Geoepidemiology of autoimmune rheumatic diseases

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Abstract | The accumulative global burden of autoimmune and inflammatory rheumatic diseases is substantial. Studying the distribution of these conditions across various global regions and ethnic groups by means of geoepidemiology might readily provide epidemiological data and also advance our understanding of their genetic and environmental underpinnings. In order to depict the geoepidemiology of autoimmune and inflammatory rheumatic diseases, namely rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, ankylosing spondylitis and Sjögren's syndrome, we present a comprehensive collection of epidemiological reports from various world regions, including the prevalence of each of these conditions. The accumulated data show that the reviewed rheumatic diseases are global phenomena, and, with some variance, seem to be relatively evenly distributed. This finding is in contrast with the obviously uneven distribution of some major nonrheumatic autoimmune conditions. In addition, geoepidemiology demonstrates that ethnogenetic susceptibility interacts with lifestyle and environmental factors, which include socioeconomic status, infectious agents (triggering or protective agents), environmental pollutants, and vitamin D (dependent on sunlight exposure), in determining the risk of developing rheumatic autoimmunity.

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Introduction

Geoepidemiology of autoimmune and inflammatory diseases means the study of the distribution of these conditions and the determinants of disease gradients across multiple regions and populations.[1] Autoimmune diseases as a group are among the leading causes of death and morbidity in the industrial world, and pose an immense socioeconomic burden.[2–5] Despite the considerable accumulative burden of these diseases, only a small number of multinational registries for a few selected autoimmune diseases have been devised.[5] Additionally, large, international epidemiological investigations were conducted for only three autoimmune conditions (that is, type 1 diabetes mellitus, multiple sclerosis, and rheumatoid arthritis [RA]).[6–8] Thus, depicting the distribution of most of these conditions, particularly of certain rheumatic conditions, requires a rigorous compilation of numerous scattered epidemiological reports. Such studies, however, should prove a worthy undertaking, as discerning the number of individuals with an autoimmune or inflammatory disease (prevalence rates) and the number of new cases per year (incidence rates), might help determine regional and global effects of these illnesses.

The first comprehensive effort to compile worldwide incidence and prevalence data across multiple autoimmune diseases was made towards the end of the previous century.[9] Nevertheless, such comprehensive data have not been presented to date with a geoepidemiological emphasis, which means that rates of such diseases across different world regions and populations have not been compared. The importance of geoepidemiology does not lie solely in geographically portraying the burden of each disease, but also in advancing our understanding of its etiologic and triggering underpinnings, which might ultimately enhance our ability to make predictions and intervene.

For a certain autoimmune disease, geoepidemiology might uncover ethnogenetic risk factors, for example, by observing a gradient of disease rates corresponding to the geographical distribution of particular HLA-types or other disease-associated genes.[10–13] Genetic risk might also come to focus when identifying disease 'hot spots', that is, salient clusters of autoimmunity cases in specific populations with a genetic composition that is distinct from that of the neighboring communities.[14] Hot spots might also bring forth environmental precipitants, for instance, when identifying clusters of autoimmune cases in particular geographical areas that are known to contain a potential environmental trigger (such as environmental pollutants).[15,16] Additionally, geoepidemiology might underscore the intricate combination of genes and environment that is entailed in the pathogenesis of autoimmunity,[17–19] by comparing ethnic migrant populations (for example West African migrants) with the native populations (for example European populations), and with the same ethnic group in their region of origin (for example West Africa). Thus, geoepidemiology can help to identify ethnogenetic differences in disease risk on one hand, and the modulating effects of social, cultural and physical environments on the other hand.[20,21]

Competing interests
The authors declare no competing interests.

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Key points

- Geoepidemiology provides a comprehensible picture of the burden of autoimmune and inflammatory rheumatic diseases across various regions and ethnicities, and helps to unravel potential causative factors
- The global distribution of rheumatic autoimmune diseases, with some variance, seems to be ubiquitous, although prominent gradients are present in the distribution of some major nonrheumatic autoimmune conditions
- Our knowledge of the genetics of rheumatic autoimmunity is supported and advanced by geoepidemiology
- The risk of developing these illnesses is also affected by environmental factors, such as socioeconomic status and exposure to infectious agents (protective or pathogenic), ultraviolet radiation and pollution

We have previously published a comprehensive compilation of geoepidemiological findings regarding major, organ-specific autoimmune conditions, namely type 1 diabetes mellitus, multiple sclerosis, autoimmune thyroid disease and inflammatory bowel disease.[1] In the present Review, we focus on several of the major autoimmune and inflammatory rheumatic diseases (AIRDs), namely RA, juvenile RA (JRA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), ankylosing spondylitis (AS) and Sjögren's syndrome (SS). For these six rheumatic conditions, proven and potential causes that might explain the depicted geographies are thoroughly discussed. Challenging methodological issues are presented as well,[22–24] as part of the discussion for each disease.

Rheumatoid arthritis

The prevalence of RA in adult populations from various world regions seems to be relatively uniform, with the prominent exceptions of Australia and Jamaica, where the prevalence is high, and Sub-Saharan Africa, where this disease is rare (Table 1 and Figure 1). Nonetheless, epidemiological patterns demonstrate influences of ethnogenetic, socioeconomic, rural–urban, and infectious factors on disease risk.

Within several regions around the globe, the risk of RA differs between distinct ethnic groups that reside in the same country, which might indicate differences in the genetic predisposition to this disease. For instance, compared with white people in the USA, several Native American tribes (such as Pima North-American Indians) show a markedly higher risk for the development of RA. Conversely, Australian Aboriginals are much more resistant to the disease than Australian white populations.[8,25,26] These differences might reflect ethnic variability in the prevalence of disease susceptibility genes (for example, the *PTPN22* risk allele, which is common in European populations, is rarely found in Asian populations).[13]

In addition to genetic variance, socioeconomic differences clearly affect disease occurrence, as disease rates seem to be generally low in some regions of the developing world. The typical age structure (that is, a high proportion of children and a low proportion of elderly people) of populations that live in deprived conditions and the decreased life expectancy might partly explain the decreased rates of RA reported in these regions.[27] Furthermore, underdiagnosis of AIRDs in such regions—owing to diminished access to medical care, low local medical expertise, and unavailability of new diagnostic procedures—might cause an erroneous reflection of disease occurrence rates, and thus bias comparisons with populations in developed countries (Box 1). In fact, studies in various developing countries, including Indonesia, China, South Africa and Iraq, and among Afro-Europeans, disclose urban–rural gradients (namely higher prevalences of RA in urban compared with rural regions), to such an extent that the rate of RA among urban residents of these populations are nearing or even surpassing those reported in developed countries with predominantly white populations (Figure 1).[27–31]

The association between urban living and the risk of RA might also suggest an environmental influence, which could be related to Western lifestyle and industrialization. For instance, smoking has been associated with RA in genetically susceptible individuals (that is, those who carry the HLA-DRB1 shared epitope).[32]

