Defining and analyzing geoepidemiology and human autoimmunity

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A B S T R A C T

Autoimmune diseases cumulatively affect 5–10% of the industrial world population and are a significant cause of morbidity and mortality. In recent decades rates are rising worldwide, and autoimmunity can no longer be associated solely with the more developed “Western” countries. Geoepidemiology of autoimmune diseases portrays the burden of these illnesses across various regions and ethnic populations. Furthermore, geoepidemiology may yield important clues to the genetic and triggering environmental mechanisms of autoimmunity.

In this review we compiled and discussed in depth abundant geoepidemiological data pertaining to four major autoimmune conditions, namely type-1 diabetes mellitus, multiple sclerosis, autoimmune thyroid disease, and inflammatory bowel disease.

The following key results manifested in this review: 1) Ethno-geographic gradients in autoimmune disease risk are attributable to a complex interplay of genetic and environmental pressures. 2) Industrial regions, particularly Northern Europe and North America, still exhibit the highest rates for most autoimmune diseases. 3) Methods particularly useful in demonstrating the significant influence of genetic and environmental factors include comparative ethnic differences studies, migration studies, and recognition of ‘hotspots’. 4) Key environmental determinants of geographical differences include diminished ultraviolet radiation exposure, Western or affluence-related lifestyle, infection exposure, environmental pollutants, nutritional factors and disease-specific precipitants (e.g., iodine exposure).

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1. Introduction

Autoimmune diseases collectively affect approximately 5–10% of the developed world population, and are a significant cause of morbidity and mortality accounting for soaring healthcare costs, comparable to those of cancer and heart disease[1–3]. In recent years accumulating data confirm that the burden of autoimmune diseases is rising in the developing world as well, making them a ubiquitous global phenomenon suspected to further rise in the upcoming decades[4–6]. The etio-pathogenesis of autoimmune diseases entails a particular combination of genetic, immune, hormonal, and environmental factors, altogether representing what was termed thirty years ago the “mosaic of autoimmunity”[7–10].

The geoepidemiology of autoimmune diseases could be described as the approach by which one compares epidemiological data of these conditions across different geographical regions and populations, in the process identifying causative genetic, environmental, and socioeconomic factors. This approach firstly provides valuable information about the global and regional burden of autoimmune illness that could shape resource-planning, policy making, funding, healthcare considerations, and therapeutic intervention. Second, in the process of scrutinizing the geographic distribution of a certain autoimmune disease, one may find that particular factors, genetic and/or environmental, present themselves with a dominant role. Moreover, in the ongoing debate of genes vs. environment, or ‘race vs. place’, geoepidemiology underscores the fact that the environmental and genetic determinants of geographic variations are intricately linked. It is like looking at a mosaic of explanations, being able to focus on a different “pebble” one at a time.

