The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by a distinctive pattern of bone and joint destruction. RA patients have an increased risk of death. The incidence and prevalence of RA vary across populations, statistical methods, and disease definitions. In North America and Northern Europe, the incidence of RA is estimated at 20 to 50 cases per 100,000 population and the prevalence at 0.5% to 1.1%. Lower incidences and prevalences have been reported in Southern Europe, and few data are available for developing countries. Some studies showed declining incidences and prevalences after the 1960s. RA is a multifactorial disease that results from interactions between genetic and environmental factors. The main genetic factors are HLA-DRB1 and the tyrosine-phosphatase gene PTPN22. Among environmental factors implicated in the development of RA, smoking shows the strongest association with RA susceptibility and is also linked to worse outcomes. The aim of this review is to discuss the available data on the incidence and prevalence of RA, as well as the genetic and environmental risk factors associated with RA.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by a distinctive pattern of bone and joint destruction. RA is also a systemic disease, and several patient subsets can be distinguished based on the presence of extra-articular manifestations. For example, the concomitant presence or absence of anti-cyclic citrullinated peptide antibody (ACPA) and rheumatoid factor (RF) defines two important patient subsets [1].

Several epidemiological studies of RA have been published. They show variations in the incidence and prevalence of RA across populations. Further variation occurs as a result of differences in statistical methods and case-ascertainment criteria. Several large prospective studies have improved our knowledge of the risk factors for RA. Unfortunately, the available epidemiological data often come from retrospective studies and underpowered case–control studies. Here, we review the main data on the epidemiology of RA and on the environmental factors involved in the disease.

2. Epidemiology

2.1. Incidence

The incidence of RA varies across populations. Estimates from North America and Northern Europe range from 20 to 50 cases per 100,000 population. In Southern Europe, lower incidences of 9 to 24 cases per 100,000 population have been reported. The incidence of RA in developing countries is unknown [2–5].

2.2. Prevalence and geographic variation

Studies done in North America and Northern Europe have shown prevalences of 0.5% to 1.1%. In Southern Europe, lower prevalences of 0.3% to 0.7% have been found [6–9]. Table 1 reports incidence and prevalence data in various populations. Prevalence data by gender and country are shown in Table 2.

We used an original case-ascertainment method to study the epidemiology of RA in the Brittany region of western France [6]. Possible cases were first identified in the general population by phone interviews conducted by trained patients with RA or other joint diseases. These possible cases were then evaluated by rheumatologists, who confirmed or refuted the diagnosis. The prevalence of RA in this study was 0.5% [6]. The case-ascertainment method was then refined and validated through a nationwide survey [10].

The few prevalence studies performed in developing countries based on the 1987 American College of Rheumatology (ACR) criteria [11] suggest significantly lower prevalences than in Northern Europe and North America, of about 0.1% to 0.5% [12,13]. Although this finding may indicate that RA is less common in developing countries, it may also reflect age distribution differences between developing countries and North America/Northern Europe. In addition, cases of mild RA may escape detection more easily in developing countries where access to medical care is limited, leading to underestimation of the prevalence of RA in studies that rely on retrospective chart review [5].

<table>
<thead>
<tr>
<th>Country</th>
<th>Females (%)</th>
<th>Males (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1.4</td>
<td>0.74</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1.16</td>
<td>0.44</td>
</tr>
<tr>
<td>Spain</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Italy</td>
<td>0.51</td>
<td>0.13</td>
</tr>
<tr>
<td>France</td>
<td>0.51</td>
<td>0.09</td>
</tr>
<tr>
<td>Greece</td>
<td>0.45</td>
<td>0.19</td>
</tr>
</tbody>
</table>

In some geographic areas, the prevalence and incidence of RA vary across ethnic groups. For example, the prevalence of RA is high among Pima Indians [14] and low in some areas of rural Africa [15]. Within ethnic groups, the incidence and prevalence of RA vary according to the geographic area of residence [16].

2.3. Time trends in the epidemiology of rheumatoid arthritis

Limited data are available on time trends of the incidence and prevalence of RA. Several longitudinal studies suggest declines in both the prevalence and the incidence of RA after the 1960s. A recent systematic review found substantial fluctuations across time periods within studies. A substantial decline in the incidence of RA over time with a shift toward an older age at onset was noted in several studies. A population-based study done in Rochester, Minnesota (US) over the 40-year period from 1955 to 1994 showed a decline in the incidence of RA from 61.2/100,000 in the first decade to 32.7/100,000 in the last decade [17]. In addition, there were indications of cyclical trends over time. In five districts of Finland, the annual incidence of RA declined by about 15% between 1980 and 1990, and the decline was largest for RF-negative disease [18].

Three factors may explain the changes in RA epidemiology over time. First, changes in study methodologies and case-ascertainment criteria may be involved. Several studies were conducted before the 1987 ACR classification criteria were issued. Also, RA is difficult to differentiate from unspecified polyarthritis, and the resulting misclassification may affect incidence figures. For example, among patients with inflammatory arthritis, only one seventh in Kuopio, Finland [19], and one fourth in southern Sweden met 1987 ACR criteria for RA. Second, geographic and ethnic factors influence incidence and prevalence data. For instance, the incidence of RA is markedly higher among Pima Indians than among other populations of North America and Europe [14]. Finally, there may be true changes in the incidence and prevalence of RA over time. Studies conducted at various time points within the same geographic regions suggest that the incidence of RA is declining over time and that this decline is greatest among women [17]. One explanation for the decline in women may be exposure to the oral contraceptives, which decreases the incidence of RA [20]. Other studies suggest a shift over time in RA onset toward older age groups. Data from the last decade suggest that the incidence of RA may be rising after four decades of decline [21].