According to the hygiene hypothesis, the rarity of RA in tropical, rural areas could be explained by protective mechanisms that are induced by endemic parasitic infections (for example, nitric-oxide-mediated immunomodulation).[21] By contrast, on the basis of evidence of cyclical changes in the incidence of RA in the USA over a 40-year period, some experts have speculated that these unique temporal trends could be attributable to variations in the epidemicity of some infections, which supports the hypothesis of an infectious etiology.[33] This seeming contradiction, namely that some infections in certain populations exert protective effects against autoimmune diseases whereas others trigger autoimmunity, is a further manifestation of the complex mosaic of autoimmunity. Indeed, epidemiological studies have implicated the involvement of various infectious agents in the protection against as well as in the pathogenesis of different autoimmune diseases.[34–38]

Studies of juvenile idiopathic arthritis (JIA), a recently devised term that includes both juvenile chronic arthritis (JCA) and JRA, have shown a marked variability in the incidence and prevalence of these conditions. This variability might in part be explained by methodological factors, particularly the differing classification criteria used in clinical studies for the various subgroups of childhood juvenile arthritis.[22]

Nevertheless, a study of a multiethnic Canadian cohort, in which a single set of criteria was used across all groups, revealed that European descent was associated with a markedly increased risk of developing JIA compared with African, Asian or Indian origin. The distribution of JIA subtypes also differed substantially across these ethnic groups.[39] Some studies have raised the possibility that JRA is not rare in Sub-Saharan Africa,[40] unlike adult RA and several other autoimmune conditions.[1] On the other hand, similarly to adult RA, the highest rates of JRA in the world have been documented in Australia (Table 1), which raises the question whether the people of this subcontinent are especially susceptible to this disease. Another similarity between JRA and adult RA is the cyclic incidence pattern of JRA reported in a Canadian province, which suggests

Table 1 | Geographical distribution of autoimmune and inflammatory rheumatic diseases

Disease	Prevalence (annual incidence) per 100,000 in various regions										
	North Am.	Central Am.	South Am.	Northern Eur.*	Southern Eur.*	Western Eur.*	Eastern Eur.*	Middle East	Asia	Sub-Sah. Africa	Austr. & NZ
Adult RA[8,27,28,30,33,45,82–89]	600–1,000 (40)	400–2,000‡	100–500	400–900 (20–40)	200–700 (<20)	500–900 (10–50)	700	200–500 Iraq 1,500§	100–800 (40–90)	Rare‖ 900§	2,000
Juvenile RA and chronic arthritis[8,42,45,90–98]	2–80 (5–14)	32 (7)	N/A	60–80 (7–21)	50 (4)	2–20 (<7)	10–140 (<13)	65	N/A	N/A	Austr. 400 (NZ 3)
SLE[28,45,50,52,61,99–107]	20–50 (1–2)¶ 50–130 (2–7)# Gainesville, GA 1,000**	50–60 (5)‡	(Brazil 9)	20–70¶ (2–7) Afro-Caribb. 100–200#	30–70 (2)	40 (5)	N/A	N/A	20–70 (3)	Rare	20¶; Abor. 80 (11)#
SSc[45,63,108–113]	13–28 (2)¶ Afr. Am. 32# Choctaw Ind. 66#	N/A	N/A	<10 (<1)	10–30 (<2)	15¶ 21#	N/A	N/A	<10	N/A	23 (2)
AS[28,45,72,74,76,78,80,114–118]	130 (7)¶ Afr. Am. 50# Am. Ind. 4,500#	N/A	N/A	150–400 (7–9) Troms, Norway 1,100–1,400**	30 (<2)	100–850	N/A	500	10–240 (Japan <1)	Rare	N/A
SS[23,28,45,119–125]	320 (4)	N/A	N/A	200–3,000	200–600 (4–5)	N/A	N/A	N/A	India rare China 330–700	N/A	N/A

*European regions are divided according to the United Nation's geoscheme created by the United Nation's Statistics Division. ‡Values for the Caribbean. §Urban population. ‖Rural population. ¶White people. #Non-white people. **Hot spot'. Abbreviations: Abor., Aboriginals; Afr., African; Am., America; AS, ankylosing spondylitis; Austr., Australia; Caribb., Caribbean; Eur., Europe; Ind., Indian; N/A, not available; NZ, New Zealand; RA, rheumatoid arthritis; SS, Sjögren's syndrome; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; Sub-Sah., Sub-Saharan.

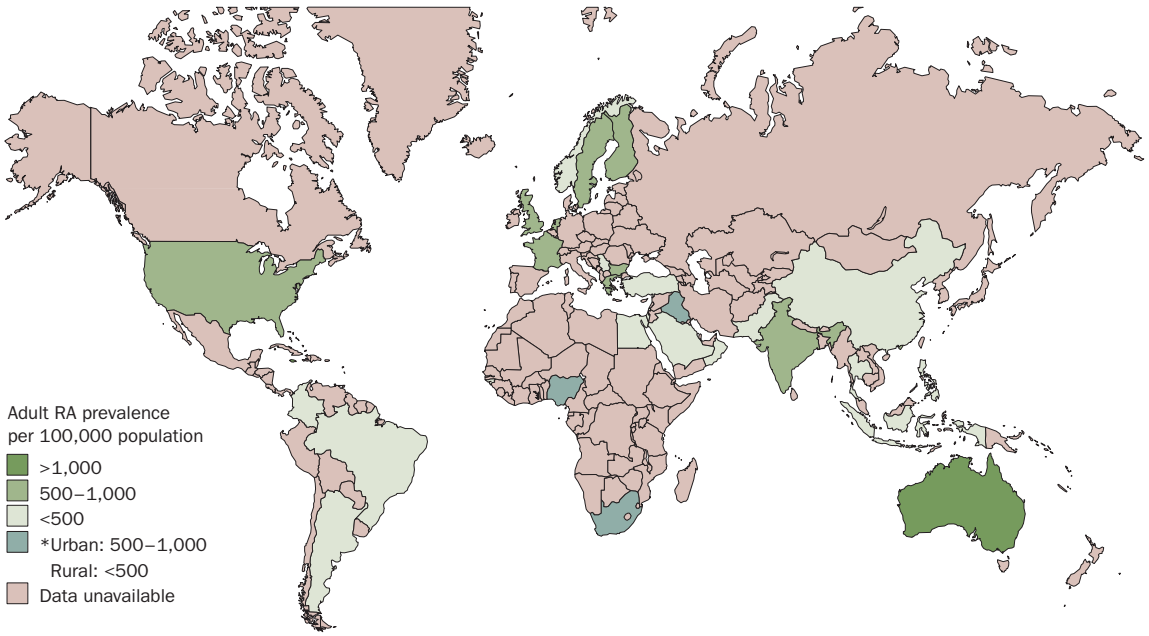

Figure 1 | Prevalence of rheumatoid arthritis in the adult population of various world regions. Abbreviation: RA, rheumatoid arthritis.

an infectious trigger. In fact, the peaks of JRA outbreaks remarkably correlated with the increases in the number of *Mycoplasma pneumoniae* infections detected in the province during the same years.[41]

Secular trends in the incidence of adult and juvenile-onset RA reveal progressively declining rates over the past four decades in various populations.[33,42–44] Interestingly, the data on several other autoimmune diseases (such as type 1 diabetes mellitus and SLE) disclose inverse patterns, namely increasing rates over the past few decades.[1,7] Nonetheless, any relatively rapid change in disease rates indicates an environmental effect, as genetic determinants are unlikely to alter disease rates within such short intervals. Taken together, both genetic and

Box 1 | Methodological limitations entailed in geoepidemiology

The task of comparing epidemiological data across diverse world regions brings about methodological challenges.

