overall incidence ranging from 0.3 per 100,000 per year in the Ukraine[15] to 31.5 per 100,000 per year among Afro-Caribbean people living in the UK[14], and the overall prevalence ranging from 3.2 per 100,000 in India[16] to 517.5 per 100,000 among Afro-Caribbean people living in the UK[14] (Supplementary information S1 (table)). Such variation might be caused by many factors involved in case identification and data collection, including whether the population studied was hospital-based or community-based, resided in a rural or an urban community, the structure of health-care delivery, the definition of SLE applied, the observation interval, and the method of case ascertainment.

The most reliable incidence and prevalence data are likely to derive from studies in countries that have public health-care systems, in which patient care is centrally managed, national health insurance data are maintained, disease registries include only patients diagnosed by a specialist as having SLE, reliable census figures are available, and estimates of incidence and prevalence are determined over many years. Taiwan is one example of a country that fulfils these criteria. Nonetheless, the overall incidence of SLE varies from 4.9 to 9.9 per 100,000 per year and its overall prevalence from 37.0 to 97.5 per 100,000 in Taiwan[17–20] (Supplementary information S1 (table)). Similar types of datum are available for other regions, but over shorter time periods[21], including estimates from South Korea[22,23], where the incidence of SLE ranges from 2.5 to 2.8 per 100,000 per year and its prevalence ranges from 20.6 to 26.5 per 100,000 (Supplementary information S1 (table)).

Two unique and particularly comprehensive strategies for case ascertainment in SLE are capture-recapture methods and the COPCORD (Community Oriented Program for Control of Rheumatic Diseases) approach. Capture-recapture methods use models to evaluate the completeness of case ascertainment by estimating the number of cases that are missed when multiple data sources are used for data analysis[8,24–26]. Two US studies using this methodology derived almost identical incidence and prevalence values: the Michigan Lupus Epidemiology and Surveillance Program[24] reported an incidence of 5.5 per 100,000 per year and a prevalence of 72.8 per 100,000 and the Georgia Lupus Registry[25] reported an incidence of 5.6 per 100,000 per year and a prevalence of 74.4 per 100,000. (Supplementary information S1 (table)) Other studies using these approaches provide incidence estimates of 1.0 per 100,000 per year in Denmark[8] and prevalence estimates of 21.9–28.3 per 100,000 in Denmark[8] and 25.4 per 100,000 in Ireland[26] (Supplementary information S1 (table)).

COPCORD was devised as a low-cost method of determining the prevalence of various rheumatic diseases, including SLE[27–34]. This approach comprises three phases (screening, pre-evaluation and evaluation by a rheumatologist) utilizing local staff or health-care workers, and requires minimal use of investigations to determine diagnoses, which makes it a particularly appropriate tool for use in developing nations. Estimates of the prevalence of SLE derived using the COPCORD approach range from 0 per 100,000 among Turkish populations in Iran[30], to 190.0 per 100,000 among white populations in Iran[29], with estimates varying depending on the ethnic group and region studied. The number of studies using this approach continues to grow[27–34].

Unfortunately, complete information, such as that obtained from comprehensive public health care systems with associated national registries, capture-recapture methods or the COPCORD approach, is not available for most nations, and other strategies for obtaining data (which probably provide less robust estimates) are applied. These strategies include identification of cases through hospital or community clinics in urban or rural areas[6,11,15,35–51], screening based on patient questionnaire responses or primary-care physician evaluations[16,52–54], analysis of SLE trial cohort or registry population data[8,12,55–58], review of private insurance or administrative databases (which might not include populations representative of the entire country[13,14,19,23,59–62]), or some combination of all of these approaches[9,10,24,26,63,64]. Community-based studies are likely to provide more accurate estimates than hospital-based ones, as the latter presumably include only patients with severe forms of SLE. Rural studies might also underestimate the incidence and prevalence of SLE, given the decreased access to specialist care in these areas. One study from the USA illustrates how prevalence estimates can vary depending on the definition of SLE used, with patient self-report of SLE diagnosis exceeding physician-confirmed diagnosis by threefold (372.0 versus 124.0 per 100,000)[46]. Methods that rely on data collected over a short time period (that is, weeks to months rather than

Box 1 | **SLE incidence and prevalence**

Incidence
The number of new cases of a disease that develop during a defined time period

Prevalence
The percentage of a population that is affected by a disease at any given time

Methods used to estimate incidence and prevalence

- Review of public and private insurance or administrative claims
- Review of hospital or clinic medical records
- Patient screening surveys and questionnaires with physician confirmation
- Analysis of data on patients included in trial cohorts or disease registries

Estimates of SLE incidence and prevalence

- Incidence: 0.3–31.5 cases per 100,000 individuals per year
- Prevalence: 3.2–517.5 cases per 100,000 individuals

SLE, systemic lupus erythematosus.

years) will probably not generate meaningful estimates of incidence and prevalence, and studies that rely solely on medical claims data or physician billing codes, without having a medical chart review performed by a rheumatologist, could either underestimate or overestimate SLE incidence and prevalence. A US study based on Medicaid claims data[65] reported a prevalence of 300.0 per 100,000, which is likely to represent an overestimate, as cases were not validated, and the sample was not representative of the general population — it included only low-income adults and their families, and patients with certain disabilities.

Patterns and trends

Despite the variations in the reported incidence and prevalence of SLE, definite trends have emerged. SLE typically presents between the ages of 15 and 45 years, with a 9:1 ratio of female to male patients[66]. Ethnic disparities are also widely recognized, with non-white populations generally having a higher incidence and prevalence of SLE compared to white populations; in the USA, the incidence and prevalence of SLE in African Americans is approximately twofold–fivefold higher than in European Americans[24,25,45,59]. In the UK, the prevalence of SLE is sixfold–eightfold higher in individuals of African ancestry and in Indo-Asian people than in white populations[7,40,67–69]. The disease is also twofold–fourfold more common among Aboriginal individuals compared to non-Aboriginal individuals living in Australia, Canada and the USA[37,39,48,58,70,71]. The incidence and prevalence of SLE is also higher in other populations that include individuals of African, Asian and Aboriginal ancestry[9,12,14,15,17,24,25,35,37,39,40,45,48,58,59,71–76].

In contrast to the high prevalence of SLE seen in individuals of African ancestry living in Europe and North America, the prevalence of SLE in Africa itself has been thought to be quite low[7]. This observation generated the 'prevalence gradient' hypothesis, which suggests that the prevalence of SLE increases when people move to other nations from Africa, supporting the role of environmental triggers in disease development. However, although some evidence supports this hypothesis, no studies of the prevalence of SLE have been conducted in western Africa; the rarity of SLE has only been determined anecdotally, from case reports and case series[7]. In contrast to this hypothesis, evidence from the UK has shown a high prevalence of SLE among recent immigrants from West Africa, many of whom developed the disease before they immigrated[40], and findings from Africa from the past decade indicate that SLE might not be as rare among African populations as previously thought[7,77]. These findings indicate that the apparently increased incidence and prevalence of SLE among people of African ancestry in Europe and North America might partly result from improved access to health care, which enables more patients to be diagnosed with SLE, as well as extending the survival of those living with SLE.

