

# Changing epidemiology of immune-mediated inflammatory diseases in immigrants: A systematic review of population-based studies

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## ABSTRACT

**Background:** Immune-mediated inflammatory diseases (IMIDs) are systemic diseases of multifactorial etiology that share aberrant immune responses as the common final pathway. With rising globalization, their incidence is increasing in developing countries and among immigrants. Our primary objective was to systematically review the epidemiology of IMIDs in immigrants and conduct a meta-analysis to estimate the risk of IMIDs in immigrant populations according to their origin and destination countries.

**Methods:** We systematically searched five biomedical databases and reviewed population-based studies, from inception through August 2018, that reported incidence or prevalence data of inflammatory bowel disease (IBD), multiple sclerosis (MS), type 1 diabetes (T1D), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriasis and psoriatic arthritis (PPA) among immigrants and the host population.

**Results:** The incidence and prevalence of IMIDs among immigrants differ from host populations, and evolve over subsequent generations. The risk of IBD among immigrants approximates that in hosts, especially among South Asians, with ulcerative colitis incidence changing prior to Crohn's disease incidence. MS risk is highest in Iranian immigrants, T1D in African immigrants and SLE in African and Iraqi immigrants. Data on other IMIDs are sparse. Significant heterogeneity between the studies precluded meta-analysis.

**Conclusion:** Based on our systematic review, the epidemiology of IMIDs among immigrants varies according to native and host countries, immigrant generation, and IMID type. The rapid evolution suggests a role for non-genetic factors and gene-environment interactions. Future studies should focus on these pattern shifts, given implications of rising global burden of IMIDs and immigration.

## 1. Introduction

Immune-mediated inflammatory diseases (IMIDs) are systemic diseases of complex, multi-factorial etiology that often lead to end-organ damage in the context of dysregulated immune response [1]. The most prevalent IMIDs include inflammatory bowel disease (IBD), multiple sclerosis (MS), type 1 diabetes (T1D), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriasis and psoriatic arthritis (PPA).

IMIDs, prevalent in 5–7% of developed Western populations, are becoming increasingly common among immigrants from developing countries [1,2]. While pathological pathways remain elusive, the

rapidity of change in their epidemiology suggests a strong contribution by non-genetic determinants and gene-environment interactions, as opposed to shifts purely in genetic proclivity [3]. Leveraging epidemiologic differences in IMIDs among immigrants from population-based studies may provide clues to mechanisms of disease pathogenesis, while identification of modifiable disease determinants could facilitate preventative and even therapeutic efforts [4]. The economic implications are also substantial, as IMIDs contribute to increasing direct and indirect health-care costs [5].

Thus, our primary objective was to perform a systematic review and meta-analysis of the literature to define the epidemiology of IMIDs in consecutive generations of immigrants compared to the host country

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population.

## 2. Methods

### 2.1. Study identification

Identification and retrieval of studies was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6]. A comprehensive search strategy, which employed both subject headings and keywords, was run in MEDLINE and Embase on the Ovid platform, Cochrane Controlled Register of Trials (CENTRAL), Global Health, and Scopus databases from the date of database inception through June 2016. In September 2018, a search update was run to capture results published between June 2016 and August 2018. The full search queries for each database are available in [Appendix A](#). Search results were exported and de-duplicated prior to each round of study selection. The review protocol is registered with PROSPERO (CRD42016043993).

### 2.2. Eligibility criteria

We included population-based studies that contained incidence or prevalence rates or ratios for the following pre-specified IMIDs in immigrant populations: IBD, inclusive of Crohn's disease (CD) or ulcerative colitis (UC), MS, T1D, SLE, RA, AS and PPA. We extracted data separately for CD and UC whenever possible, and for IBD when such data were not reported. A population-based study was defined as one which involved all residents within a defined geographical area and was representative of the population encompassed within that region. Study designs which did not fit this definition were excluded. If more than one study was found with data from the same cohort, we prioritized the most recent data, followed by data encompassing the longest duration of follow-up, or data with the most people. Studies on persons of different racial or ethnic background residing within a host country, but with no data on immigration status, were excluded. Studies published in languages other than in English were excluded. We searched reference lists of all included studies or relevant reviews for eligible studies.