This geoepidemiological review presents abundant compilation of epidemiological data from studies that have been carried out in many countries and ethno-geographical groups, hopefully depicting the global distribution of some major autoimmune diseases (Table 1, Figs. 1–3). The focus will primarily be on descriptive epidemiology, providing basic epidemiological measures of disease occurrence, namely incidence rates (relating the annual count of new cases per 100,000 of the population concerned) and prevalence.
Table 1
Geographical distribution of autoimmune diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>F/M ratio</th>
<th>HLA associated With disease</th>
<th>Prevalence and annual incidence/100,000</th>
<th>North America</th>
<th>Central America &amp; Caribbean</th>
<th>South America</th>
<th>North Europeb</th>
<th>South Europeb</th>
<th>West Europeb</th>
<th>East Europeb</th>
<th>Middle East</th>
<th>Asia</th>
<th>Africaa</th>
<th>Oceaniaa</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Incidence</td>
<td>USA:</td>
<td>15–20</td>
<td>Puerto R.,</td>
<td>Baltic: &lt;12</td>
<td>Sardinia,</td>
<td>Baltic: &lt;12</td>
<td>Sardinia,</td>
<td>6–22</td>
<td>&lt;5</td>
<td>&lt;10</td>
<td>14–22</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Canada: 20–25</td>
<td>Virgin Is.: 10–20</td>
<td></td>
<td>It.: 38h&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Multiple sclerosis (MS)</td>
<td>3:1</td>
<td>DR2/DR3/DRA/DRB1</td>
<td>Prevalence</td>
<td>90–120</td>
<td>&lt;20</td>
<td>50–200</td>
<td>30–100</td>
<td>60–120</td>
<td>20–80</td>
<td>20–60</td>
<td>&lt;5</td>
<td>Saudi Arabia: &lt;10</td>
<td>&lt;5</td>
<td>60–100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Incidence</td>
<td></td>
<td>Puerto R., Uruguay: 30</td>
<td>Sardinia,</td>
<td>150&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Sardinia,</td>
<td>Saudi Arabia: &lt;10</td>
<td>Siberia: 20–60&lt;sup&gt;h&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>It.:</td>
<td></td>
<td></td>
<td>Sub-Sahara: &lt;5</td>
<td>Sub-Sahara: &lt;5</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Incidence</td>
<td>40</td>
<td>40–90</td>
<td>20–40</td>
<td>20–40</td>
<td>Childhood: 3</td>
<td>Childhood: &lt;3</td>
<td>Childhood: &lt;10</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism/Hashimoto's disease</td>
<td>7–18:1</td>
<td>DR3/DR4/DR5/DR11/DRB4</td>
<td>Prevalence</td>
<td>3000–5000</td>
<td>Clinical: 300–550</td>
<td>Childhood: &lt;3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rare</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Incidence</td>
<td>40</td>
<td>40–90</td>
<td>20–40</td>
<td>20–40</td>
<td>Childhood: &lt;3</td>
<td>Childhood: &lt;10</td>
<td>Childhood: &lt;10</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Incidence</td>
<td>2.5–20</td>
<td>UC: &lt;3</td>
<td>UC: 10–20</td>
<td>CD: 8–40</td>
<td>UC: 2–16</td>
<td>UC: 3–10</td>
<td>CD: 5–8</td>
<td>Israel: UC: 9</td>
<td>UC: 2–6</td>
<td>3–5&lt;sup&gt;i&lt;/sup&gt;</td>
<td>&lt;2&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Female to Male ratio.
<sup>b</sup> European regions divided according to the United Nations geoscheme created by the United Nations Statistics Division (UNSD).
<sup>c</sup> Sub-Sahara unless specified for N. Africa.
<sup>d</sup> Australia and New Zealand.
<sup>e</sup> Values for Central America.
<sup>f</sup> Values for Caribbean.
<sup>g</sup> ‘Hotspot’.
<sup>h</sup> Caucasians.
<sup>i</sup> Non-Caucasians.
rates (total number of disease cases per 100,000 of the population concerned at a given point of time), as well as identification of determinants of disease occurrence. Although it is purely observational, in essence, geoepidemiology utilizes both descriptive and analytical epidemiological approaches. Table 2 presents a comparison of the main observational epidemiological study designs applied in the geopneipidemiology of autoimmune diseases. Furthermore, geoepidemiology offers unique observational methodologies, herein termed the geoepidemiology ‘tool-box’. These methods are applied in this review regarding four prototypic autoimmune diseases, demonstrating how geoepidemiology may provide not only important descriptive data, but also valuable tools to understanding the causation of these illnesses.

2. The geoepidemiology ‘tool-box’

For a particular autoimmune disease, a unique assortment of etiological factors can be assembled by utilizing a variety of unique
geoepidemiology “tools” (Box 1). The chief methods are herein briefly presented, to be thoroughly exemplified throughout the discussions of each autoimmune disease. Of note, the methods presented are only artificially separated for illustrative purposes, as most of them interact and overlap. Indeed, it is only by means of combining as many as possible of the approaches laid here, that the full potential of ascertaining genetic and environmental mechanisms of autoimmunity may be realized.

2.1. Genetic risk

In recent years there has been a rapid accumulation of data regarding the complex genetics of autoimmunity. The available results to date suggest that there is a wide heterogeneity in the genetics underlying autoimmune diseases, multiple genes are involved in predisposition to each disease, and while some diseases share common genetic risks, others do not overlap [11,12].

Geoepidemiological methods may contribute to the ongoing research in advancing our understanding of the genetics underlying autoimmunity. First, the general contribution of ethno-genetic factors to an autoimmune disease risk can be generally demonstrated based on consistent racial differences between different racial groups sharing the same geographical residence (e.g., within the US or Europe). Second, the geographic distribution of disease rates may be compared with the distribution of particular genotypes (e.g., human leukocyte antigens (HLA)) associated with the autoimmune disease [12–15].