Temporal considerations
Diagnostic advances, modifications to disease criteria, changing methodological standards, improved standard of living and health care resources, and actual trends in disease rates are examples of temporal bias that can arise when comparing regions in which epidemiological data has been collected at disparate times. This discrepancy is especially critical in cases where there is a lack of up-to-date data in particular regions.

Socioeconomic factors
Access to medical care, medical expertise, availability of new diagnostic procedures, degree of public awareness, and investigators' resources can vary between developed and developing world regions, and can bias comparisons of data from these areas.

Epidemiological methodology
Comparing data derived from community-based studies versus hospital-based or clinical case studies (with inherent differences in case ascertainment), and comparing data derived from large versus small epidemiological investigations (which might be subject to chance fluctuation), constitute major biases when comparing different studies.

environmental factors should be considered in order to understand the geoepidemiology of RA.

Systemic lupus erythematosus

The global distribution of SLE is relatively homogenous, with the exceptions of some regions of Africa where its rate is low, and Brazil, where its rate is relatively high (Table 1). Nevertheless, the geoepidemiology of this disease demonstrates ethnic variance, which might be explained by genetic susceptibility as well as environmental factors, including exposure to infectious agents (protective or pathogenic), ultraviolet radiation and environmental pollution.

Ethnogenetic variation in the risk of SLE can be observed between distinct ethnic groups that live in the same geographical region. Compared with white people, people of Chinese descent seem to be at a slightly higher risk, and North American Indians and Australian Aboriginals are exceptionally susceptible to SLE.[20,45–50] Ethnic background determines not only the risk of developing SLE, but also the clinical course and outcome of the disease. Findings from the ongoing LUMINA (Lupus in Minorities: Nature versus Nurture) study,[5] which is conducted by the NIH, reveal that African American and Hispanic American patients with SLE tend to develop the disease earlier in life, present with more-severe symptoms at the time of diagnosis, and have more-severe disease overall than white patients. African American and white women differ in terms of their ages at menarche, menstrual cycle patterns, birth rates, and patterns of oral contraceptive and menopausal hormone use,[51] all of which exert differential exposure to estrogens. Thus, exposure to estrogens might be one of the ethnicity-dependant factors that affect SLE manifestations.

Although SLE is considered to be rare in West Africa, people of West African and Afro-Caribbean descent (these populations are considered to be genetically related) who live in Europe or the USA have a markedly higher disease risk when compared with European or American white people.[20,40,52,53] An elevated risk was also documented in West Africans who have only recently migrated from their homeland,[52] which might demonstrate that this population's predisposition to SLE has been dormant until the introduction of a new physical environment or cultural setting.

As in the case of RA, the existence of an environmental selective pressure against SLE in Africa has been postulated. According to this hypothesis, exposure to malaria and numerous other parasitic infections renders Africans who live in endemic conditions more resistant to certain autoimmune diseases than other populations.[21,53] Plausibly, when Africans migrate to a nonendemic environment and abandon their native, protective conditions, they might not only lose this selective advantage, but in fact manifest an innate disadvantage compared with white people who have adapted to live in relatively 'parasite-free' conditions.[21] According to an alternative hypothesis, antimalarial drugs that are commonly used in Africa (such as chloroquine) are also efficient for treating and delaying SLE, and cessation of the use of such drugs upon migration to nonendemic regions might materialize the predisposition of this population to this disease.[54]

Another environmental factor that might explain the reduced resistance of people from Africa who live in Europe or the USA is their reduced exposure to sunlight compared with those who live closer to the Equator. The decreased penetration of ultraviolet rays through the skin in these individuals could result in critically reduced levels of vitamin D, a hormone that is known to have an important immunomodulatory role.[55–57]

Smoking, which has been associated with an increased risk of SLE as well as of RA in genetically susceptible individuals, offers another possibility of a risk factor related to Western culture.[58] Taken together, Africans who migrate far away from their native environmental and cultural conditions seem to have an increased susceptibility to SLE, which might be attributable to gene–environment interactions.

The role of the environment in determining the epidemiology of SLE is further attested by the observation that lack of access to piped water during childhood is a risk factor for this disease in some ethnic groups.[59] This observation suggests that poor hygiene and possibly the exposure to certain infectious agents (particularly viruses and bacteria) in early life could lead to susceptibility to, rather than protection against, SLE, as was suggested in the case of parasitic infections in African populations.[34,38] The contrasting roles of infections revealed by geoepidemiological studies of SLE is also supported by clinical findings.[60]

Industrial pollution was also associated with SLE in two US hot spots, namely Nogales, AZ, and Gainesville, GA, where the highest disease prevalences (up to 1,000 per 100,000 people) have ever been documented.[15,61] The results of both studies, however, should be interpreted with caution. The Gainesville study's extraordinary

prevalence rates were based on a modest-sized survey (that is, data from 300 individuals), and in Nogales, an investigation led by the Centers for Disease Control and Prevention failed to detect a difference in the presence of environmental pollutants in patients with SLE compared with control individuals who resided in the same community. Nonetheless, findings of animal and *in vitro* studies, and several reports that linked occupational exposures, such as silica dust, mercury, pesticides and solvents metals, to an increased risk of SLE, also indicate industrial pollution as a potential risk factor.[62]

In conclusion, whereas the global distribution of SLE seems to be relatively homogenous, an intricate interplay of various genetic and environmental factors might influence the risk of this disease.

Systemic sclerosis

Geoepidemiological studies of SSc reveal a higher frequency of this condition in the USA and Australia than in continental Europe, the UK, and some regions of Asia (Table 1). Within Europe, a general north–south gradient is evident: rates are lower in Northern Europe (Figure 2).[63] Interestingly, an inverse gradient can be observed in the distribution of other autoimmune conditions, such as type 1 diabetes mellitus, multiple sclerosis, and inflammatory bowel disease: the rates of these diseases seem to increase with distance from the Equator.[1,6,7,57,64] However, the relatively high rates of SSc in North America and Australia are comparable to the gradients observed in the distribution of the above mentioned conditions and are not compatible with the inverse pattern suggested for Europe. Thus, the suggested north–south gradient within Europe should be further investigated in order to establish whether this pattern is simply attributable to chance variability.