Clearly, many factors (primarily the methodologies used for case identification and data collection, the age, sex, and ethnic make-up of the population being studied, but also those contributing to the health disparities discussed in the next section) influence estimates of SLE incidence and prevalence. The global burden of SLE is, therefore, still not fully defined.

Health disparities

Health disparities are inequalities in health status among members of a given population. In addition to the differences in SLE incidence and prevalence already discussed, a range of other health disparities are well known to exist for SLE. Aspects of disease development, manifestations and severity are influenced by ethnicity, factors associated with socioeconomic status (including financial and educational status and levels of health insurance, social support and medication compliance) as well as by environmental and occupational exposures. All these factors can further influence the incidence and prevalence of SLE. Below we outline these varying influences (TABLE 2).

Ethnicity

Generally, patients of African ancestry and those from Asian, Hispanic and Aboriginal populations not only develop SLE earlier than do patients from white populations, but also tend to have a more acute disease onset, a greater number of (and more severe) clinical manifestations, higher disease activity and damage, and higher mortality[9,12,14,15,17,24,25,35,37,39,40,45,48,58,59,71–76,78–80]. Despite the fact that mortality from SLE has decreased significantly in the past few decades, it remains higher in Asian populations and patients of African ancestry than in white populations[74,81–84], and deaths from SLE among African American women aged 45–64 years actually increased by almost 70% from 1979 to 1998 in the USA[85]. Survival in patients with SLE is shorter in parts of Asia and the developing world than in North America and Europe, which indicates the potential additional importance of environmental and other socioeconomic factors in the prognosis of SLE. However, we must acknowledge that not all studies take into consideration the baseline mortality in the general population when making these comparisons, and it is not always evident whether similar ethnic groups are being compared[70,86].

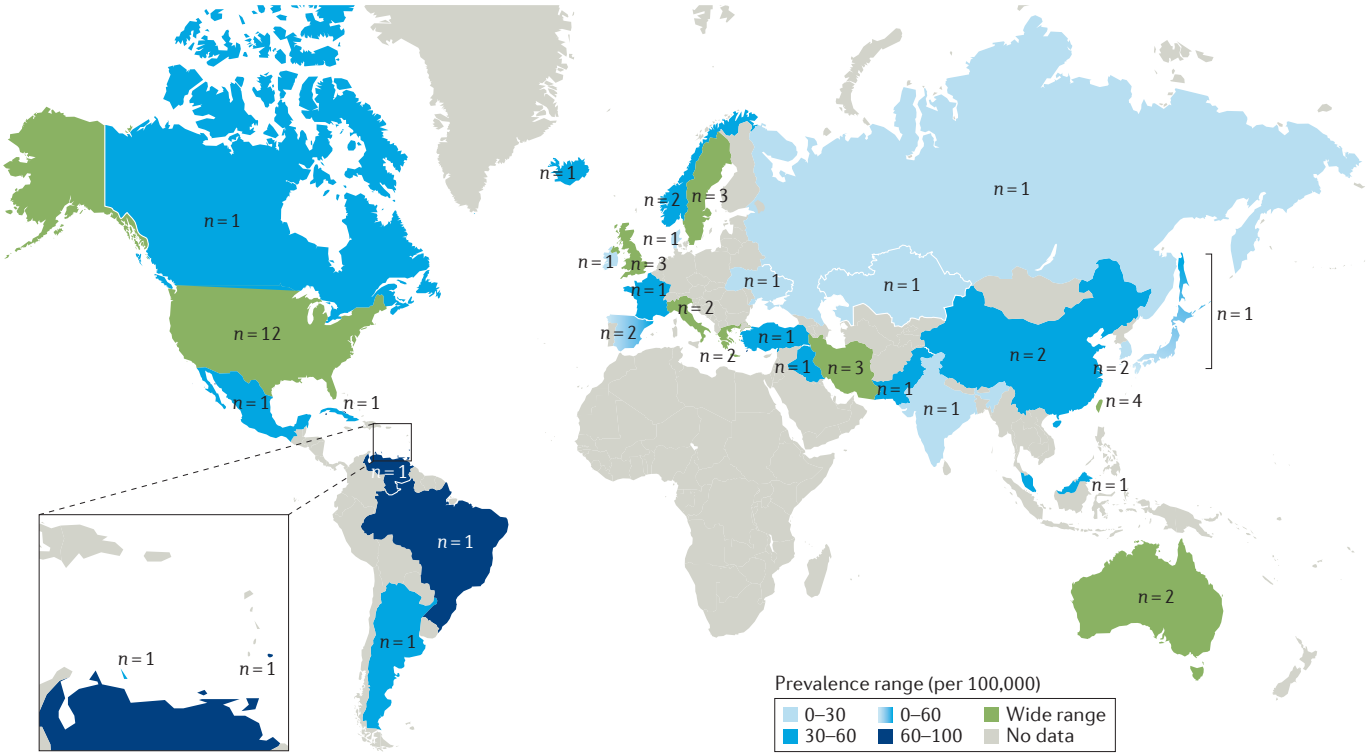

Figure 1 | **Overall worldwide prevalence ranges for SLE.** Reported SLE prevalence ranges per country (per 100,000 of the population) are shown, as denoted by the key. The number of studies (*n* =) indicate those from which each prevalence range was determined. Note the dual shading of Spain, indicating that the prevalence values span two neighbouring ranges. Precise overall prevalence ranges per country are outlined in TABLE 1, in which data for Mainland China and Taiwan are listed independently. *Nature Reviews Rheumatology* remains neutral with regard to jurisdictional claims in published maps.

Considerable evidence indicates that lupus nephritis is more prevalent in patients of African ancestry and Asian and Hispanic populations than in white populations[9,24,25,35,56,59,67,79,86–94]. Individuals of African ancestry accumulate more renal damage and are more likely to develop (and die from) end-stage renal disease than are those from white, Hispanic or Asian populations[7,24,86,88–92,95,96]. Although the majority of these comparative data originate from US studies, a single study also shows a greater incidence of lupus nephritis among Asian patients in Asia than among white patients in the USA[94]. These findings imply that, irrespective of their place of residence, Asian patients are more likely than white patients to develop renal disease, emphasizing the importance of ethnicity in the development of lupus nephritis.

Data regarding other organ manifestations of SLE are less definitive than those for lupus nephritis, but a few trends have emerged. Regardless of age and sex, Asian and Hispanic patients and those of African ancestry tend to have more haematologic, serologic and immunologic manifestations of SLE compared to white patients[24,25,70,73,79,80,82,87,88,90,97–99]. Discoid lupus seems to be more common in patients of African ancestry than in white patients[7,24,25,75,87,88,90,98], whereas white patients experience a higher frequency of photosensitivity and malar rash than do patients of African ancestry[7,24,25,75,88–90,98]. Indian patients with SLE tend to have an increased risk of neurological involvement[7,35,82,88,100], whereas the evidence for patients of Asian, Hispanic and African ancestry is mixed[7,72,78–80,82,89,90,96,97,101,102]. However, disparities can also exist within ethnic groups: in the LUMINA (Lupus in Minorities: Nature Versus Nurture) study cohort, Puerto Rican Hispanic patients exhibited a higher frequency of cutaneous manifestations, less renal and neurological involvement, less disease activity and less organ damage than did Texan Hispanic patients (who were of Mexican or Central American ancestry)[72,93,97], which further supports the possibility that environmental and socioeconomic influences are important.