Table 2
Observational study designs and their relevance in Geoepidemiology of autoimmunity.

<table>
<thead>
<tr>
<th>Type of epidemiological design</th>
<th>Characteristics</th>
<th>Relevance to autoimmune disease geoepidemiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecological</td>
<td>Data at the population or group level</td>
<td>Provides descriptive data, e.g., new input of disease cases (incidence rates) over time in the studied population and the proportion of cases present in a given population at a given point of time (prevalence rates). Following a fixed disease group (e.g., a cohort of autoimmune disease subjects) over time provides data on morbidity (e.g., the development of complications), mortality, and co-occurrence of diseases. Specifications according to age, gender, ethnicity, geography and other determinants. Allows calculation of correlation coefficient for associations with potential exposures (e.g., specific environmental exposures). Good for generating hypotheses but not for establishing cause–effect relationships.</td>
</tr>
<tr>
<td>Cohort</td>
<td>Group exposed to a particular factor and another group not exposed to the factor are followed up over time to determine (compare) occurrence of disease</td>
<td>Provides analytical (etiological) observations. Quantification of effect of exposure on disease etiology and natural history by Hazard ratio or Relative risk. Allows judgments of causality to be made. Limited efficacy in testing hypotheses in rare diseases (i.e., autoimmune).</td>
</tr>
<tr>
<td>Case-control</td>
<td>Disease group is compared to non-disease control group with respect to exposures</td>
<td>Provides analytical (etiological) observations. Quantification of effect of exposure on disease etiology and natural history by Odds ratio. Enables studying multiple exposures at once. May suggest a cause–effect relationship (however, not establish one). Particularly suitable for testing hypotheses in rare diseases (i.e., autoimmune).</td>
</tr>
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</table>

* [46,85–87].
increased occurrence of IBD [37]. Although yet to be proven, indeed Westernized diet, have been longed considered involved in the intestinal environmental factors, such as intestinal microbes and several reports suggest a positive association of animal meat, fat, sweets and sugar with the occurrence of IBD, whereas fruit, vegetables, and fiber consumption seem to decrease the risk of the disease [37,21]. In fact, there is evidence supporting the benefits of nutritional therapy as both primary and adjuvant therapy for IBD [21,38]. Last, but not the least, the effect of nutrition on autoimmunity is perhaps most clearly demonstrated in celiac disease, for which Gluten-free diet is currently the only effective mode of treatment [39]. In recent years, an association between anti-Gluten or anti-Gladin antibodies and other autoimmune disease (e.g., MS) as well as the role of Gluten-free diet for other autoimmune diseases has been suggested [40].

In addition to dietary habits, which undoubtedly vary across countries and ethnic groups, all above-mentioned environmental factors should be influenced by the cultural and physical environment. Thus, known and possibly novel environmental determinants should manifest through the geoepidemiological looking glass. Indeed, latitudinal gradients (of increasing disease rates) inversely associated with sunlight-ultraviolet radiation exposure (and thus vitamin-D synthesis) [16,41], distinctive temporal phenomena in particular regions suggestive of infectious trigger [42], or known specific exposures for particular autoimmune diseases (e.g., country-specific dietary iodine intake habits) [43], all exemplify the unique contribution of this epidemiological approach in identifying the environmental influences. Furthermore, it is evident that many of the environmental risk factors tied with autoimmunity seem closely related to the “Western” lifestyle. Socioeconomic determinants of autoimmune disease risk can be disclosed through global developed-developing countries gradients and through affluence associations within regions (e.g., rural-urban gradients) [44,45]. The global rapid temporal trends in autoimmune disease frequencies could more readily be explained based on changing lifestyle-environmental reasons, perhaps associated with the global process of “westernization”. For, it is improbable that population genetics could shape disease risk in very short intervals [46].

2.2. The contribution of environmental factors

The role of environmental factors in the development of autoimmunity has been extensively studied [8–10]. Evidence implicate several of these factors, such as infections, tobacco use (i.e., smoking), ultraviolet rays (sun) exposure, nutrition, xenobiotics, as well as physical and psychological stresses in the pathogenesis of autoimmune [8,9,16–21].