### 2.3. Definitions

Immigrants are non-national persons who move to a country (referred hereafter as "host country") for the purpose of settlement [7]; this group is referred to as "first-generation immigrants", while their offsprings who are born in the host country are "second-generation immigrants." Refugees are persons who flee their home country (referred hereafter as "native country") for the fear of persecution. For the purpose of this review, refugees and immigrants are jointly referred to as immigrants, although we acknowledge the differences in circumstances. All studies used established criteria for the diagnosis of each IMID or diagnosis codes within registries.

### 2.4. Study selection and data abstraction

Study selection and data extraction were performed by at least two of three investigators independently (MA, AP, JB). Any discrepancy was resolved by joint review of the study in question with consensus reached by a third arbiter when needed. Data were extracted per the Cochrane Consumers and Communication Review Group's template [8]; the name and year of the study, the country and region where it was conducted, study period, definition of immigrants, results and interpretation. We abstracted additional data when available, including IMID type, immigrants' native country, generation, age at migration, and host population details including effect estimates for incidence and prevalence of IMIDs ([Appendix tables 1–6](#)).

### 2.5. Risk of bias and study quality

The risk of bias and quality of studies were evaluated by two investigators independently (MA, JB), and jointly in case of discrepancy, using either the cohort or modified cross-sectional studies instrument of the Newcastle-Ottawa Scale (NOS) ([Appendix tables 7a and b](#)) [9,10]. Studies are evaluated in three domains, i.e., selection, comparability, and outcome and can be awarded up to four (five if cross-sectional), two and three points, respectively. A score of seven or higher indicates a high-quality study.

### 2.6. Qualitative and quantitative analysis

We synthesized the abstracted data in a qualitative analysis. To ensure consistency across studies, we used the United Nations (UN) assignment of countries and regions [11]. We determined temporal trends in the number of cases of IMIDs with available data in highest-incidence-immigrant groups, based on immigration rates in Sweden or the UK [12,13].

We planned a priori to perform a meta-analysis analyzing the risk of each IMID in immigrant populations compared to the host country, with sub-analysis according to immigrant generation and region where possible. However, the studies eligible for inclusion in this review were widely heterogenous in design, assessment of migration status and populations being studied and lacked comparability, thus precluding meaningful quantitative pooling of data and meta-analysis.

## 3. Results

We identified a total of 4220 studies eligible for inclusion, of which 3522 were excluded during the title/abstract screening process based on lack of relevance to our study question. After review of the remaining 698 full texts, 17, 21, 12, 5, 1, 1 and 0 studies, pertaining to IBD, MS, T1D, SLE, RA, AS and PPA, respectively, met criteria for inclusion ([Fig. 1](#), [Appendix Fig. 1a – g](#)). No additional studies were identified on review of references lists. We did not identify any relevant abstracts or correspondences. All full texts were available except four studies on MS [14–17] and one on T1D [18]. As we did not find any population-based study on the incidence or prevalence of PPA in immigrants in the literature, we do not discuss this IMID further.

### 3.1. Inflammatory bowel disease

Among 17 included studies on IBD [19–35], the most common host countries were UK (N = 7) [19–25] and Israel (N = 4) [26–29]. Other host countries were Denmark, Italy, Estonia, Malta (EpiCom cohort) [25,30], Sweden [31], The Netherlands [32] Germany [33] and Canada [34,35]. The risk of IBD in consecutive generations was reported in 3 studies [30,31,35] and according to age at immigration in one study [35]. Incidence and prevalence data are summarized in [Appendix tables 1a and b](#), respectively.

Between 1972 and 1980, South Asian immigrants (predominantly Indian) to Leicestershire, UK had higher UC incidence and similar CD incidence compared with British. Similar incidence between immigrants and host population was then noted between 1981 and 1989 [19,20]. Finally, in the 1990s, UC incidence in South Asians was significantly higher than that in European immigrants and the host UK population [23]. Most recently, between 2015 and 2016, the incidence of IBD, especially UC, continued to increase in South Asian (Indian) immigrants in the UK compared with the host population, as well as a more severe disease phenotype and younger age of onset in the second-generation [24]. During the same period (1990–2016), epidemiological data from South Asia demonstrated lower incidence (UC: 0.60–6.02 per 10<sup>5</sup> persons and CD: 0.09–3.91 per 10<sup>5</sup> persons) [2].