Technological advances, including high-throughput genotyping and whole-genome sequencing, have contributed evidence for a role of genetic variation in SLE. Although an in-depth discussion of genetic variation in SLE is beyond the scope of this Review, many gene polymorphisms have been reported to be associated with disease manifestations, autoantibody profiles and clinical outcomes in patients with SLE, which might help to explain some, but not all, of the ethnic differences in disease presentation and progression[80].

Socioeconomic status

On the basis of studies that have examined both genetic and socioeconomic factors in patients with SLE[73,103], some researchers propose that genetic factors are most

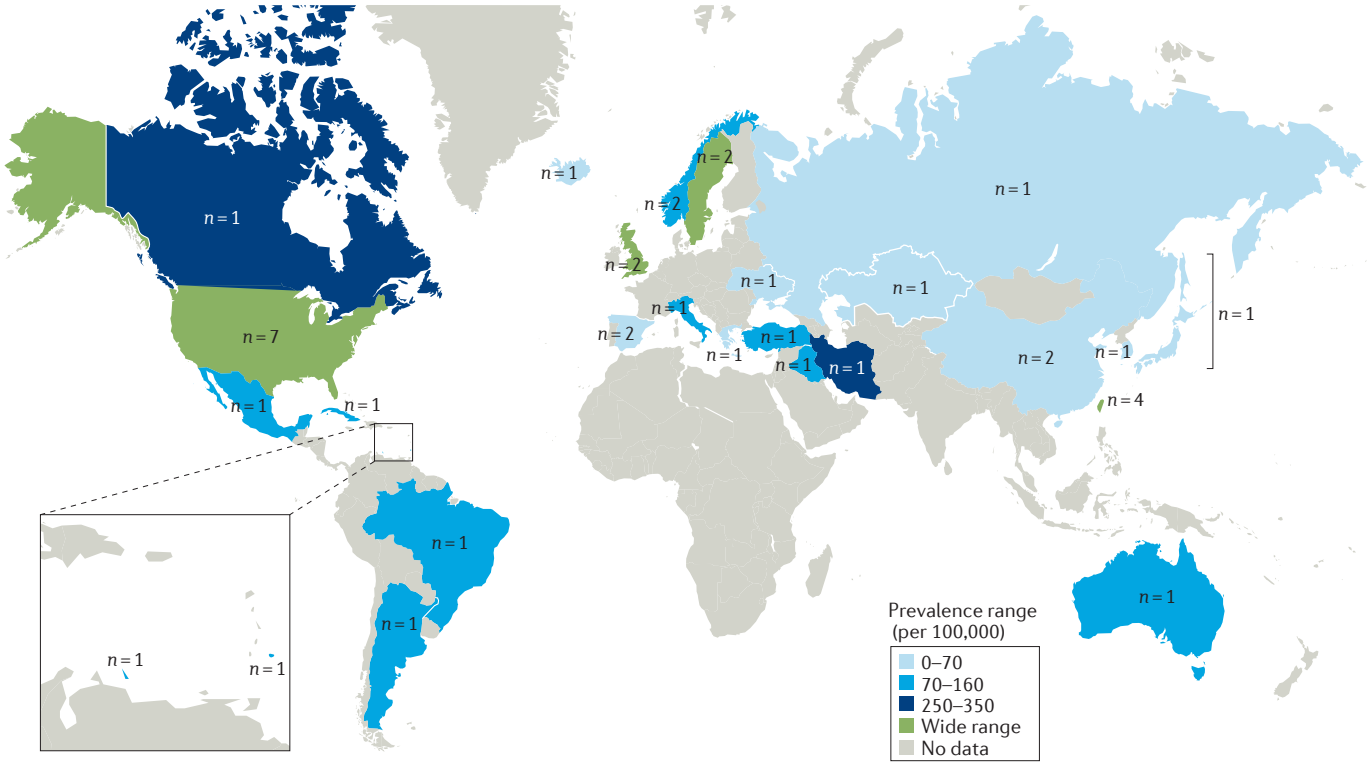

Figure 2 | **Worldwide female prevalence ranges for SLE.** The figure shows the SLE prevalence ranges in women per country (per 100,000 of the population) as denoted by the key. The number of studies (*n* =) indicate those from which each prevalence range was determined. Precise female prevalence ranges per country are outlined in TABLE 1, in which data for Mainland China and Taiwan are listed independently. *Nature Reviews Rheumatology* remains neutral with regard to jurisdictional claims in published maps.

important at disease onset, whereas socioeconomic factors become more important over time[75,88]. Thus, differences in disease manifestations and course are likely to be the result of a complex interplay between genes and the environment, and it is often difficult to determine which factors predominate[75]. In many countries, socioeconomic status is highly related to ethnicity, with non-white individuals generally having a lower socioeconomic status than white people[88,90,104]. Low socioeconomic status has been associated with several adverse outcomes in patients with SLE, such as high disease activity, increased damage accrual, work disability and mortality[59,68,72,75,79,88,89,99,105–113]. As previously noted, the results of many studies show higher mortality among Asian, Hispanic and First Nations patients and those of African ancestry compared with white patients with SLE[7,37,70,72,74,75,78,81,82,85–89,91,92,95,96,99,114]. However, in some studies that adjusted for socioeconomic status, this difference was no longer observed[70,72,90], suggesting that some health disparities are partially independent of ethnicity and so might be amenable to intervention. Stratification by socioeconomic status must be interpreted with caution[115] as the results might be influenced not only by ethnicity but also by health outcomes, potentially creating a bias in the association observed between ethnic group and health outcomes. However, in a study of white female patients with SLE in the USA (in which the effects of ethnicity and socioeconomic status are not entangled owing to the focus on a single ethnic group) higher mortality was observed in women from areas with increased poverty[114], emphasizing that socioeconomic status can have an important effect on mortality even in a subgroup that generally has a favourable prognosis.