Focusing on the nutritional factor as an example, in recent years we are witnessing important advances in “nutritional immunology” [22]. The role of vitamins, essential constituents of human diet, is currently becoming the focus of attention. Particularly, vitamin D is drawing a great deal of interest, for it has been shown to be a crucial modulator of the innate and adaptive arms of the immune system [17,23]. Moreover, others and we have persistently found that low levels of vitamin D are associated with various autoimmune diseases [24–29]. The accumulating evidence supporting the beneficial effects of vitamin D supplementation on experimental models of autoimmunity as well as on autoimmune diseases, make this simple dietary agent a promising therapeutic approach for the future [30–33]. Abundant additional examples of the effects of dietary habits on specific autoimmune conditions exist [34–39]. Early exposure to cows’ milk protein, for example, has been identified as a risk factor for development of type-1 diabetes mellitus, especially in genetically susceptible individuals [35]. Increased iodine consumption is strongly implicated as a trigger for autoimmune thyroiditis, in genetically susceptible individuals [36]. In the case of inflammatory bowel disease (IBD), intestinal environmental factors, such as intestinal microbes and Westernized diet, have been longed considered involved in the increased occurrence of IBD [37]. Although yet to be proven, indeed several reports suggest a positive association of animal meat, fat, sweets and sugar with the occurrence of IBD, whereas fruit, vegetables, and fiber consumption seem to decrease the risk of the disease [37,21].

Methods for unraveling genetic risk:
- Comparative ethnic differences — allows discovering differing risks between distinct ethnic groups sharing the same geographical residence.
- Matching genetics data with geographical disease gradients — enables correlations between rates of disease and distribution of genotypes.

Methods for unraveling environmental influences:
- Latitudinal gradients — may link a disease to ultraviolet levels dependent upon distance from the equator.
- Temporal phenomena — may advance hypotheses regarding cyclic (e.g., infections) or secular (e.g., urbanization) factors.
- Global developing-developed gradients — might disclose socioeconomic factors between countries, and between different regions of the same country (rural-urban gradients).
- Ethnic lifestyle differences — may expose cultural dependent environmental exposures, such as dietary factors (e.g., iodine intake habits).

Unique methods distinguishing genetic and/or environmental factors:
- Studies in migrant populations offer an opportunity to investigate genetic differences on the one hand, and modulating effects of changing lifestyles and physical environments on the other hand.
- Recognizing disease ‘hotspots’ could point to specific population genetic risk, or, alternatively to the localization of environmental exposures.

2.3. Immigration

Immigrants provide an opportunity to study the effects of changes in physical, social, and cultural environments on disease risk. Briefly, if a particular migrant community’s autoimmune disease risk persists in the host country, remaining closer to that in their country of origin and distinct from the host population’s risk, genetic differences are highlighted. On the other hand, if this difference between the local and migrant populations is demonstrated to ‘wear off’, the modulating effect of the shared lifestyle-environment comes to focus. Thus, studying migrant populations is an important method in demonstrating the intricate role of both genetic and lifestyle-environmental factors.

2.4. Recognizing autoimmune disease ‘hotspots’

Last, exceptional spatial clustering of autoimmune disease cases, know as disease ‘hotspots’, could bring to focus unique genetic or environmental mechanisms. For instance, striking autoimmune disease frequencies in a case of a well defined community possessing a genetic composition distinct form that of the neighbouring regions (e.g., the island of Sardinia); could point to a shared genetic susceptibility [47,48]. In other cases, a ‘hotspot’ may not represent a distinct ethnic group, but rather an exact location of a known potential environmental exposure (e.g., hazardous waste sites) [49]. Therefore, geoepidemiology provides an additional tool for distinguishing potential risk factors.

3. Methodological considerations

There are challenging methodological issues entailed in geoepidemiology. First, socioeconomic factors may bias comparisons...
between developed and developing counties, therefore not truly reflecting ethno-geographic differences. Access to medical care, local medical expertise, availability of and accessibility to new diagnostic procedures, degree of public awareness and misconceptions among professionals are all deprived factors that could account for under-diagnosis of autoimmune disease in developing countries.

Other methodological discrepancies such as variability in classification criteria, inconsistency in methods used for testing, and diagnosis difficulties of subclinical cases, render the comparison across multiple epidemiological studies difficult in some diseases. Bias may also arise when comparing hospital based or clinical case studies, which capture mostly pre-diagnosed and severe cases, with true community based studies.