In the case of SSc, various sources indicate ethnic variability in disease risk. In general, higher incidence, prevalence and mortality rates have been reported in African American populations compared with white populations. Furthermore, African Americans have an increased risk of having anti SCL-70 autoantibodies, and an increased predisposition to the diffuse form of SSc.[65,66] Other ethnic groups, such as Choctaw Indians in Oklahoma, USA, seem to have an exceptionally high risk of developing SSc.[45] In fact, potential susceptibility genes for this condition were mapped on the basis of the observation that Choctaw Indians exhibit considerable linkage disequilibria in a number of regions of the genome.[14,67,68]

Discoveries of two SSc hot spots have yielded interesting hypotheses pertaining to causal factors; one of these hypotheses suggests genetic predisposition whereas the other discloses environmental hazards. In a rural province near Rome, a 1,000-fold increase was found in the prevalence of SSc compared with other regions of Italy.[69] In the population of this province, high frequencies of specific HLA haplotypes were observed compared with healthy individuals from other villages. This finding suggests a relatively homogenous genetic background of these inhabitants that might confer disease susceptibility, although these haplotypes are not known to be disease-associated.[69] Spatial clustering of SSc cases has also been recorded in three areas of London, UK. Of note, all three hot spots are in close proximity to major airports, which has been suggested to be an environmental trigger.[16] Indeed, certain environmental pollutants (such as trichloroethylene and silica) have been implicated in the pathogenesis of SSc.[5]

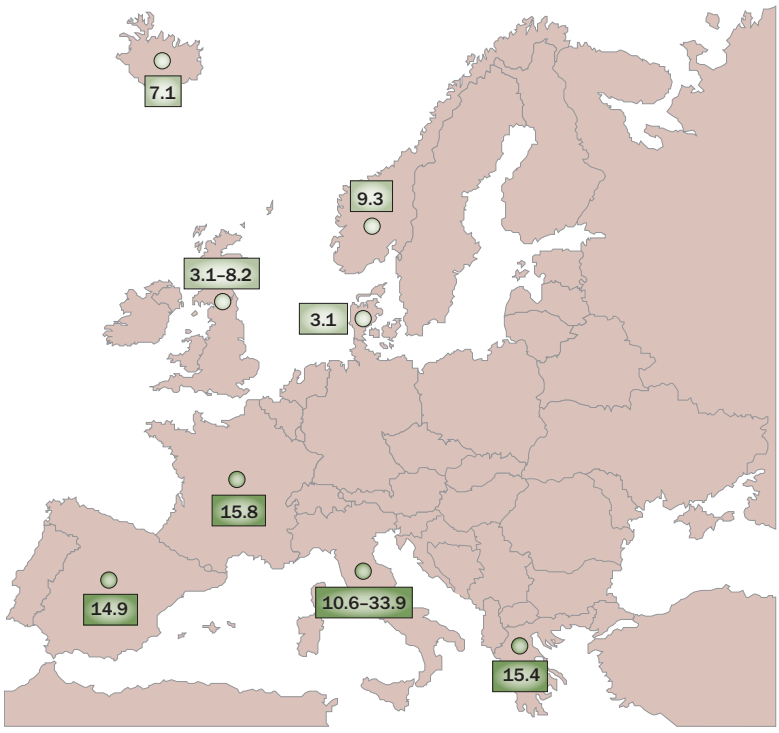

Figure 2 | Prevalence rates of systemic sclerosis per 100,000 people in various European countries. Note the general increase in the prevalence moving from Northern to Southern European regions.

Overall, geoepidemiological studies of SSc underscore ethnogenetic determinants of disease risk on one hand, and possible unique environmental triggers on the other hand.

Ankylosing spondylitis

The geographic distribution of AS clearly demonstrates the existence of a genetic predisposition to AIRDs. The prevalence of HLA-B27, a well-known disease-associated haplotype, parallels the global gradients of AS rates (Table 1, Figure 3). Populations with a high percentage of HLA-B27 carriers, such as North American Pima Indians, Alaskan Eskimos and Northern Norway Laps, have the highest disease frequencies. Similar rates of AS were reported among Americans, Europeans and other ethnic groups (for example Han Chinese) that have similar HLA-B27 status. Populations with a low frequency of HLA-B27 (for example Japanese people) demonstrate the lowest frequencies of AS.[28,45,70–75]

AS is less frequent among African Americans compared with white people in the USA and is also considered to be rare in Sub-Saharan Africa (Figure 3), suggested to reflect the low prevalence of HLA-B27 in African populations.[76–78] However, this hypothesis has been partly challenged by data concerning a particular West African population

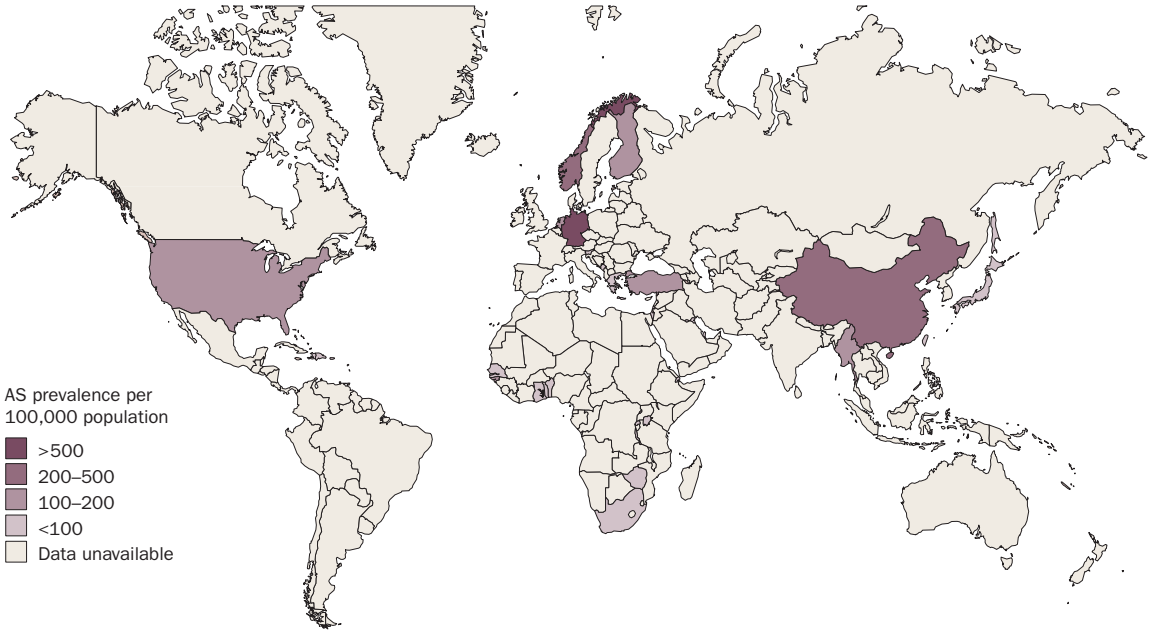

Figure 3 | Prevalence of ankylosing spondylitis in various world regions. Abbreviation: AS, ankylosing spondylitis.

where AS was rare but the frequency of HLA-B27 was found to be similar to that in most white populations.[79] This observation joins previous evidence from the USA, where it was shown that, among HLA-B27-positive individuals, the relative risk of developing AS was markedly lower in African Americans than in white people.[80]

Taken together, three possible explanations exist for the relative lack of association between HLA-B27 and AS among West Africans and African Americans. First, additional genetic susceptibility factors (other than HLA-B27), which are not present in these African populations, might also confer a risk for this condition. Second, ethnic variability could be explained by environmental modulators. Finally, an interaction of environmental and genetic factors might have a protective effect against AS in African populations. The hypothesis that malaria infection affects gene selection offers a unique mechanism that demonstrates a fascinating interplay between genetic and environmental factors, and its influence on the risk of AIRDs. This hypothesis is based on the observation that several allelic polymorphisms of HLA-B27 that are not associated with disease risk (for example HLA-B*2703) are found in areas where malaria is endemic (such as West Africa). According to this hypothesis, the genetic subtypes associated with a low risk of AS were positively selected over high-risk subtypes owing to their protective effect against *Plasmodium falciparum*, the pathogen that causes malaria, which is endemic to these regions.[12] Hence, the geoepidemiology of AS might demonstrate a reciprocal relationship between genes and exposure to certain infections that confer protection against autoimmunity.