Financial status and poverty

Several large cohort studies have demonstrated that poverty is associated with higher disease activity, increased organ damage and higher mortality in patients with SLE of varying ethnic backgrounds, compared to patients with SLE of higher financial status[79,97,104,105,116–119]. The LUMINA cohort, initiated in 1994, includes over 600 patients with SLE of white, Hispanic and African American ethnicity from Alabama, Texas and Puerto Rico[72,73,97,99,116,117]. LUMINA cohort studies demonstrated that patients with SLE living below the poverty line were four times more likely to die than those with incomes above this level[97,116,117]. The GLADEL (Grupo Latino Americano de Estudio de Lupus) cohort, started in 1997, includes almost 1,500 patients with SLE of mestizo, white or 'other' ethnicity, recruited from 34 centres in Latin America[79]. Increased organ damage (OR 1.4) and mortality were observed in those with low incomes, with 70.6% of the patients who died belonging to the lower and middle socioeconomic groups[79]. The Hopkins cohort, begun in 1987, includes over 2,000 patients with SLE, primarily white and African American, seen by one

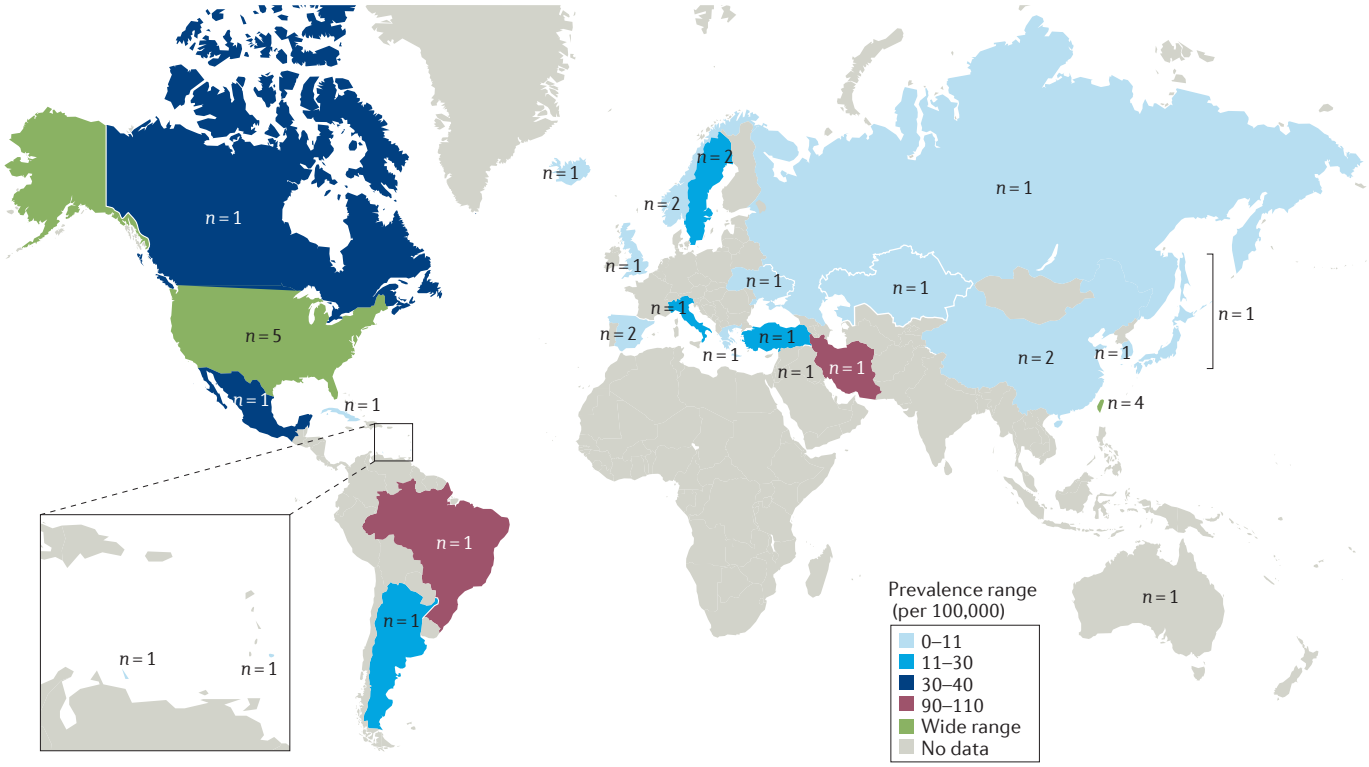

Figure 3 | **Worldwide male prevalence ranges for SLE.** The figure shows the SLE prevalence ranges in men per country (per 100,000 of the population) as denoted by the key. The number of studies (n =) indicate those from which each prevalence range was determined. Precise male prevalence ranges per country are outlined in TABLE 1, in which data for Mainland China and Taiwan are listed independently. Nature Reviews Rheumatology remains neutral with regard to jurisdictional claims in published maps.

provider in the USA[119]; patients with an annual household income below $25,000 had an estimated 20-year survival of 70%, compared with 86% for those above this threshold[118]. Poverty has also been associated with lower mental functioning in patients with SLE[105] and has been shown to contribute to the progression of lupus nephritis, independent of ethnicity[120,121]. Data from the USA have shown that high-income patients who develop end-stage renal disease secondary to lupus nephritis have improved survival, and that this association might counteract the mortality difference between African American and non-African American groups outlined above[92].

Education

Multiple SLE studies, including those involving the LUMINA and GLADEL cohorts, have shown that low education levels are linked to high disease activity, increased organ damage, low physical functioning and high mortality[79,104,105,116,117,122]. Low educational attainment in patients is correlated with physician underdiagnosis of SLE in non-white (Asian, African American and Asian or Pacific Islander) populations, and might also influence patients' satisfaction with their care, as well as their compliance with treatment[80,122]. Generally, Hispanic and African American individuals in the USA have lower levels of education than their white counterparts, and might also have limited English language skills. These limitations can interfere with the ability of patients to understand practitioners and with the capacity of health workers to provide proper care[104,123]. However, a high educational level does not always correlate with improved disease outcomes, and this association can be modified by ethnicity. A population-based study found that although high levels of education among white patients with SLE were associated with reduced mortality, a similar association was not seen in African American patients or women of Asian or Pacific Islander ethnicity[122].

Health insurance

Another factor that is closely related to financial status and education, and contributes to health disparities, is the ability to obtain medical insurance and to access health care resources. Lack of health insurance, which disproportionately affects non-white populations in the USA, might delay or prevent access to specialist rheumatology care, and can limit the treatment options available to patients[123]. In the USA, having private insurance has been linked to lower disease activity in patients with SLE of all ethnic groups, whereas public insurance, or lack of insurance, has been associated with increased disease activity, increased hospitalizations and increased mortality[74,89,99]. Financial status, educational level and health insurance are likely to act in synergy, rather than independently, to influence outcomes in SLE.

Table 1 | **SLE prevalence by country**

Country	Prevalence range (per 100,000 of the population)		
	Overall	Females	Males
Taiwan	37.0–97.5	66.6–179.4	8.4–28.5
South Korea	18.8–26.5	35.7–45.8	5.5–7.5
Malaysia	43.0	N/D	N/D
Mainland China	30.0–37.6	60–67.8	0–6.2
Japan	3.7–37.7	6.6–68.4	0.83–7.0
India	3.2	N/D	N/D
Pakistan	50.0	N/D	N/D
Iran	40.0–190.0	250.0	110.0
Iraq	53.6	88.7	N/D
Australia	19.3–92.8	127.0	N/D
Norway	44.9–51.8	89.3–91.0	9.7–10.7
Denmark	21.9–28.3	N/D	N/D
Russia	9.0	15.8	0.5
Ukraine	14.9	23.8	3.7
Kazakhstan	20.6	35.9	1.8
UK	24.0–517.5	35.0–177.0	3.7
Spain	17.5–34.1	29.2–57.9	5.8–8.3
Italy	57.9–81.0	100.1	12.0
France	47.0	N/D	N/D
Turkey	59.0	104.0	12.0
Greece	39.5–110.0	69.3	9.5
Iceland	35.9	62.0	7.2
Sweden	39.0–85.0	64.8–144.0	11.7–25.0
Ireland	25.4	N/D	N/D
USA	42.0–300.0	45.0–408.2	4.4–54.0
Canada	31.9–51.0	271.0–322.0	32.0
Brazil	98.0	110.0	90.0
Argentina	58.6	83.2	23.0
Venezuela	70.0	N/D	N/D
Curacao	47.0	83.8	8.5
Mexico	60.0	80.0	40.0
Cuba	60.0	100.0	0
Barbados	84.1	152.6	10.1

Values for this table were derived from Supplementary table 1, using the highest and lowest overall prevalence values, the highest and lowest female prevalence values, and the highest and lowest male prevalence values per country (where data are available). N/D, not determined.