Nonetheless, when amassing together numerous studies across various regions, it may yield a consistency that could generally reflect the global distribution of a particular disease. Furthermore, in certain autoimmune diseases large global scale standardized investigations were carried out to collect prevalence or incidence data, allowing for accurate comparison across populations.

4. Type-1 diabetes mellitus (T1D)

Across the 100 populations worldwide for which incidence data regarding T1D exists, a 350-fold variation in rates is evident, and seems to reflect the global distribution of major ethnic populations (Table 1, Fig. 1) [5,13]. The rates are generally highest in European Caucasian populations, particularly in Northern Europe and areas originally settled by people from this region, namely North America, Australia, and New Zealand. The rates in the Baltic countries are considerably lower when compared to their Scandinavian neighbours, stressing the ethno-genetic and/or the social-lifestyle differences. Incidence is generally low in Asia with the exception of high rates in Kuwait. Intermediate rates were documented in the Middle Eastern countries rates including those in North Africa. In Central America and the Caribbean incidence ranges from low to intermediate, with exceptions of high rates recorded in Puerto Rico and Virgin Islands.

Investigations within Europe suggest that a substantial part of the transnational variation in the incidence of T1D is explained by variations between populations in the distribution of particular human leukocyte antigen (HLA)-DQ genotypes that confer a high risk this disease in the general population [13]. Furthermore, a recent advance in the genetics of T1D quite accurately coincides with the European geographic picture of disease rates. One of the single nucleotide polymorphisms (SNPs) recently associated with T1D is the PTPN22 risk allele, an intracellular (tyrosine phosphatase) signalling molecule [12]. Of note, there is a gradient of increasing frequency of this allele moving from southern to northern geographic regions within Europe [50], strikingly comparable to the actual disease distribution within this continent (Fig. 1). Nevertheless, since multiple genes are involved in the predisposition to autoimmune diseases in general and to TID in particular, the PTPN22 SNP cannot account for the entire genetic variance with respect to risk of T1D between European populations.

One salient exception is located in one of the rather southermmost points in Europe, in which the highest T1D rates in the world have been recorded, however in this hotspot named Sardinia the PTPN22 frequencies are low [50] (Fig. 1). The population of this Italian island, home to the most ancient human settlements in the Mediterranean area, possesses a well-preserved particular genetic composition that is unique in the European phylogenetic tree [47]. The extent of this population’s T1D susceptibility is underscored by the fact that disease rates were up to 5 times higher in Sardinia than all recorded rates across nearly continental Italy, thus in a way controlling for confounding environmental influence. In fact, Sardinian migrants to Germany were found to retain a high incidence of T1D, while rates in children from continental Italy residing in Germany were similar to those in their home country, attesting the predominant role of genetic factors [51]. Therefore, it is plausible that this particular population shares T1D marked risk genetic variants, overshadowing the lack of the PTPN22 allele association. Indeed, among several other susceptibility loci discovered to date, Sardinians were shown to possess a very high frequency of the HLA class II-DR3 haplotype, associated with T1D risk, while they rarely possess the HLA-DR2 haplotype, considered dominantly protective for T1D [52,53].

Not all T1D geopidemiological phenomena could be understood based purely on ethno-genetic considerations, bringing forth environmental influences. First, different ethnic groups’ second-generation migrants, exhibit incidence rates nearing those of the host European population rather than those in their native countries [54]. Thus, disclosing the ‘wearing-off’ of genetic differences over generations, plausibly due to the environmental modulating aspect of geographical residence.

In addition, the evidence supporting the belief that T1D is a wealth-related disease further demonstrate how unique lifestyle-environmental factors might modulate diseases predisposition. Reports of within-country regional variations in T1D incidence are accumulating from around the globe [5,44]. European studies have shown a variable pattern of rural-urban gradients, with evidence pointing to higher disease rates in more affluent areas within countries [44]. Furthermore, rising levels of T1D incidence correlate with the increasing gross national product of countries [55]. In fact, the magnitude of global increases in incidence observed over the last decades could more readily be explained based on changing lifestyle-environmental pressures, for it is unlikely that susceptibility genes could significantly alter in such short time [46]. Recent predictions estimate that if present trends continue, new cases of T1D in European children less than 5 years of age will double between 2005 and 2020, and prevalence among children younger than 15 will rise by 70% [56]. It has been suggested that Western-related lifestyle factors, such as increased weight and height development, caesarean section deliveries, or reduced frequency of certain early infections might explain the rapid increase in T1D incidence [56].