In the EpiCom cohort, the incidence of IBD in 2010 in immigrants from developing countries approached that of their host countries [25],

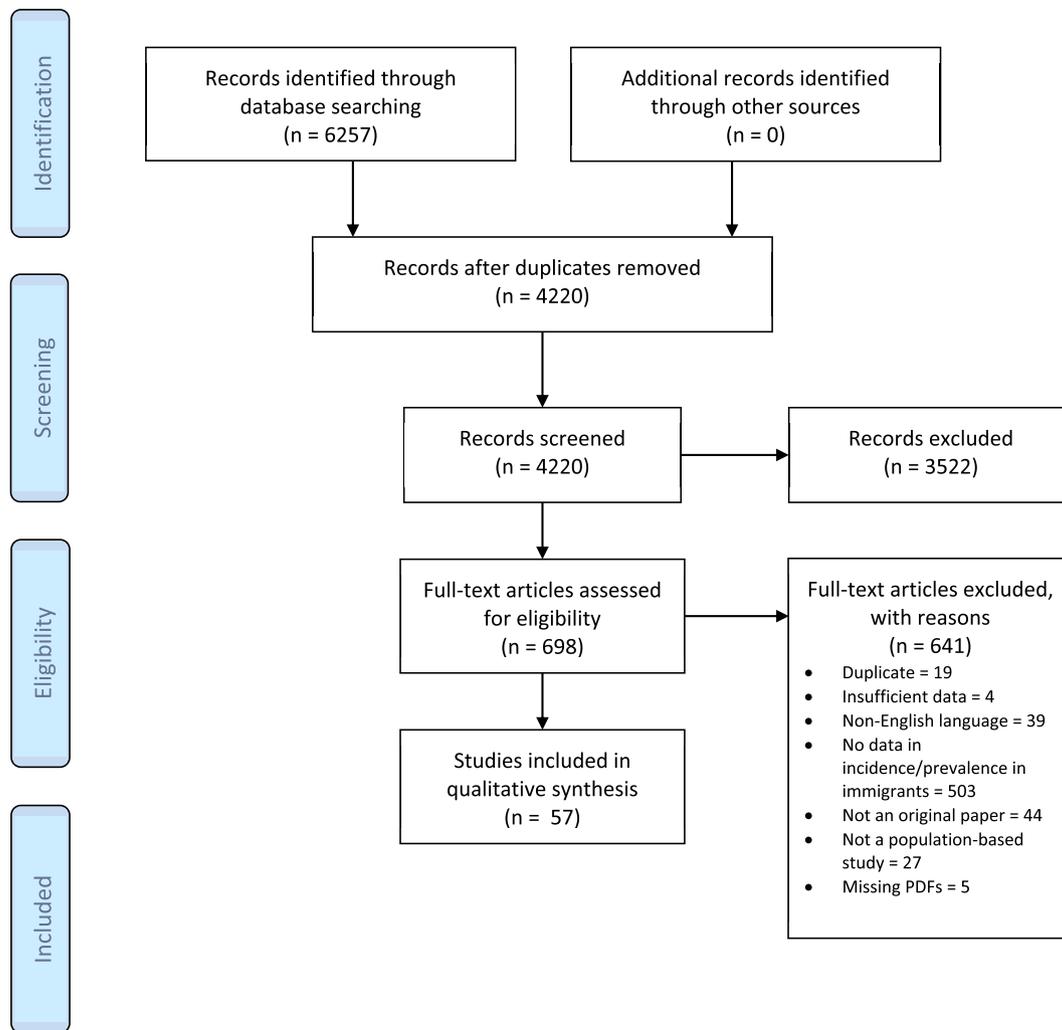


Fig. 1. PRISMA 2009 flow diagram, all immune-mediated inflammatory diseases.