Social support and health perceptions

Social support is another component of a patient's socioeconomic status that modulates disease activity, damage accrual and level of functioning[70,99,105]. Adequate social support acts as a positive factor that enables patients and their families to better navigate, understand and use the health care system. Poor social support is associated with increased disease activity and impaired mental functioning, whereas lack of self-efficacy in disease management is associated with decreased mental and physical functioning[99,105]. These associations might also be affected by ethnic differences. For example, in the LUMINA cohort study, low levels of social support, high degrees of helplessness and poor coping styles were seen in Texan Hispanic and African American patients, but not in Puerto Rican Hispanic or white patients[73,99,104].

Adverse health perceptions and maladaptive illness-related behaviours worsen disease outcomes, medication beliefs and compliance; they are also influenced by ethnicity[80]. Compared to white British patients with SLE, British patients of South Asian origin with SLE are more focused on the harmful effects (rather than the potential benefits) of prescription medications[124]. In consequence, patients of South Asian origin stop taking DMARDs sooner than do those of Northern European origin, owing to concerns regarding medication toxicity[124]. African American patients are also less willing than white American patients to take medications to treat SLE, and studies report decreased compliance in this ethnic group[89,91,104].

Environmental and occupational factors

Smoking. Smoking is more common among individuals of low socioeconomic status than in other groups. Multiple studies have examined the relationship between smoking and SLE, with conflicting results[68,125–131]. Data on whether a dose–response relationship exists are also conflicting[128]. A 2015 meta-analysis showed that both former smoking and current smoking increase the risk of developing SLE, but this association was modified by geography; the risk of SLE was increased in current smokers in Europe and East Asia but not in North America, whereas the risk of developing SLE was increased in former smokers only in Europe[126]. Current smoking might also increase disease activity, with one study showing higher disease activity in current smokers compared to former or never smokers[130]. Furthermore, smoking might exacerbate the severity of organ involvement; some studies show increased pleuritis, peritonitis, neuropsychiatric symptoms and end-stage renal disease among smokers[128,129,131].

Alcohol. The effect of alcohol on SLE is unclear. Alcohol consumption protects against the development of SLE in some, but not all, studies[127,128,132–135]. Some reports even suggest a dose–response relationship, with successive increments in alcohol consumption linked to further reductions in the risk of developing SLE[127]. A US case–control study found that, although current drinking levels were inversely associated with the risk of developing SLE, alcohol consumption before diagnosis showed no such correlation[134]. However, a tendency of patients to quit drinking just before or shortly after being diagnosed with SLE could partially explain these findings[134]. A meta-analysis of six case–control studies showed that a moderate alcohol intake protected against the development of SLE, but this association was less clear in a cohort study[132,135]. Many potential reasons might underlie these inconsistencies, including differences in the types and patterns of alcohol consumption, patient selection and recall bias, or uncontrolled confounding variables such as patients' educational levels. To date,

Table 2 | **The effect of ethnicity, socioeconomic status and environmental exposures on health disparities in patients with SLE**

Variable	Resultant health disparities
Ethnicity	• Disease prevalence, severity and mortality are increased in African American populations compared to white populations • Lupus nephritis is more common in African American patients than in white patients, and patients of African ancestry seem to have the worst outcomes • Haematologic, serologic and immunologic manifestations are more common in African American patients than in white patients • Discoid lupus is most common in patients of African ancestry • Malar rash and photosensitivity are most common in white patients
Socioeconomic factors	Financial status: • Poor socioeconomic status is associated with increased disease activity, organ damage, work disability and mortality • Differences in socioeconomic status might account for some of the disease disparities related to ethnicity • Poverty is associated with high disease activity, increased organ damage and mortality • Poverty is associated with reduced mental functioning • Poverty contributes to the progression of lupus nephritis
	Education: • Low education levels are linked to high disease activity, increased organ damage, decreased physical functioning and increased mortality • Low education level is related to under-diagnosis of SLE in African American populations and poor treatment compliance • Language barriers might impact patient care
	Health insurance: • Lack of insurance might delay or prevent access to rheumatology care, and can limit treatment options • In the USA, private insurance is linked to low disease activity • Public insurance, or lack of insurance, is associated with increased disease activity, hospitalizations and mortality
	Social support and treatment compliance: • Poor social support is associated with high disease activity and poor mental functioning • South Asian patients and patients of African ancestry seem less willing to take medications for SLE, and might have poorer compliance, compared to white patients
Environmental exposures	• Smoking might increase the risk of developing SLE, exacerbate disease activity and worsen organ damage • Alcohol might decrease the risk of developing SLE, but studies are conflicting • Silica exposure increases the risk of developing SLE • Pollution might increase the risk of SLE and increase disease activity • Solvent exposure might increase SLE risk and mortality • The association between pesticides and SLE is controversial • SLE patients have lower vitamin D levels than controls in many studies, but whether low vitamin D levels contribute to SLE development or are a consequence of the disease is unclear; whether vitamin D supplementation improves disease activity is controversial • Whether UV exposure retards or promotes the development of SLE, or improves or exacerbates existing SLE, is unresolved

The supporting references for this table are discussed in the text. The literature search strategy is outlined in the Review criteria. SLE, systemic lupus erythematosus.

no large, well-controlled, prospective cohort study has examined the association between long-term alcohol consumption and SLE risk. Thus, although the available data suggest that moderate alcohol consumption might be associated with a decreased risk of developing SLE, the evidence for this protective effect remains limited.

Silica. Case reports, case–control studies and observational cohorts have shown that exposure to silica is positively associated with the development of SLE[136–143]. Work in mines, quarries, foundries, roadways, construction, masonry, farming, sandblasting and the production of pottery, glass and tiles result in a relatively high exposure to silica. Cohort studies have demonstrated a tenfold higher risk of developing SLE in patients exposed to very high levels of silica compared to non-exposed patients[141,142]. Silica might also interact with other environmental factors to influence SLE development. A US case–control study suggested a possible interaction between silica and smoking, as the risk of developing SLE was increased in smokers who were exposed to high levels of silica, but not in smokers with low silica exposures[140]. By contrast, a Canadian case–control study found that silica-exposed people who had never smoked had an increased risk of developing SLE compared with never-smokers without silica exposure, but that silica exposure did not increase the risk of SLE in people who had ever smoked[137]. Overall, the balance of evidence seems to support the notion that silica exposure contributes to SLE development, but how smoking or other exposures might modify this risk remains unknown.