Last, data from different parts of the world depict a latitudinal gradient in the incidence of T1D, meaning that rates increase with distance from equator and inversely with ultraviolet radiation (UVR). Thus, suggesting the pathogenic role of decline in immunoregulatory qualities of UVR, such as vitamin-D synthesis [16,17,41]. However, the phenomenon might not be as strong as previously believed [5]. Plausibly, the faster increase in T1D rates in countries traditionally associated with low incidence (e.g., in regions closer to the equator) [56] is progressively attenuating the historical latitudinal gradient.

Taken together, a combination of genetic and environmental explanations appears to be required in order to understand the epidemiology of T1D. The global distribution of the disease generally corresponds to the distribution of major ethnic populations. The hotspot Sardinia may represent a particularly genetically susceptible ethnic group. Migration studies, a disease-affluence association, temporal trends, and a latitudinal gradient in disease rates attest the modulatory role of the environment.

5. Multiple sclerosis (MS)

The epidemiology of MS demonstrates the key role of ethno-genetic factors in disease risk as it is significantly more prevalent in Caucasians compared to Blacks and Asians. Some ethnic populations seem particularly disease resistant, such as the Northern Norwegians (Laps), Australian Aboriginals, New Zealand Maoris, natives of the Southern part of the former Soviet Union, and North and South-American Indians [57,58].

The global distribution of MS strikingly resembles the T1D pattern; again representing variable genetic susceptibility of major
ethnic populations (Table 1, Fig. 2). Highest rates are recorded in Northern Europe, the British Isles and Scandinavia in particular, and the areas originally settled from these locations, which are North America, Australia and New Zealand. Of note, the rates in Middle Eastern and North African Arabs are relatively homogeneous. In Kuwait, however, significantly higher rates were detected in Arabs compared to mostly Asian non-Arab population. Furthermore, compared to Kuwaiti indigenous Arabs, much higher prevalence was detected in Palestinians, most of which were born in Kuwait, stressing ethno-genetic determinacy within populations [59,60]. Like the case in T1D, among the highest MS rates in the world were recorded in the hotspot Sardinia, emphasizing the possible genetic susceptibility of this ethnically homogenous community to MS as well [48]. Indeed, often genetics render a tendency to multiple autoimmune diseases in general, and specifically MS and T1D are known to share common susceptibility alleles, such as HLA class II genotypes DRB1 and DQB1 (highly prevalent in Sardinians), and genetic locus of the interleukin 2 receptor A (IL2RA) [12,52,61]. Another hotspot is a small Croatian mountain community named Gorski Kotar, a salient exception to the relatively low rates in the rest of this country. Located on the frontier between Croatia and Slovenia, this hotspot perhaps pinpoints, ethno-geographically, the shift from the MS high-risk Caucasian descent region (i.e., Slovenia), to lower risk Croatia [57,62,63].

Notwithstanding ethno-genetic determinacy, MS geoepidemiology also demonstrates how lifestyle-environmental factors play an important role in modulating disease risk. Perhaps merely coincidental, nonetheless, epidemiological findings may very well adjoin the growing concern for the autoimmune disease-triggering risk entailed in exposure to various xenobiotics and heavy metals [19,20]. In response to citizen concerns in five small Illinois (US) rural towns, subsequent investigations recently reported among the highest MS prevalence rates ever documented (up to 300 cases per 100,000 population) [49]. Of note, an analysis in one of these towns (Morrison) has revealed no significant commonalities in the backgrounds of disease cases other than residence, raising the possibility of some environmental cause, yet to be appropriately explored. In fact, two of the investigated hotspots were situated on US Environmental Protection Agency (EPA) Superfund clean up sites (a program to clean up uncontrolled hazardous waste sites), one town being home to a closed Army depot and the other previously being the site of significant environmental heavy-metal exposure from a zinc smelter. Of the three remaining towns, the first had sludge from the Chicago Metropolitan Sanitary District spread on its agricultural fields; the second (Morrison) is home to an electrical products plant; and the last is an agricultural community subject to fertilizer use and pesticide spraying [49].