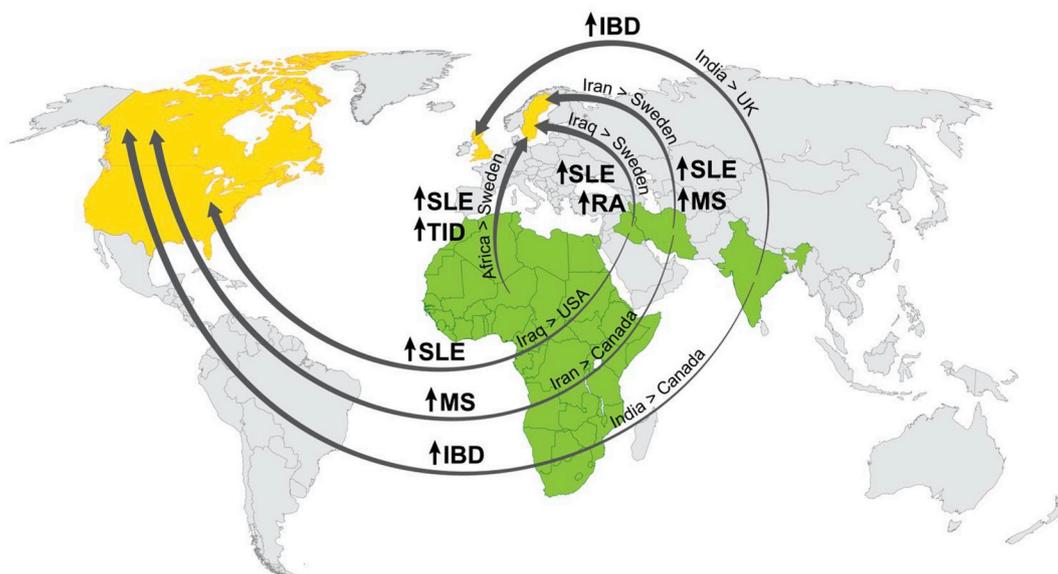


Fig. 2. Change in immune-mediated inflammatory diseases (IMIDs) epidemiology with migration from developing to developed countries.



Fig. 3. a and b: Number of new IMID cases among immigrants between 2008 and 2017, based on references [12,13,24,44,57,71].

especially among South Asians who immigrated to the UK. However, this pattern was specific to UK. In Sweden, most first-generation immigrants had lower incidence of UC and CD compared with Swedes, which persisted in the second generation in some groups but increased in others [31]. In the Netherlands between 1979 and 1983, of 7037 immigrants, 4 were diagnosed with UC subsequent to immigration and none were diagnosed with CD [32] and in Germany, between 1991 and 1995, the incidence in the Turkish immigrants (largest immigrant group) was lower than the host population [33].

Interestingly, Jewish immigrants from Europe and North America acquired a higher IBD incidence than the host Jewish population of Israel in the 1960s–1980s, followed by a striking rise in IBD incidence in Israeli Jews in the 1990s that eventually surpassed that in immigrants [26,27].

Regarding immigrants to Canada, IBD incidence in South Asian (primarily Punjabi) immigrant children was higher than other immigrants [34]. While the risk of IBD was lower in all first-generation

immigrants to Canada than in the host population, it was inversely associated with the age of immigration with a 14% (CI 11, 18) increase in risk of IBD per decade decrease in age at immigration. The risk of IBD in second-generation immigrants from Western Europe, Northern America, Western and Southern Asia, and Africa approached that in the native Canadian population, while that in immigrants from Eastern Asia and the Oceania remained low [35].

While most studies estimated the incidence of IBD in immigrants from a lower-to a higher-incidence country, Hammer et al. [30] reported the reverse; i.e., the incidence of IBD in immigrants from the Faroe Islands (FI) (higher incidence) to Denmark (lower incidence). First-generation Faroese immigrants had a higher risk of UC, especially in the first 10 years of living in Denmark. This excess risk of UC disappeared over two generations. Regarding CD incidence, compared with the Danes, there was only an increased risk among third-generation Faroese immigrant women, but not among third-generation Faroese men nor first- or second-generation Faroese immigrants.