Industrial emissions, pollution, solvents and pesticides. Little research has evaluated the effects of pollution, solvents and pesticides on the development of SLE, but some evidence suggests that pollution does contribute to SLE development and disease activity[136,144]. A Canadian study showed that increased levels of air pollution were associated with increased disease activity, as reflected by the increased presence of urinary casts and levels of antibodies against double-stranded DNA[145]. Exposure to solvents has been associated with an increased risk of developing SLE, and with increased mortality[137,146,147]. A study conducted in Arizona also reported an increase

Box 2 | **Direct costs of SLE: definitions and estimates**

Direct costs of SLE include the value of resources used in its prevention, diagnosis, treatment and the rehabilitation of patients.

Direct health care costs

- Conventional inpatient care — stays in hospitals and rehabilitation facilities and all related services
- Conventional outpatient care — prescribed and nonprescribed medications, visits to physicians and ancillary health care providers, laboratory tests, imaging procedures, emergency room visits, outpatient surgical procedures, assistive devices
- Complementary and alternative health care providers and therapies

Direct non-health-care costs

- Transportation to health care visits
- Assistance (for example, childcare) to attend health care visits

Methods used to estimate direct costs

- Patient self-report
- Review of medical charts
- Review of private or public insurance data from national reimbursement schedules, provider charges and insurer reimbursement

Estimated direct costs of SLE per patient per year*

- $1,847.00 (catastrophic-illness-related costs only)
- $33,223.00 (all cost components included, for the general SLE population)
- $71,334.00 (patients with lupus nephritis)
- Between $13,494.00 and $55,344.00 (severe or active SLE)

*Expressed in 2015 US dollars. SLE, systemic lupus erythematosus.

in the number of symptoms in patients with SLE who had been exposed to solvent-contaminated well water[148]. By contrast, two case–control studies from the USA showed no increased risk of SLE in patients exposed to solvents[143,147]. Evidence regarding exposure to pesticides and the risk of developing SLE is conflicting[68,139,146].

Vitamin D and sunlight or UV exposure. Vitamin D is believed to be an immune mediator, and multiple studies (although not all) have shown that patients with SLE have lower vitamin D levels than controls[149–153]. Low levels of sunlight exposure are linked to vitamin D deficiency; patients with SLE are, therefore, at a particularly high risk of vitamin D deficiency owing to photosensitivity and consequent sun avoidance. Moreover, their place of residence and ethnicity will further influence their vitamin D status[150]. However, whether low vitamin D levels are a consequence of SLE or have a causative role in its development is not clear. Animal models show that vitamin D deficiency contributes to the development of SLE, and that vitamin D supplements can reduce SLE symptoms[150,154,155]. However, the data are less definitive in humans. Some studies show that low vitamin D levels are associated with increased SLE disease activity[150,151,153,156–159], but others (including one meta-analysis) do not support this relationship[149,152,160,161]. Furthermore, supplementation with vitamin D has shown benefit in some studies but not others[149,156,162].

Conflicting evidence also exists regarding the role of UV exposure in the development of SLE. A UK study showed an increased disease incidence in northern regions of the UK, where UV levels become progressively lower with increasing latitudes[163], whereas a study from Sweden reported that women with highly sun-sensitive skin types and patients who had experienced severe sunburn during their youth showed an increased risk of developing SLE[133]. Also unresolved is whether UV exposure improves or exacerbates existing SLE. A study from Hong Kong showed that most disease flares occurred in December and January[164], whereas the Hopkins Cohort in the USA experienced exacerbations of arthritis and skin manifestations during the spring and summer[165]. Geographic patterns of SLE mortality in the USA have been suggested to be consistent with regional differences in UV levels, with one study reporting higher mortality among African American and white patients with SLE in areas with high levels of UV exposure[114].

The burden of SLE

Economic implications

Understanding the economic burden of SLE is crucial to determining the optimal allocation of health care resources, with the ultimate goal of improving patients' outcomes. However, accurate calculation of disease-related costs is very challenging, and estimates must incorporate both direct (BOX 2) and indirect (BOX 3) costs. Direct costs are the value of resources used in the prevention, diagnosis, treatment and rehabilitation of a disease; indirect costs represent the value of economic productivity lost owing to disease-related disability in both labour and non-labour market activities[166]. Whereas assessments of health resource utilization can be based on patient self-reported data or review of medical charts or insurance databases, diminished productivity is almost always derived from patient self-reported data. Distinguishing which costs are attributable directly to SLE and which are attributable to comorbidities (which might not be associated with SLE) is difficult, so most cost-of-illness estimates for SLE incorporate all health resource utilization and diminished productivity, regardless of the cause.

Direct costs. Although SLE currently cannot be cured, survival and life expectancy have increased over the past few decades as a result of improvements in diagnosis and treatment. However, SLE can still cause considerable organ damage, potentially leading to high morbidity and mortality. As such, the direct costs of the disease can be substantial[166–188] (TABLE 3, Supplementary information S2 (table)), reaching up to $71,334.00 per patient per year[184], and are increased by the development of organ dysfunction such as lupus nephritis[168,175,179,183–185,188], disease flares[176,178,179], high disease activity[174,177,185,187] and disease of long duration[167] (TABLE 3, Supplementary information S2 (table)). Data from the USA indicate that the direct costs in patients with lupus nephritis exceed those in the general population by sixfold, and Canadian data show that direct costs are almost five times greater in patients with end-stage renal disease than in those without renal damage[185] (TABLE 3, Supplementary information S2 (table)). Furthermore, studies from mainland China, Canada and the USA show that SLE patients who are experiencing flares and severe disease incur direct

Box 3 | **Indirect costs of SLE: definitions and estimates**

Indirect costs of SLE include the value of economic productivity lost owing to disease-related work disability in both labour and non-labour market activities.

Methods used to estimate indirect costs

- Patient self-report of time loss from labour and non-labour market activities
- Review of employer disability and absence databases
- Review of social insurance data on time lost from labour market activities

Methods for calculating time lost

- Human capital approach: includes all time loss in labour and non-labour market activities for the entire duration of the impairment
- Friction cost approach: includes only time loss in labour market activities and values time lost only until the disabled worker can be replaced
- Calculating labour market time loss: age-matched and sex-matched employment income
- Calculating non-labour market time loss: opportunity costs (values time in the home as equivalent to time in the labour market, based on age-matched and sex-matched employment income); replacement costs (based on the market value of the services provided by the patient at home)

Indirect cost estimates of SLE per patient per year*

- $1,252.00–20,046.00 for the general SLE population
- Up to $18,034.00 for patients with lupus nephritis

*Expressed in 2015 US dollars. SLE, systemic lupus erythematosus.

costs twofold–sixfold higher than in patients with mild disease who do not experience flares[174,176,187] (TABLE 3, Supplementary information S2 (table)).