Early studies in migrant populations, on the one hand, have stressed ethno-genetic factors by showing that the low MS risk in adult migrants from tropical countries to the UK remains, throughout life, much lower compared to the indigenous Caucasian population [64]. On the other hand, this difference seems to ‘wear off’ in second-generation migrants [65]. Similarly, in Israel, on the one hand second-generation migrants of African or Asian ethnicity exhibit significantly lower MS risk compared to that among those of European or American descent. However, the second-generation African or Asian migrants also show significantly higher risk compared to migrants of the same ethnicity not born in Israel, underscoring how the environment may indeed modify MS risk [56,67].

An interesting geoepidemiological phenomenon has been documented in the Faroes, Iceland and the region of Rostock, Germany, where MS seemed to outbreak in a cyclic epidemic pattern. It was hypothesized that variations in the epidemicity of some infection could account for these trends [42,68].

A recent large international study conducted by the World Health Organization (WHO) established that the median MS prevalence is greatest in high-income countries (89/105), followed by upper middle (32/105), lower middle (10/105) and low-income countries (0.5/105) [4]. This socioeconomic gradient could reflect the same disease–affluence association put forth in T1D. Alternatively, the unequal distribution of important MS diagnostic tools (e.g., MRI scanners) may account for under-recording of MS in many low-income countries, including some in Eastern Europe [4].

Last, the latitudinal gradient of MS, comparable to the T1D pattern of increasing disease frequency with distance from the equator, has been established as a global phenomenon, as well as within Europe, the US, Australia and New Zealand [4,69]. Likewise, an association between rising disease risk and diminished ultraviolet radiation (UVR) was demonstrated [41]. The decline in immunoregulatory qualities of UVR, such as vitamin-D synthesis, may indeed render susceptibility to different autoimmune diseases [16,17,70]. However, the updated distribution of MS shows many exceptions to the previously believed disease—latitude direct relationship. Similar to the trend observed in T1D, there might also be an attenuation of the MS latitude gradient over the last decades, possibly a result of a more rapid increase in MS incidence in regions closer to the equator [69]. In fact, such a rapid change in MS incidence as was recently documented in different regions could reflect either enhanced diagnosis or a true change in lifestyle-environmental conditions, for population genetics should be expected to shape disease risk much more slowly.

In conclusion, MS geoepidemiology provides ample evidence for genetic determinacy of autoimmune disease risk on the one hand, and for the significant modulating environmental effects on the other hand. The global distribution of MS represents variable genetic susceptibility of major ethnic populations. The hotspot Sardinia perhaps exemplifies population genetics rendering risk for multiple autoimmune conditions. Migration studies, industrial pollution hotspots, socioeconomic gradients, latitudinal gradients, unique temporal phenomena, and temporal trends indicate that lifestyle-environmental conditions greatly influence MS epidemiology.

6. Autoimmune thyroid diseases (AITD)

Although the autoimmune thyroid diseases are perhaps the most common of all autoimmune conditions (Table 1), comparing AITD incidence rates across different studies is a complicated task. The chief methodological discrepancies include variability in assessment techniques, diagnosis difficulties because of the nonspecific disease symptoms, and difficulties in ensuring that all cases and only those cases of thyroid disease caused by autoimmunity, whether subclinical or overt, are considered [71]. In addition, there is paucity of epidemiological data from world regions other than the US and Northern Europe, perhaps reflecting overshadowing by the more significant problem of iodine-related thyroid disease in the rest of the world.

Nevertheless, comparative studies have shown ethno-genetic differences. AITD incidence rates are slightly higher among Asians when compared with Caucasians. The lowest rates were consistently found among Black Africans indigenous and outside of Africa [72,73]. Furthermore, an analysis of possible environmental explanations for the African American — Caucasian US racial differences, such as region, poverty status and urban vs. rural residence, has yielded no other association but racial [72].

On the other hand, it seems that the incidence of Graves’ disease (GD) is increasing rapidly in urban South African blacks, possibly reflecting the increasing dietary iodine intake tied with the process of urbanization [73]. In fact, AITD geoepidemiology underscores the established role of iodine as a key environmental modulator in the development of thyroid autoimmunity [74], as varying levels of...
iodine intake between locations coincide with AITD rates [43,75,76]. For example, in line with the above a higher incidence of GD was documented in Iceland, which has a relatively high iodine intake, contrasted with hyperthyroidism due to multinodular toxic goitre that was more common in East-Jutland Denmark, an area with a low average iodine intake [75]. In addition, a particularly high incidence of childhood GD has been documented in Hong-Kong China, due to high consumption of seaweed, could be a lifestyle contributing factor to the observed variation [43,76]. Overall, AITD geoepidemiology demonstrates the interplay of genes and environment. It further brings to focus evidence for a plausible unique environmental determinant of AITD distribution, namely dietary iodine intake.