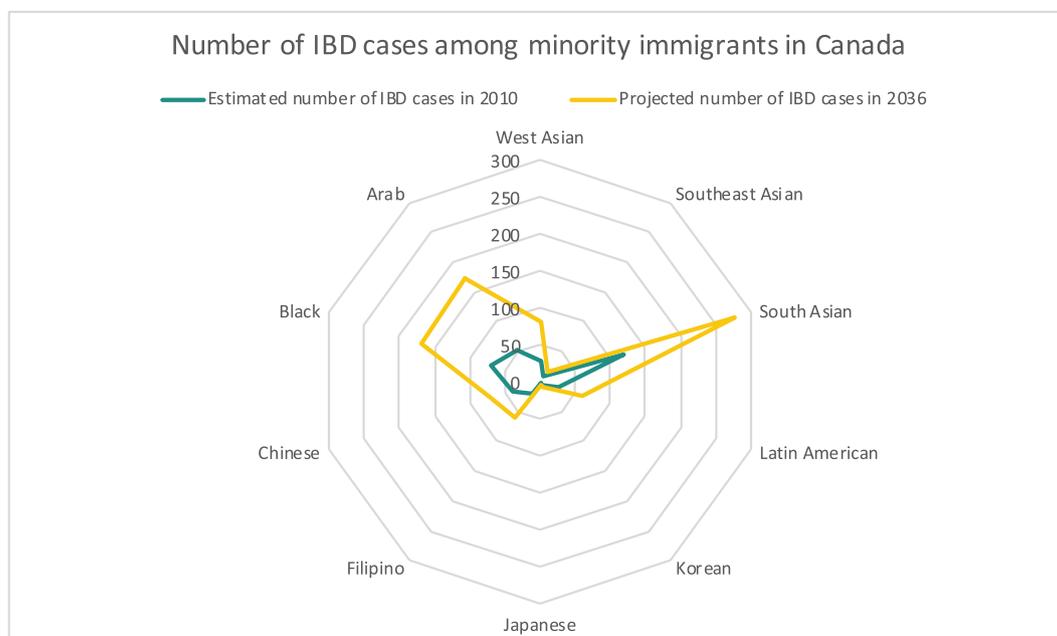


Fig. 4. Number of new IBD cases in minority immigrants to Canada in 2010 and projected number in 2036 based on references [35,99].

### 3.1.1. Summary

The main patterns of IBD in immigrants are the following: IBD incidence varies widely across countries but is consistently high in developed Western populations [25,31,32,35]. Among immigrants, IBD incidence approximates that in the host country over subsequent generations; UC incidence changes first, followed by CD, depending on age at immigration and duration of residence [30,34]. This is especially notable among South Asians [19,20,23–25]. Younger age of immigration is associated with higher risk of IBD [34]. These findings favor the impact of immigrant genetic factors in UC and host country environmental factors in CD pathophysiology.

### 3.2. Multiple sclerosis

A total of 21 studies reported MS epidemiology among immigrants. The most common host countries were Australia and Tasmania (N = 6) [36–41], Norway (N = 2) [42,43], Sweden (N = 2) [44,45], and Israel (N = 2) [46,47]. Other host countries were the UK [48], Germany [49], Estonia [50], Malta [51], Iran [52], West Indies [53], Hawaii [54] and Canada [55] with one study from each country. Two studies reported MS prevalence in subsequent immigrant generations [43,50]. Results are summarized in Appendix tables 2a and b.

MS incidence is consistently high in Europe, especially Nordic countries and UK and Ireland (UKI), as described below. Among Irish, other European, North American and Australian immigrants, and host British, MS incidence was similar, and significantly higher than in Asian, African and Caribbean immigrants between 1960 and 1972 [48]. Similarly, host Germans and Estonians had higher MS prevalence than immigrants [48,49]; though in Estonia, rates approached the host population with subsequent immigrant generations [50]. Further South in Malta, MS prevalence in 1999 was ten times lower in host Maltese than among other European, Canadian and Australian immigrants [51]. In addition to being expectedly highest in North American and Europeans, MS incidence and prevalence were highest among Middle Eastern immigrants (predominantly Iranian) to Norway in the 2000s [42,43]. In this study, 92% of immigrants had immigrated after the age of 15 years [43]. Similarly, MS risk as well as prevalence in 1950s–2000s among Iranian immigrants to Sweden was comparable to the hosts and markedly higher than that in Iran [44,45]. Among Pakistani immigrants to Norway, MS prevalence was higher in second-generation than in first-