Indirect costs. Given the chronic and unpredictable nature of SLE, the disease can significantly impair the ability of patients to work[108,109,189] and lead to high indirect costs[167–169,171,172,185,190] (Supplementary information S2 (table)). As SLE primarily affects women, the indirect costs encountered through diminished non-labour market activities (such as childcare and household work) are also considerable, and several studies have shown that indirect costs actually exceed direct costs by twofold–fourfold[167–169,171,172,185,190] (Supplementary information S2 (table)).

The inability to work profoundly affects both the individual and society. Work loss contributes to further indirect costs through decreased socialization, low self-esteem and the reduced ability to support dependents; limited access to employer benefits such as health insurance, child care and pension plans; and the inability to save financially for retirement[88,108,109,191]. Work disability is common in patients with SLE, with 15–51% of patients reporting cessation of employment 2–15 years after diagnosis[107,110,112,192–194], and over 60% being unemployed after 20 years[112,191,195]. Employment rates among patients with SLE are substantially lower than in the general population[196]. Although many studies do not directly compare individuals with SLE to healthy controls, data from the USA show that the unemployment rate within 1 year of diagnosis is 26% in patients with SLE, compared to only 9% in controls[111]. In Germany, employment among patients with SLE is 17–47% lower than the population average, depending on disease duration and sex[197].

Work limitations in SLE have been associated with a variety of demographic, disease and job-related factors, including older age, low educational attainment, African ancestry, poverty, prolonged disease duration, high disease activity and damage, fatigue, musculoskeletal manifestations, neurocognitive involvement, anxiety, depression, increased pain, and physically and cognitively demanding types of work[75,88,107–110,112,191–193,195,198–201]. Even if patients with SLE remain employed, disease flares, organ damage and general poor health can decrease their productivity as well as contribute to an increased risk of permanent disability. Many individuals with SLE are compelled to reduce their working hours, alter their jobs, take extended sick leave or eventually claim disability assistance[107,112,189,191,194,195,199,200]. These limitations extend beyond their effects on work duties; the same demographic and disease-related factors are associated with a decreased ability to perform daily activities including studying, carrying out housework, caring for children and participating in leisure activities[194,198,200].

Intangible losses

Beyond the financial burden, intangible losses should also be considered, as SLE contributes to decreased HRQoL via a wide range of adverse psychosocial factors[196]. HRQoL is a measure of a patient's physical and functional health, and also provides a view of their social environment and psychological beliefs, which might influence their response to illness[202]. Patients with SLE experience a lower HRQoL than do the general population, and the reductions are similar to, or even exceed, those for other chronic diseases[70,113,189,196,198]. Patients with SLE report reductions in all aspects of HRQoL, including physical and mental health, vitality, pain, and social and emotional functioning[196]. HRQoL is influenced by a complicated interplay between disease and environmental factors, and determinants include disease manifestations, particularly fatigue, disease activity and damage accrual, as well as the patient's level of helplessness and ability to cope with the disease[70,189,196]. Multiple other symptoms have been associated with poor HRQoL, including depression, anxiety, pain, sleep disturbances, and neuropsychiatric and cutaneous manifestations[113,189,196].

Surprisingly, clinical measures of disease activity and organ damage do not always correlate with HRQoL[196]. However, decreasing disease activity can improve HRQoL[113,202]. Older age, female sex, poverty, low educational attainment, lack of social support, and unemployment are also associated with decreased HRQoL. Additionally, poor HRQoL is a determinant of reduced treatment compliance[202], and the 2010 EULAR guidelines for monitoring patients with SLE consequently recommend that HRQoL should be assessed at every clinic visit[203]. However, given the multiple challenges faced by clinicians treating these patients — including the need to address diverse and complex organ manifestations, considerable comorbidities and the adverse effects of numerous, and potentially toxic, therapies — it is likely that assessment of HRQoL is often neglected, thereby contributing to poorer outcomes and higher direct and indirect costs.

Table 3 | **Summary of SLE cost studies**

Authors	Country and study period‡	Population	Total direct costs* per patient per year	Total indirect costs* per patient per year
Asia				
Chiu & Lai (2010)[17]	Taiwan, 2000–2007	22,182 patients with SLE	$1,847.00	N/A
Cho *et al.* (2014)[172]	South Korea, 2012	201 patients with SLE from one specialty centre	• Overall: $4,940.00 • Renal involvement: $5,803.00	• Overall: $6,923.00 • Renal involvement: $8,951.00
Zhu *et al.* (2009)[174] Zhu *et al.* (2009)[173]	Hong Kong, Mainland China, 2006–2007	306 patients with SLE from one specialty centre	• Overall: $9,740.00 • Flare versus no flare: $19,970.00 versus $7,141.00	• Overall: $6,009.00 • Flare versus no flare: $6,812.00 versus $5,805.00
Europe				
Sutcliffe *et al.* (2001)[171]	UK, 1995	105 patients from one SLE clinic	$6,070.00	$12,309.00
Doria *et al.* (2014)[170]	France, Germany, Italy, Spain, UK, 2010–2011	427 patients with SLE from multiple clinical cohorts	$5,007.00	N/A
Jonsen *et al.* (2015)[168]	Sweden, 2002–2010	127 patients with SLE included in a national database versus 508 controls without SLE	• Overall: $5,984.00 • LN versus controls: $10,017.00 versus $1,606.00	• Overall: $15,657.00 • LN versus controls: $17,486.00 versus $5,585.00
Bexelius *et al.* (2013)[169]	Sweden, not specified	339 patients with SLE enrolled in an advocacy association	$10,606.00	$20,046.00
Huscher *et al.* (2006)[167]	Germany, 2002	844 patients with SLE from a national rheumatology database	$4,887.00	• Sick leave and permanent disability: HCA $17,184.00 • Permanent work disability: FCA $2,283.00
North America				
• Panopalis *et al.* (2007)[190] • Clarke *et al.* (2004)[186] • Clarke *et al.* (2008)[185]	USA, Canada, UK* 1995–2001	500 patients (269 in USA, 231 in Canada, 215 in UK) with SLE from hospital-based clinical cohorts	• USA: $5,457.00 • Canada: $4,271.00 • UK: $4,756.00 • SDI renal subscale: 0, $4,973.00; 1, $6,815.00; 2, $12,517.00; 3, $24,342.00	Labour market activity: • HCA: $15,297.00 (USA); $10,417.00 (Canada); $11,379.00 (UK) • FCA: $1,250.00 (USA); $1,760.00 (Canada); $1,346.00 (UK) • Non-labour market activity: • HCA: $1,415.00 (USA); $1,471.00 (Canada); $2,311.00 (UK) • SDI renal subscale: 0, $15,363.00; 1, $17,258.00; 2, $16,379.00; 3, $18,034.00
Li *et al.* (2009)[175]	USA, 2000–2004	2,298 patients with SLE versus 2,298 matched controls without SLE	• Year of first claim: SLE, $19,042.00; LN, $32,503.00; controls, $10,957.00 • 5 consecutive years after first claim: SLE, $28,239.00; LN, $59,861.00; controls, $18,547.00	N/A
Carls *et al.* (2009)[184]	USA, 2000–2004	6,269 patients with SLE versus 6,269 matched controls without SLE	• SLE versus controls, $23,826.00 versus $8,875.00 • LN versus controls, $71,334.00 versus $14,083.00	Absenteeism, SLE versus controls: $4,238.00 versus $4,909.00: • LN versus controls: $5,841.00 versus $5,561.00 • Short-term disability, SLE versus controls: $2,742.00 versus $1,295.00 • LN versus controls $1,252.00 versus $472.00
Oglesby *et al.* (2014)[182]	USA, 2000–2010	4,166 patients with SLE	Time to SLE diagnosis, ≤6 months versus ≥6 months from symptom onset: $17,670.00 versus $22,751.00	N/A
Campbell *et al.* (2009)[111]	USA, 2001	51 patients with SLE versus 51 matched controls without SLE	N/A	Average salary loss, SLE versus controls: $6,781.00 versus $995.00