In conclusion, AS might be the AIRD that most clearly demonstrates the ethnogenetic determinants of the gradients of these conditions. Moreover, studies of this disease put forward a unique mechanism of the reciprocal modulating effects of genetic and environmental factors.

Sjögren's syndrome

Wide variability has been reported in the prevalence of SS in different countries and in various regions of certain countries, which might result from several methodological issues. In the studies from which these data were derived, five different sets of criteria were used for disease classification, which resulted in up to 10-fold differences between the inclusion rates used in various studies, and the methods used for the objective testing of lacrymal and salivary gland function were also inconsistent.[23,24,81]

The geoepidemiology of this disease is difficult to decipher, mostly because of the paucity of epidemiological data from regions outside of Europe and North America. Nevertheless, the existing data (Table 1) suggest that the highest rates of SS are reported in Northern Europe, the rates in North America and mainland Europe seem to be comparable, and the lowest rates are observed in some parts of Asia.

Conclusions

A thorough analysis of the epidemiological reports that are summarized in this Review clearly shows a general paucity of reliable and up-to-date data on the incidence and prevalence of AIRDs. Most available data are derived from small, scattered epidemiological investigations with various methodological discrepancies (Box 1). Data are especially scarce for SS, SSc and AS, particularly for regions outside of the USA and Europe. Nonetheless, the strength of this Review is most probably 'in numbers'. The overview of numerous reports from as many geographical regions as possible provides a relatively lucid overall picture of the distribution of AIRDs (Table 1). Unlike the data available for nonrheumatic autoimmune diseases, which clearly show that the highest rates for such conditions are found in predominantly white, industrial populations,[1] AIRDs seem to be relatively ubiquitous. Africa seems to be a remarkable exception,

as the rheumatic conditions for which solid data exist (namely, RA, SLE and AS) are all reported to be rare in Sub-Saharan Africa. The epidemiological evidence strongly supports the genetic underpinning of AIRDs. In fact, in case of some conditions (such as SSc), geoepidemiology spurred clinical and laboratory research, which subsequently led to advances in our knowledge of the genetic factors underlying rheumatic conditions. Finally, evidence from studies of migrant populations, recognitions of rheumatic disease hot spots, and recordings of temporal phenomena and secular trends underscore the modulating role of lifestyle and environmental factors in determining the risk of AIRDs.

Although most environmental risk factors have been identified in associational (observational) studies, the accumulated data imply that the associations between AIRDs and lifestyle and environmental factors, such as exposure to environmental pollutants, certain infections, ultraviolet radiation and living in hygienic conditions, should be seriously considered. As most of the hypotheses presented here regarding the specific roles of genetic and environmental factors are yet to be established in terms of causal relationships, multinational, epidemiological collaborations, with a special emphasis on guidelines for judging causality, are warranted.

Review criteria

A MEDLINE search was conducted for articles published between 1965 and 2009, using the key words "rheumatoid arthritis", "juvenile rheumatoid arthritis", "systemic lupus erythematosus", "systemic sclerosis", "ankylosing spondylitis", "Sjögren's syndrome", "geo-epidemiology", "geography", "distribution", "global burden", "latitude", "incidence", "prevalence", "genetics", "risk factors", "infection" and "environment", in combination with the names of specific world regions and countries. Bibliographies of reviewed articles and databases of major health organizations (such as WHO and NIH) were also searched. Rates chosen for presentation in this Review were the most recent available for each geographical region. However, under specific circumstances, studies from previous years were incorporated.