generation immigrants in 2005 [43]. In Israel, in 1995, MS prevalence was highest among European/American Jews. It was higher in second generation Asian and African immigrant Jews than the first [46]. MS was infrequent among Israeli Arabs [46,47] and Afghan immigrants to Iran [52].

In Australia and Tasmania, MS prevalence was significantly higher in UKI immigrants than in the host countries [36–40], particularly among those who immigrated at age > 15 years [36]. The incidence of MS among immigrants was almost double that of the host Australian population. This overlapped with the immigration influx from the UKI between 1966 and 1981 [36,41], along with a corresponding increase in prevalence of MS in the country overall [41]. In South Africa, between 1958 and 1966, MS incidence was again highest among European immigrants, lower among other immigrants and lowest among host South Africans [56].

In the Americas, the incidence of MS according to age at immigration was studied in “return immigrants”, i.e., persons who immigrated from the West Indies, the Caribbean to France and subsequently returned to the Islands in 1995–2004. MS incidence was nearly twice as high in migrants than in non-migrants, and significantly higher if migration to France occurred at age < 15 years versus older [53]. All immigrants who moved to Hawaii, Polynesia at age < 15 years had lower MS prevalence between 1960 and 1969 than those who moved at age > 15 years [54]. In a Canadian study, MS prevalence in 2012 was higher in Iranians than in the host population, similar to data from Europe [55].

### 3.2.1. Summary

Of the included studies, MS incidence was highest in Nordic countries, the UKI and North America [36–40,44,45,48,49,51,55,56], which are all located at Northern latitude; especially if early years of life are spent in these countries, both among hosts as well as immigrants. Iranians have a high baseline risk when residing in Iran which increases with immigration to such countries [44,45].

### 3.3. Type 1 diabetes

Of 12 population-based studies that reported T1D in immigrants, seven were from Nordic countries; Sweden (N = 4) [57–60], Norway (N = 2) [61,62] and Finland (N = 1) [63], and three from other

European countries; Estonia [64], Italy [65] and UK [66]. One study was from Israel [67] and one from Canada [68]. Five studies reported T1D risk in second-generation immigrants [59,60,63,67,68], one study reported risk according to country of origin of parent(s) [57], and none reported T1D risk according to age of immigration. Results are summarized in Appendix tables 3a and b.

African immigrants to Nordic countries had a consistently higher risk of T1D between 1987 and 2008 compared to other first-generation immigrants, including those from Asia and South America [57–59,61–63]. Within Africa, the native country was not specified in most studies except one in which the prevalence of T1D in Somali children was comparable to that in the host Norwegians [63]. In Sweden, between 1987 and 2002, T1D incidence was lowest among those with both immigrant parents, higher in those with one Swedish and one immigrant parent, and highest in the Swedish [57]. In another Swedish study, between 1980 and 2005, the incidence of T1D rose in the second generation, irrespective of parents' racial background [60]. Estonians, who are genetically similar to the Finnish, had higher T1D incidence between 1980 and 1989 than immigrants [64]. Similarly, Italians had higher crude T1D incidence than immigrants in 1998–2015 [65]. However, in the UK in 1989–1998, the incidence of T1D among South Asians was comparable to the host population [66]. Immigrants from Western countries to Israel had similar, while immigrants from Africa and Asia had lower T1D prevalence compared with hosts in 1963 [67].

In Ontario, Canada, between 1994 and 2008, T1D incidence in first-generation South Asian immigrants was comparable to that in host Canadians and lower in other immigrant groups. In the second-generation, T1D incidence was lower in all immigrants, including South Asians [68].