Table 3 (cont.) | **Summary of SLE cost studies**

Authors	Country and study period‡	Population	Total direct costs* per patient per year	Total indirect costs* per patient per year
Kan *et al.* (2013)[178]	USA, 2002–2009	178 patients with SLE	• Overall: $32,516.00 • Mild flare: $19,549.00 • Moderate flare: $24,406.00 • Severe flare: $55,344.00	N/A
Panopalis *et al.* (2008)[166]	USA, 2003–2005	815 patients with SLE	$15,969.00	Productivity cost: $10,937.00
• Furst *et al.* (2013)[180] • Furst *et al.* (2013)[181]	USA, 2003–2008	907 patients with LN, versus 2,721 matched controls; 1,062 patients with NPSLE versus 3,186 matched controls; 1,278 patients with newly diagnosed SLE versus 3,834 matched controls; 10,152 patients with existing SLE versus 30,456 matched controls	• LN versus controls: $37,233.00 versus $5,948.00 • NPSLE versus controls: $33,750.00 versus $5,168.00 • Newly diagnosed versus existing SLE: $21,333.00 versus $17,227.00	N/A
Garris *et al.* (2013)[176]	USA, 2004–2005	2,990 patients with SLE	• Overall: $16,629.00 • Mild disease: $5,963.00 • Moderate disease: $12,329.00 • Severe disease: $40,133.00	N/A
Narayanan *et al.* (2013)[179]	USA, 2004–2008	13,460 patients with SLE versus 13,460 matched controls	SLE versus controls: $33,223.00 versus $26,955.00	• Absenteeism, SLE versus controls: $6,777.00 versus $3,497.00 • Short term disability, SLE versus controls: $6,805.00 versus $3,713.00
Kan *et al.* (2013)[177]	USA, 2004–2011	178 patients with SLE	• Overall: $19,987.00 • SLEDAI 0, $15,297.00; 0–2, $23,766.00; 2–4, $23,425.00; >4, $15,528.00	N/A
Pelletier *et al.* (2009)[183]	USA, 2007	15,590 patients with SLE	• Overall: $14,115.00 • LN versus no LN: $33,969.00 versus $13,331.00	N/A
Aghdassi *et al.* (2011)[188]	Canada, 2004–2009	141 patients with SLE	LN versus no LN: $11,677.00 versus $9,812.00	N/A
Clarke *et al.* (2015)[187]	Canada, 2007–2009	109 patients with SLE	• Overall: $9,512.00 • Severe versus mild disease: $13,494.00 versus $5,306.00 • Flare versus no flare: $10,148.00 versus $4,983.00	N/A

FCA, the friction cost approach to estimation of indirect costs, which includes only time loss in labour market activities during the time it takes to replace the disabled worker (the friction period); HCA, the human capital approach to estimation of indirect costs, which includes time loss in both labour and non-labour market activities for the entire duration of the impairment; LN, lupus nephritis; NPSLE, neuropsychiatric SLE; SLE, systemic lupus erythematosus; SLEDAI: SLE disease activity index; SDI, Systemic Lupus International Collaborating Clinics (SLICC)–American College of Rheumatology Damage Index (also known as the SLICC damage index). *All amounts converted to 2015 US dollars using power purchasing parities for each non-US currency and adjusted for inflation using the US consumer price index. Power purchasing parities provide a more accurate comparison than exchange rates alone, as they also account for the general price level in different countries. If the year of currency was not specified, it was assumed to be that of the last year of data collection. ‡Year(s) expenses were incurred. §Data from the Tri-Nation Study have been included in the North America section, despite the inclusion of the UK, because the SDI renal subscale data refer to all three countries.

Conclusions

SLE is an extremely heterogeneous disease in terms of development, presentation, manifestations and severity, and its global burden remains incompletely understood. The incidence and prevalence of SLE vary considerably; this variation is likely to be partly attributable to ethnic and geographic differences, the definition of SLE applied, and the methods of case ascertainment. However, the extremely varied estimates for SLE incidence and prevalence make it difficult to apportion resources appropriately for patient care; this challenge emphasizes the importance of further research applying a consistent disease definition and using standardized methodologies to overcome the problem of obtaining accurate data, with the aim of improving patient outcomes through appropriate health care planning and resource allocation.

Substantial evidence indicates that SLE develops more frequently, has a more severe disease course, causes more organ damage and has a higher mortality among Asian and Aboriginal populations and individuals of African ancestry than in white individuals. Data also clearly show that socioeconomic disparities (such as poverty, low educational status, lack of health insurance and poor social support, which are generally more common among non-white populations) operate collectively, as well as independently, to negatively influence the course and outcomes of SLE.

Various environmental exposures, including cigarette smoking, silica, pollution and solvents, might also increase the risk of developing SLE and influence disease severity and manifestations. Whether alcohol intake confers a protective effect on SLE development remains controversial, and the contribution of vitamin D and UV radiation levels to the pathogenesis of SLE is also unclear. Given the many and diverse manifestations of SLE, the treatment of patients — particularly those with lupus nephritis — is likely to incur substantial direct and indirect costs, and the patients themselves can experience a considerably impaired HRQoL. By describing the global burden of SLE and its determinants, we hope that this article will help to inform efforts to reduce health disparities and improve outcomes in patients with SLE, while decreasing costs and increasing productivity.

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A.E.C. and E.E.C. researched data for the article, contributed substantially to discussions of its content, and wrote the manuscript. All authors (A.E.C., E.E.C and S.G.B) undertook review and editing of the manuscript before submission.

Competing interests
A.A.C. declares that she has served as a consultant for AstraZeneca, Bristol–Myers Squibb and Eli Lilly. The other authors declare no competing interests.

Review criteria
Articles for inclusion in this Review were obtained through multiple PubMed searches conducted using the search term "lupus" in combination with the search terms "race", "ethnicity", "socioeconomic status", "poverty", "education", "health insurance", "social support", "smoking", "alcohol", "silica", "pollution", "solvents", "pesticides" and "vitamin D". The resulting abstracts were then reviewed by a single individual. No date range was specified and only full-text studies in English were included. Any additional relevant references found in review articles or primary articles that met these criteria were also included.

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