1. Shapira, Y., Agmon-Levin, N. & Shoenfeld, Y. Defining and analyzing geoepidemiology and human autoimmunity. *J. Autoimmun.* **34**, J168–J177 (2010).
2. Shoenfeld, Y., Selmi, C., Zimlichman, E. & Gershwin, M. E. The autoimmunologist: geoepidemiology, a new center of gravity, and prime time for autoimmunity. *J. Autoimmun.* **31**, 325–330 (2008).
3. Cooper, G. S. & Stroehla, B. C. The epidemiology of autoimmune diseases. *Autoimmun. Rev.* **2**, 119–125 (2003).
4. Eaton, W. W., Rose, N. R., Kalaydjian, A., Pedersen, M. G. & Mortensen, P. B. Epidemiology of autoimmune diseases in Denmark. *J. Autoimmun.* **29**, 1–9 (2007).
5. NIH Autoimmune Diseases Coordinating Committee. *Progress in Autoimmune Diseases Research (*National Institutes of Health, Bethesda, 2005).
6. WHO. *Atlas—Multiple Sclerosis Resources in the World* (WHO, Geneva, 2008).
7. DIAMOND Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990–1999. *Diabet. Med.* **23**, 857–866 (2006).
8. Symmons, D., Mathers, C. & Pfleger, B. Global Burden of Disease 2000: the global burden of rheumatoid arthritis in the year 2000 (WHO, Geneva, 2000).
9. Jacobson, D. L., Gange, S. J., Rose, N. R. & Graham, N. M. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin. Immunol. Immunopathol.* **84**, 223–243 (1997).
10. Gregersen, P. K. & Olsson, L. Recent advances in the genetics of autoimmune disease. *Annu. Rev. Immunol.* **27**, 363–391 (2009).
11. Rønningen, K. S., Keiding, N. & Green, A.; EURODIAB ACE Study Group. Correlations between the incidence of childhood-onset type I diabetes in Europe and HLA genotypes. *Diabetologia* **44**, 51–59 (2001).
12. Mathieu, A. *et al.* The interplay between the geographic distribution of HLA-B27 alleles and their role in infectious and autoimmune disease: A unifying hypothesis. *Autoimmun. Rev.* **8**, 420–425 (2009).
13. Kochi, Y., Suzuki, A., Yamada, R. & Yamamoto, K. Genetics of rheumatoid arthritis: underlying evidence of ethnic differences. *J. Autoimmun.* **32**, 158–162 (2009).
14. Zhou, X. *et al.* Genome-wide association study for regions of systemic sclerosis susceptibility in a Choctaw Indian population with high disease prevalence. *Arthritis Rheum.* **48**, 2585–2592 (2003).
15. Balluz, L. *et al.* Investigation of systemic lupus erythematosus in Nogales, Arizona. *Am. J. Epidemiol.* **154**, 1029–1036 (2001).
16. Silman, A. J., Howard, Y., Hicklin, A. J. & Black, C. Geographical clustering of scleroderma in south and west London. *Br. J. Rheumatol*. **29**, 93–96 (1990).
17. Shoenfeld, Y. *et al.* The mosaic of autoimmunity: genetic factors involved in autoimmune diseases. *Isr. Med. Assoc. J.* **10**, 3–7 (2008).
18. Shoenfeld, Y. *et al.* The mosaic of autoimmunity: hormonal and environmental factors involved in autoimmune diseases. *Isr. Med. Assoc. J.* **10**, 8–12 (2008).
19. Hewagama, A. & Richardson, B. The genetics and epigenetics of autoimmune diseases. *J. Autoimmun.* **33**, 3–11 (2009).
20. Hopkinson, N. D., Doherty, M. & Powell, R. J. Clinical features and race specific incidence/ prevalence rates of systemic lupus erythematosus in a geographically complete cohort of patients. *Ann. Rheum. Dis.* **53**, 675–680 (1994).
21. Clark, I. A., Al-Yaman, F. M., Cowden, W. B. & Rockett, K. A. Does malarial tolerance, through nitric oxide, explain the low incidence of autoimmune disease in tropical Africa? *Lancet* **348**, 1492–1494 (1996).
22. Manners, P. J. & Bower, C. Worldwide prevalence of juvenile arthritis—why does it vary so much? *J. Rheumatol.* **29**, 1520–1530 (2002).
23. Fox, R. I. Epidemiology, pathogenesis, animal models, and treatment of Sjögren's syndrome. *Curr. Opin. Rheumatol.* **6**, 501–508 (1994).
24. Vinagre, F., Santos, M. J., Prata, A., da Silva, J. C. & Santos, A. I. Assessment of salivary gland function in Sjögren's syndrome: the role of salivary gland scintigraphy. *Autoimmun. Rev.* **8**, 672–676 (2009).
25. Minaur, N., Sawyers, S., Parker, J. & Darmawan, J. Rheumatic disease in an Australian Aboriginal community in North Queensland, Australia. A WHO-ILAR COPCORD survey. *J. Rheumatol.* **31**, 965–972 (2004).
26. Silman, A. J. *et al.* Absence of rheumatoid arthritis in a Nigerian population. *J. Rheumatol.* **20**, 618–622 (1993).
27. Darmawan, J., Muirden, K. D., Valkenburg, H. A. & Wigley, R. D. The epidemiology of rheumatoid arthritis in Indonesia. *Br. J. Rheumatol.* **32**, 537–540 (1993).
28. Zeng, Q. Y. *et al.* Rheumatic diseases in China. *Arthritis Res. Ther.* **10**, R17 (2008).
29. Kalla, A. A. Rheumatoid arthritis in the developing world. *Best Pract. Res. Clin. Rheumatol.* **17**, 863–875 (2003).
30. Al Rawi, Z. S., Alazzawi, A. J., Alajili, F. M. & Alwakil, R. Rheumatoid arthritis in population samples in Iraq. *Ann. Rheum. Dis.* **37**, 73–75 (1978).
31. Solomon, L., Robin, G. & Valkenburg, H. A. Rheumatoid arthritis in an urban South African Negro population. *Ann. Rheum. Dis.* **34**, 128–135 (1975).
32. Bang, S. Y. *et al.* Smoking increases rheumatoid arthritis susceptibility in individuals carrying the HLA-DRB1 shared epitope, regardless of rheumatoid factor or anti-cyclic citrullinated peptide antibody status. *Arthritis Rheum.* **62**, 369–377 (2010).
33. Doran, M. F., Pond, G. R., Crowson, C. S., O'Fallon, W. M. & Gabriel, S. E. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. *Arthritis Rheum.* **46**, 625–631 (2002).
34. Kivity, S., Agmon-Levin, N., Blank, M. & Shoenfeld, Y. Infections and autoimmunity—friends or foes? *Trends Immunol.* **30**, 409–414 (2009).
35. Lidar, M. *et al.* Infectious serologies and autoantibodies in inflammatory bowel disease: Insinuations at a true pathogenic role. *Ann. NY Acad. Sci.* **1173**, 640–648 (2009).