### 3.3.1. Summary

T1D is most common among the Nordic, other European and African populations and possibly among South Asians [57–59,61–63]. Higher T1D incidence occurred among those with two Swedish parents compared with those with one [57]. T1D risk increased in subsequent immigrant generations in Sweden [60], but not necessarily in Canada [66,68].

## 3.4. Systemic lupus erythematosus

Five population-based studies provided data on SLE epidemiology among immigrants of which two were from the UK [69,70], and one each from Sweden [71], Norway [72] and the United States (US) [73]. The Swedish study reported risk of SLE according to immigrant generation [71], while no studies reported risk of SLE according to age at immigration. Results are summarized in Appendix tables 4a and b.

The incidence of SLE-related hospital admissions between 1964 and 2004, in the MigMed Swedish database, was highest in first generation immigrants from Iraq, Iran, and the continents of Africa and South America, and higher than host Swedes. It was higher in most second-generation immigrants, especially among Iraqis and Africans, compared with the first generation [71]. Between 1998 and 2008, SLE prevalence was higher in Asian immigrants compared with European immigrants and Norwegian hosts [72]. The number of African and South American immigrants were too small in this study to provide meaningful estimates. Similarly in the UK, SLE prevalence among South Asian immigrants was three times higher compared with the host population in 1999 [69], and similarly higher in Caribbean and African immigrants compared with the host population [70].

Based on a US study from one state (Michigan), SLE incidence was significantly higher among Arab and Chaldean (Iraqi Catholic) immigrants, especially women, compared to Caucasian Americans, but similar to African Americans between 2002 and 2005 [73].

### 3.4.1. Summary

In contrast to other IMIDs, SLE incidence does not seem to be significant among the Nordic hosts [71,72]. SLE incidence is highest among African, Iraqi and South Asian immigrants, particularly among women and successive immigrant generations [69–73].

## 3.5. Rheumatoid arthritis

The only population-based study that reported RA estimates was also based on the MigMed database, between 1964 and 2004 [71]. The incidence of hospitalization for RA among first-generation immigrants was highest in those from Iraq and Finland, while immigrants from North America and other Nordic countries (Denmark and Norway) had rates similar to the host Swedish population. All other immigrant groups had lower rates compared to the host population. Among second-generation immigrants, while the incidence remained high in those with Iraqi or Finnish parent(s), there was an increase among second-generation immigrants from some, but not all countries. Results are summarized in Appendix table 5.

### 3.5.1. Summary

These limited data suggest higher incidence among the Nordics, North Americans and Iraqis. There was increasing incidence in some, but not all subsequent immigrant generations.

## 3.6. Ankylosing spondylitis

AS incidence data in immigrants is also derived from the MigMed database [71]. Immigrants from Norway and Finland had a higher incidence of AS-related hospitalization than the host Swedish population, while other immigrant groups had comparable incidence to the Swedes. Its incidence was higher among second-generation Austrians, but similar among first-generation Austrians compared to the host Swede population. There were no generational differences among other immigrant groups. Results are summarized in Appendix table 6.

### 3.6.1. Summary

Data from one study suggest AS incidence primarily in the Nordic [71], implicating genetic risk factors.

## 4. Discussion

In this comprehensive systematic review, we found that the epidemiology of IMIDs is different in immigrants compared to host populations, with the magnitude of effect dependent IMID type, country of origin and host country, time period, immigrant generation, and age of immigration.

Among immigrants to European and North American countries, the risk of IMIDs increases in subsequent generations in certain populations. African-descent immigrants have a higher incidence of T1D and SLE. South Asians are at risk for IBD, especially UC [24,34] (Fig. 2). Iranian immigrants are susceptible to MS [44,45,55], Iraqis to SLE and RA [71] while Israeli Arabs appear to be protected against MS [47]. Data on East Asian and South American immigrants to developed countries were limited in these population-based studies. Similarly, studies on IMIDs in non-Western countries are too sparse to determine risks among immigrants prior to immigration.