7. Inflammatory bowel diseases (IBDs)

The geoepidemiology of IBD entails particularly challenging methodological issues, due to a gradual disease onset, no single gold standard for diagnosis and a broad differential diagnosis [6]. Although data are limited, ethnic differences in disease risk are apparent. Compared to Caucasians, Asian Americans, Americans of Hispanic background, and North American Indians are at lower IBD risk, especially of Crohn's disease (CD) [77]. It seems that IBD risk among African Americans and African Caribbeans is similar to that in Caucasian host populations [78].

Mirroring the pattern seen in T1D and MS, Northern Europe and Northern America, the geographic regions historically associated with IBD, have the highest incidence and prevalence rates for both ulcerative colitis (UC) and CD (Table 1, Fig. 3).

Migration studies have demonstrated the significance of both ethno-genetic and environmental factors. South Asian immigrants to the UK maintained lower CD rates compared to Caucasian natives. However, this ethnic difference disappeared in their first-generation offspring, demonstrating the modulating effect of the environment [79]. In fact, the incidence of UC among second-generation South Asian migrants was more than two-fold higher than that among native Europeans [80]. Studies in Israel have shown, on the one hand, that IBD risk is higher among Israelis of European or American descent compared to those of Asian or African descent. On the other hand, these ethnic differences seem to be narrowing over time, suggesting the effect of the shared environmental conditions [81].

Similar to the gradients observed in T1D and MS, the European Collaborative Study on Inflammatory Bowel Disease confirmed in the previous decade that the incidence rates of IBD are higher in Northern Europe than in the south (Fig. 3), the CD incidence gradient being more pronounced than UC [82]. A similar north-south gradient has been also documented in the US [45]. However, the updated European gradient was far less prominent than previously believed. Thus, as was suggested with regard to the gradients attenuation observed in T1D and MS, it is plausible that the IBD attenuation reflects the rapidly increasing IBD rates in other parts of the world, namely southern or central Europe, Asia, Africa, and Latin America, whereas populations carrying worms enjoy immunosuppressive benefits [83]. Similarly, we have recently demonstrated that exposure to Helicobacter pylori might have a protective role in IBD, whereas exposure to Hepatitis C virus and Toxoplasma gondii seems pathogenic [83]. Indeed, there is a wide variability in the geographic distribution of these and other infectious agents, thus it seems plausible that their protective or pathogenic affects should interact with genetic susceptibility in influencing disease global gradients. Once more, IBD join the above geoepidemiological discussions, underscoring the intricate role of both genetics and the environment in determining risk of autoimmunity.

8. Concluding remarks

The geoepidemiology of autoimmune diseases dispenses a variety of valuable tools, altogether contributing to the ongoing quest for picking up the clues for the etio-pathogenesis of autoimmunity. Having presented substantial data depicting the global distribution of major autoimmune conditions, key conclusions may possibly be drawn from this review.

First, ethno-genetic differences are significant determinants of autoimmune disease risk. Furthermore, in general, the industrial regions, particularly Northern Europe and North America, still exhibit the highest prevalence and incidence rates for most autoimmunity. Nevertheless, in recent decades it appears that autoimmune diseases are emerging particularly in the regions not previously associated with autoimmunity risk, namely urban residential areas in Africa, Southern and Eastern Europe, Asia, and Latin America. In concert with ample evidence provided by the geoepidemiological investigation, it seems that environmental factors coinciding with Western lifestyle are increasingly becoming the focus of attention. Among other factors, sunlight (UVR) exposure affecting vitamin D levels, nutritional habits (e.g., dietary iodine intake), xenobiotics, and hygiene have been identified to date as leading candidates.

In conclusion, conducting multicenter studies exploring diverse combinations of similar and different ethnic groups, residing at similar and different regions, may prove a useful approach to unveiling genetic and environmental determinants of autoimmunity.

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References