36. Ram, M. *et al.* The putative protective role of hepatitis B virus (HBV) infection from autoimmune disorders. *Autoimmun. Rev.* **7**, 621–625 (2008).
37. Agmon-Levin, N. *et al.* Prevalence of hepatitis C serum antibody in autoimmune diseases. *J. Autoimmun.* **32**, 261–266 (2009).
38. Zandman-Goddard, G. *et al.* Neuropsychiatric lupus and infectious triggers. *Lupus* **17**, 380–384 (2008).
39. Saurenmann, R. K. *et al.* Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. *Arthritis Rheum.* **56**, 1974–1984 (2007).
40. McGill, P. E. & Oyoo, G. O. Rheumatic disorders in sub-Saharan Africa. *East Afr. Med. J.* **79**, 214–216 (2002).
41. Oen, K., Fast, M. & Postl, B. Epidemiology of juvenile rheumatoid arthritis in Manitoba, Canada, 1975–92: cycles in incidence. *J. Rheumatol*. **22**, 745–750 (1995).
42. Peterson, L. S., Mason, T., Nelson, A. M., O'Fallon, W. M. & Gabriel, S. E. Juvenile rheumatoid arthritis in Rochester, Minnesota 1960–1993. Is the epidemiology changing? *Arthritis Rheum.* **39**, 1385–1390 (1996).
43. Enzer, I. *et al.* An epidemiologic study of trends in prevalence of rheumatoid factor seropositivity in Pima Indians: evidence of a decline due to both secular and birth-cohort influences. *Arthritis Rheum.* **46**, 1729–1734 (2002).
44. Kaipiainen-Seppanen, O. & Savolainen, A. Changes in the incidence of juvenile rheumatoid arthritis in Finland. *Rheumatology (Oxford)* **40**, 928–932 (2001).
45. Helmick, C. G. *et al.* Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum.* **58**, 15–25 (2008).
46. Samanta, A., Feehally, J., Roy, S. & Nichol, F. E. High prevalence of systemic disease and mortality in Asian subjects with systemic lupus erythematosus. *Ann. Rheum. Dis.* **50**, 490–492 (1991).
47. Maskarinec, G. & Katz, A. R. Prevalence of systemic lupus erythematosus in Hawaii: is there a difference between ethnic groups? *Hawaii Med. J.* **54**, 406–409 (1995).
49. Seagasothy, M. & Phillips, P. A. Systemic lupus erythematosus in Aborigines and Caucasians in central Australia: a comparative study. *Lupus* **10**, 439–444 (2001).
50. Peschken, C. A. & Esdaile, J. M. Systemic lupus erythematosus in North American Indians: a population based study. *J. Rheumatol.* **27**, 1884–1891 (2000).
51. Bernstein, L., Teal, C. R., Joslyn, S. & Wilson, J. Ethnicity-related variation in breast cancer risk factors. *Cancer* **97** (Suppl.), 222–229 (2003).
52. Molokhia, M., McKeigue, P. M., Cuadrado, M. & Hughes, G. Systemic lupus erythematosus in migrants from west Africa compared with Afro-Caribbean people in the UK. *Lancet* **357**, 1414–1415 (2001).
53. Bae, S., Fraser, P. & Liang, M. H. The epidemiology of systemic lupus erythematosus in populations of African ancestry. *Arthritis Rheum.* **41**, 2091–2099 (1998).
54. Westlake, S. L. & Edwards, C. J. Anti-malarials and lupus in West Africa use and lupus in Africans. *Lupus* **18**, 193–195 (2009).
55. Shoenfeld, N., Amital, H. & Shoenfeld, Y. The effect of melanism and vitamin D synthesis on the incidence of autoimmune disease. *Nat. Clin. Pract. Rheumatol.* **5**, 99–105 (2009).
56. Shapira, Y., Agmon-Levin, N. & Shoenfeld, Y. Mycobacterium tuberculosis, autoimmunity and vitamin D. *Clin. Rev. Allergy Immunol.* **38**, 169–177 (2010).
57. Ponsonby, A. L., McMichael, A. & van der Mei, I. Ultraviolet radiation and autoimmune disease: insights from epidemiological research. *Toxicology* **181–182**, 71–78 (2002).
58. Kiyohara, C. *et al.* Cigarette smoking, N-acetyltransferase 2 polymorphisms and systemic lupus erythematosus in a Japanese population. *Lupus* **18**, 630–638 (2009).
59. Molokhia, M. & McKeigue, P. Systemic lupus erythematosus: genes versus environment in high risk populations. *Lupus* **15**, 827–832 (2006).
60. Berkun, Y. *et al.* Infectious antibodies in systemic lupus erythematosus patients. *Lupus* **18**, 1129–1135 (2009).
61. Kardestuncer, T. & Frumkin, H. Systemic lupus erythematosus in relation to environmental pollution: an investigation in an African-American community in North Georgia. *Arch. Environ. Health* **52**, 85–90 (1997).
62. Parks, C. G. & Cooper, G. S. Occupational exposures and risk of systemic lupus erythematosus: a review of the evidence and exposure assessment methods in population- and clinic-based studies. *Lupus* **15**, 728–736 (2006).
63. Chifflot, H., Fautrel, B., Sordet, C., Chatelus, E. & Sibilia, J. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin. Arthritis Rheum.* **37**, 223–235 (2008).
64. Shivananda, S. *et al.* Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* **39**, 690–697 (1996).
65. Mayes, M. D. *et al.* Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum.* **48**, 2246–2255 (2003).
66. Laing, T. J. *et al.* Racial differences in scleroderma among women in Michigan. *Arthritis Rheum.* **40**, 734–742 (1997).
67. Tan, F. K. *et al.* HLA haplotypes and microsatellite polymorphisms in and around the major histocompatibility complex region in a Native American population with a high prevalence of scleroderma (systemic sclerosis). *Tissue Antigens* **53**, 74–80 (1999).
68. Tan, F. K. *et al.* Association of fibrillin 1 single-nucleotide polymorphism haplotypes with systemic sclerosis in Choctaw and Japanese populations. *Arthritis Rheum.* **44**, 893–901 (2001).
69. Valesini, G., Litta, A. & Bonavita, M. S. Geographical clustering of scleroderma in a rural area in the province of Rome. *Clin. Exp. Rheumatol.* **11**, 41–47 (1993).
70. Van der Linden, S. M., Valkenburg, H. A., de Jongh, B. M. & Cats, A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals: a comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum.* **27**, 241–249 (1984).
71. Hukuda, S. *et al.* Spondyloarthropathies in Japan: nationwide questionnaire survey performed by the Japan Ankylosing Spondylitis Society. *J. Rheumatol.* **28**, 554–559 (2001).
72. Khan, M. A. Spondyloarthropathies in non-Caucasian populations of the world. In *Advances in Inflammation Research. Vol. 9: the Spondyloarthropathies* (eds Ziff, M. & Cohen, S. B.) 91–99 (Raven Press, New York, (1985).
73. Gofton, J. P., Bennett, P. H., Smythe, H. A. & Decker, J. L. Sacroilitis and ankylosing spondylitis in North American Indians. *Ann. Rheum. Dis.* **31**, 474–481 (1972).
74. Boyer, G. S. *et al.* Prevalence of spondyloarthropathies in Alaskan Eskimos. *J. Rheumatol.* **21**, 2292–2297 (1994).
75. Braun, J., Bollow, M. & Remlinger, G. Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum.* **41**, 58–67 (1998).
76. Mijiyawa, M., Oniankitan, O. & Khan, M. A. Spondyloarthropathies in sub-Saharan Africa. *Curr. Opin. Rheumatol.* **12**, 281–286 (2000).
77. Baum, J. & Ziff, M. The rarity of ankylosing spondylitis in the black race. *Arthritis Rheum.* **14**, 12–18 (1971).
78. Hill, A. V. *et al.* HLA class I typing by PCR: HLA-B27 and an African B27 subtype. *Lancet* **337**, 640–642 (1991).
79. Brown, M. A. *et al.* Ankylosing spondylitis in West Africans—evidence for a non-HLA-B27 protective effect. *Ann. Rheum. Dis.* **56**, 68–70 (1997).
80. Khan, M. A. *et al.* HLA-B27 in ankylosing spondylitis: differences in frequency and relative risk in American blacks and Caucasians. *J. Rheumatol.* **3** (Suppl.), 39–43 (1977).
81. Silman, A. J. & Rooney, B. K. Epidemiology of Sjögren's syndrome. In *The 100-year Anniversary of Henrik Sjögren* (eds Eriksson, E. & Jonsson, R.) 53–57 (Hygiea, Jönköping, 1999).
82. Alamanosa, Y. & Drosos, A. A. Epidemiology of adult rheumatoid arthritis. *Autoimmun. Rev.* **4**, 130–136 (2005).
83. Symmons, D. *et al.* The prevalence of rheumatoid arthritis in the United Kingdom; new estimates for a new century. *Rheumatology (Oxford)* **41**, 793–800 (2002).
84. Stojanovic, R., Vlajinac, H., Palic-Obradovic, D., Janosevic, S. & Adanja, B. Prevalence of rheumatoid arthritis in Belgrade, Yugoslavia. *Br. J. Rheumatol.* **37**, 729–732 (1998).
85. Shichikawa, K. *et al.* Changes in the incidence and prevalence of rheumatoid arthritis in Kamitonda, Wakayama, Japan, 1965–1996. *Ann. Rheum. Dis.* **58**, 751–756 (1999).
86. Spindler, A. *et al.* Prevalence of rheumatoid arthritis in Tucuman, Argentina. *J. Rheumatol.* **29**, 1166–1170 (2002).
87. Simonsson, M., Bergman, S., Jacobsson, L. T., Petersson, I. F. & Svensson, B. The prevalence of rheumatoid arthritis in Sweden. *Scand. J. Rheumatol.* **28**, 340–343 (1999).
88. Riise, T., Jacobsen, B. K. & Gran, J. T. Incidence and prevalence of rheumatoid arthritis in the county of Troms, northern Norway. *J. Rheumatol.* **27**, 1386–1389 (2000).
89. Drosos, A. A. *et al.* Epidemiology of adult rheumatoid arthritis in northwest Greece 1987–1995. *J. Rheumatol.* **24**, 2129–2133 (1997).
90. Arguedas, O., Fasth, A., Andersson-Gäre, B. & Porras, O. Juvenile chronic arthritis in urban San José, Costa Rica: a 2 year prospective study. *J. Rheumatol.* **25**, 1844–1850 (1998).
91. Pruunsild, C. *et al.* Prevalence and short-term outcome of juvenile idiopathic arthritis: a population-based study in Estonia. *Clin. Exp. Rheumatol.* **25**, 649–653 (2007).
92. Martínez Mengual, L., Fernández Menéndez, J. M. & Solís Sánchez, G. Epidemiological study of juvenile idiopathic arthtitis in the last sixteen years in Asturias (Spain). *An. Pediatr.* **66**, 24–30 (2007).
93. Hanova, P., Pavelka, K., Dostal, C., Holcatova, I. & Pikhart, H. Epidemiology of rheumatoid arthritis, juvenile idiopathic arthritis and gout in two regions of the Czech Republic in a descriptive population-based survey in 2002–2003. *Clin. Exp. Rheumatol.* **24**, 499–507 (2006).