These data implicate both non-genetic and genetic factors in the risk of various IMIDs, albeit to different degrees. Park et al. demonstrated that patients with IBD are twice as likely to develop other IMIDs [74]. Being breast-fed is associated with a decrease in the risk of IBD, MS, T1D and AS [3,75–78]; the former especially when it is for longer than 12 months [3,75]. The practice of breast-feeding varies across countries and cultures [79] with immigrants more likely to breast-feed exclusively [80]. Early childhood exposure(s) (protective in country of origin, or noxious in emigrant country) seem to impact IBD and MS risk;

but the critical age and duration of exposure are not clear [35,42,43,47,53]. Dysbiosis is implicated in immune dysfunction and the pathogenesis of IMIDs [81]. Vangay et al. demonstrated that migration from Thailand to the US was associated with an immediate loss of gut microbiome diversity, compounded in subsequent generations [82].

In addition to factors that impact the overall inflammatory milieu, specific risk factors for IBD include enteric infections, antibiotic exposure, lack of physical activity and diet [3,83]. Food emulsifiers are associated with mucus layer depletion and intestinal mucosal inflammation [84]. Factors implicated in MS pathogenesis include Northern latitude, stressors, low vitamin D and Epstein-Barr virus infection [85–87]. Conversely, childhood infections in developing countries may be protective against MS [46]. Maternal smoking during pregnancy and in-utero exposure to iron have been linked to T1D [88,89]. The “accelerator hypothesis” i.e., metabolic syndrome increasing the risk of T1D, although implicated, is not established [90]. According to the “prevalence gradient hypothesis”, SLE risk, low among African hosts, increases with migration away from Africa [91]. However, there are limited epidemiological data from Africa to corroborate. Smoking and depression are also implicated in SLE [92,93]. Strong gene-environment interactions are implicated in RA pathogenesis [94]. Genetic risk factors in specific populations include HLA-DRB1\*1501 allele and tumor necrosis factor- $\alpha$  polymorphisms among Iranians for MS [95], HLA allele DR3-DQ2 among Somali for T1D [63] and HLA-B27 among the Nordic for AS [71,96].

With rising immigration to developed countries such as the UK, Sweden, the US and Canada [12,97–99], IMIDs among immigrants have increased in the last decade (Fig. 3a and b). According to projected population statistics, the number of immigrants, and therefore IMIDs (e.g. IBD), will continue to rise (Fig. 4). Given rising numbers of documented [4] and undocumented immigrants [100] to developed countries, especially as the latter group has limited access to basic amenities and health-care [101,102], it is important to account for increasing disease burden and associated economic implications.

This review had several limitations. Studies included in this report are widely heterogeneous in design, populations, data collected, assessment of migration status, and diagnostic criteria for IMIDs, which significantly limits comparability. Use of hospitalization data for IMIDs, which are primarily ambulatory diseases, could underrepresent disease burden. These studies have been conducted over different time periods which can be associated with shifts in environmental exposures. While there are multiple studies from countries with reliable national databases such as Sweden, the UK and Canada, there are little data from developing countries. Limited access to health-care among immigrants in host countries could lead to under-diagnosis. The time interval between immigration and IMID diagnosis, an important variable, is not reported in several studies. While we have robust epidemiological data for IBD, MS and T1D, it is limited for SLE, RA and AS, and lacking for PPA.

Despite this, our data synthesis is largely cohesive and consistent with the existing knowledge. This is the first study to consolidate the available data and review incidence and prevalence data on the most common IMIDs in immigrants to guide future research. This study also emphasizes the impact of rising immigration and rising risk of IMIDs in immigrants on health economics. Future studies are needed to delineate IMID risk in native countries, temporal and generational trends in immigrants, the impact of age at immigration and the duration of residence in host countries.

### Conflicts of interest

The corresponding author confirms on behalf of all authors that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

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### Transparency declaration

The manuscript's guarantor (JB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethical approval was not required for this study.

There was no patient or public involvement in this study.

### Authorship statement

Johan Burisch is the submission's guarantor and takes responsibility for the integrity of the work as a whole, from inception to published article.

### Author contributions

MA and JB: study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content; SS: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content; AP: acquisition of data, analysis and interpretation of data; RP: search strategy design and execution, data management; JFC: study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

All authors approved the final version of the manuscript.

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## Appendix A. Supplementary data

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