94. Danner, S. et al. Epidemiology of juvenile idiopathic arthritis in Alsace, France. *J. Rheumatol.* **33**, 1377–1381 (2006).
95. von Koskull, S., Truckenbrodt, H., Holle, R. & Hörmann, A. Incidence and prevalence of juvenile arthritis in an urban population of southern Germany: a prospective study. *Ann. Rheum. Dis.* **60**, 940–945 (2001).
96. Manners, P. J. & Diepeveen, D. A. Prevalence of juvenile chronic arthritis in a population of 12-year-old children in urban Australia. *Pediatrics* **98**, 84–90 (1996).
97. Gare, B. A. & Fasth, A. Epidemiology of juvenile chronic arthritis in southwestern Sweden: a 5-year prospective population study. *Pediatrics* **90**, 950–958 (1992).
98. Oen, K. G. & Cheang, M. Epidemiology of chronic arthritis in childhood. *Semin. Arthritis Rheum.* **26**, 575–591 (1996).
99. Gudmundsson, S. & Steinsson, K. Systemic lupus erythematosus in Iceland 1975 through 1984. A nationwide epidemiological study in an unselected population. *J. Rheumatol.* **17**, 1162–1167 (1990).
100. Voss, A., Green, A. & Junker, P. Systemic lupus erythematosus in Denmark: clinical and epidemiological characterization of a county-based cohort. *Scand. J. Rheumatol.* **27**, 98–105 (1998).
101. Nossent, J. C. Systemic lupus erythematosus on the Caribbean island of Curaçao: an epidemiological investigation. *Ann. Rheum. Dis.* **51**, 1197–1201 (1992).
102. Nossent, H. C. Systemic lupus erythematosus in the Arctic region of Norway. *J. Rheumatol.* **28**, 539–546 (2001).
103. Vilar, M. J. & Sato, E. I. Estimating the incidence of systemic lupus erythematosus in a tropical region (Natal, Brazil). *Lupus* **11**, 528–532 (2002).
104. Lopez, P., Mozo, L., Gutierrez, C. & Suarez, A. Epidemiology of systemic lupus erythematosus in a northern Spanish population: gender and age influence on immunological features. *Lupus* **12**, 860–865 (2003).
105. Deligny, C. *et al.* Systemic lupus erythematosus in Martinique: an epidemiologic study. *Rev. Med. Interne* **23**, 21–29 (2002).
106. Somers, E. C., Thomas, S. L., Smeeth, L., Schoonen, W. M. & Hall, A. J. Incidence of systemic lupus erythematosus in the United Kingdom, 1990–1999. *Arthritis Rheum.* **57**, 612–618 (2007).
107. Michelle, P. Epidemiology of systemic lupus erythematosus. *Best Pract. Res. Clin. Rheumatol.* **16**, 847–858 (2002).
108. Arias-Nuñez, M. C. *et al.* Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. *Medicine* **87**, 272–280 (2008).
109. Roberts-Thomson, P. J. *et al.* Scleroderma in South Australia: epidemiological observations of possible pathogenic significance. *Intern. Med. J.* **31**, 220–229 (2001).
110. Geirsson, A. J., Steinsson, K., Guthmundsson, S. & Sigurthsson, V. Systemic sclerosis in Iceland. A nationwide epidemiological study. *Ann. Rheum. Dis.* **53**, 502–505 (1994).
111. Alamanos, Y. *et al.* Epidemiology of systemic sclerosis in northwest Greece 1981 to 2002. *Semin. Arthritis Rheum.* **34**, 714–720 (2005).
112. Tamaki, T., Mori, S. & Takehara, K. Epidemiological study of patients with systemic sclerosis in Tokyo. *Arch. Dermatol. Res.* **283**, 366–371 (1991).
113. Le Guern, V. *et al.* Prevalence of systemic sclerosis in a French multi-ethnic county. *Rheumatology (Oxford)* **43**, 1129–1137 (2004).
114. Onen, F. *et al.* Prevalence of ankylosing spondylitis and related spondyloarthritides in an urban area of Izmir, Turkey. *J. Rheumatol.* **35**, 305–309 (2008).
115. Kaipiainen-Seppanen, O., Aho, K. & Heliovaara, M. Incidence and prevalence of ankylosing spondylitis in Finland. *J. Rheumatol.* **24**, 496–499 (1997).
116. Alamanos, Y. *et al.* Epidemiology of ankylosing spondylitis in Northwest Greece, 1983–2002. *Rheumatology (Oxford)* **43**, 615–618 (2004).
117. Carbone, L. D. *et al.* Ankylosing spondylitis in Rochester, Minnesota, 1935–1989: is the epidemiology changing? *Arthritis Rheum.* **35**, 1476–1482 (1992).
118. Bakland, G., Nossent, H. C. & Gran, J. T. Incidence and prevalence of ankylosing spondylitis in Northern Norway. *Arthritis Rheum.* **53**, 850–855 (2005).
119. Bowman, S. J., Ibrahim, G. H., Holmes, G., Hamburger, J. & Ainsworth, J. R. Estimating the prevalence among Caucasian women of primary Sjögren's syndrome in two general practices in Birmingham, UK. *Scand. J. Rheumatol.* **33**, 39–43 (2004).
120. Pillemer, S. R. *et al.* Incidence of physician-diagnosed primary Sjögren's syndrome in residents of Olmsted County, Minnesota. *Mayo Clin. Proc.* **76**, 593–599 (2001).
121. Thomas, E., Hay, E. M., Hajeer, A. & Silman, A. J. Sjögren's syndrome: a community-based study of prevalence and impact. *Br. J. Rheumatol.* **37**, 1069–1076 (1998).
122. Bjerrum, K. B. Keratoconjunctivitis sicca and primary Sjögren's syndrome in a Danish population aged 30–60 years. *Acta Ophthalmol. Scand.* **75**, 281–286 (1997).
123. Wakai, K. et al. Estimated prevalence of Sjögren's syndrome in Japan: findings from a nationwide epidemiological survey. *J. Epidemiol.* **5**, 125–129 (1995).
124. Alamanos, Y. *et al.* Epidemiology of primary Sjögren's syndrome in north-west Greece, 1982–2003. *Rheumatology (Oxford)* **45**, 187–191 (2006).
125. Plesivcnik Novljan, M. *et al.* Incidence of primary Sjögren's syndrome in Slovenia. *Ann. Rheum. Dis.* **63**, 874–876 (2004).