2.4. Mortality

Mortality rates are higher among RA patients than in the general population. The life expectancy decrease is about 3 to 10 years. The excess mortality associated with RA has remained unchanged over the last two to three decades. In addition, recent studies show that RA patients have not experienced the survival gains seen in the general population, so that the gap between the two has widened [22]. The main causes of death in RA patients are cardiovascular, infectious, haematological, gastrointestinal, and pulmonary complications.
3. Risk factors for rheumatoid arthritis

RA is a multifactorial disease that results from interactions between genetic and environmental factors. Personal and lifestyle factors influence the course of the disease. A comparison of smoking history between twins with RA and their unaffected co-twins established that smoking was closely associated with RA [23]. In this study, of the 13 pairs of monozygotic twins discordant for RA and smoking history, the twin who had RA was also the twin with a history of smoking in 12 of the pairs. Below we discuss the main factors believed to influence the development and/or course of RA.

3.1. Genetic factors

Genetic factors contribute 50% to 60% of the risk of developing RA. The gene most strongly associated with RA is the HLA-DRB1 gene in the major histocompatibility complex, where specific alleles within the DRB1*04 and *01 clusters encode the “shared-epitope” sequences within the expressed DRB1 molecule [24]. HLA-DRB1 may contribute up to one-third of the genetic susceptibility to RA. Among other genes, the main RA susceptibility factor is the tyrosine-phosphatase gene PTPN22 on chromosome 1. A missense C-to-T substitution at nucleotide position 1856 of this gene leads to substitution of tryptophan (W) for arginine (R) at residue 620 of the protein product. The resulting gain of function, with enhanced regulation of T-cell receptor (TCR) signalling during thymic selection, permits autoantigen-specific T cells to escape clonal deletion, thereby predisposing to autoimmunity [25]. This PTPN22 polymorphism is not seen in Asian populations. A vast collaborative epidemiological study duplicated the findings in Swedish, Dutch, and US populations, showing multiplicative effects between smoking and the shared-epitope, as well as between the PTPN22 polymorphism and the shared-epitope. The HLA-DRB1 shared-epitope and PTPN22 risk alleles are associated only with the RA pattern characterized by the presence of ACPA, RF, or both.

Polymorphisms of TRAF1-C5 and TNFAIP3 have also been described in RA. Other non-HLA genetic risk factors such as STAT4 [26] and CTLA4 [27] have been identified in European populations, although not with genome-wide significance.

A case–control study in a Dutch cohort was conducted to assess the impact on RA susceptibility of three recently described loci, namely, STAT4, IL2/IL21, and CTLA4. These loci were genotyped in 877 RA patients and 886 healthy individuals. The results showed that each of these three loci was associated with RA (odds ratios, 1.19 [P = 0.031], 0.84 [P = 0.051], and 0.87 [P = 0.041], respectively). These results constitute convincing evidence that STAT4 and CTLA4 are associated with RA and highly suggestive evidence that IL2/IL21 is associated with RA in Caucasian individuals [28].

Substantial differences in genetic RA susceptibility factors have been found between European and Asian populations. HLA-DRB1 is the only known genetic factor that is associated with RA in all the populations studied to date [29]. PTPN22 polymorphisms have been identified in European populations but are rarely found in Asian populations. On the contrary, polymorphisms of PADI4 (which encodes an enzyme that converts the arginine residues of proteins into citrullines, which can then be recognized by ACPAs in the sera of RA patients) have been found more consistently in Asian than in European populations [29].

3.2. Age and gender

RA is far more common in women than in men, the female-to-male ratio being 3:1. However, the mechanism by which gender influences the susceptibility to RA remains unclear. Differences in sex hormones may be involved. The peak age at RA onset is the fifth decade, which is a time of hormonal changes in women. However, recent studies suggest a shift toward an older age at onset in recent years, with this change being greater in women than in men.

3.3. Socioeconomic factors

Socioeconomic factors affect the course and outcome of RA but do not seem to influence the risk of developing RA.

3.4. Hormonal factors

The predominance of RA in females suggests a role for hormonal factors. In addition, estrogens stimulate the immune system. Low testosterone levels have been reported in men with RA [30]. A history of child-bearing may protect against RA. In patients with RA, pregnancy often leads to a remission, followed by a flare-up after delivery. Hormone replacement therapy (HRT) may decrease the RA risk in women who carry the HLA-DRB1 *01 and/or *04 alleles [31]. One possible explanation to this finding is that HRT protects against the production of ACPA (OR = 0.43; 95% CI, 0.24–0.77; P = 0.006). Nevertheless, these results must be confirmed in other populations.

3.5. Ethnicity

Some ethnic and racial groups are at higher risk for RA than others. This high risk may be related to differences in the distribution and interactions of genetic and environmental factors. Comparisons of populations with similar genetic backgrounds but different lifestyles can shed light on the influence of non-genetic factors. We used a standardized questionnaire to screen the nuns of the nine largest Roman Catholic communities in Brittany, as well as 1706 adult females from the general population. We found similar prevalences of RA in these two groups (1.66% vs. 1.33%) [32].

3.6. Environmental factors

The effects of several environmental factors on the risk and outcome of RA have been studied. Environmental factors that affect RA may act many years before the disease becomes clinically apparent. Here, we discuss the main environmental factors implicated in the development of RA.

3.6.1. Smoking

Among environmental factors, smoking has by far the strongest association with RA. Smoking increases susceptibility to RA and adversely affects the clinical course of the disease, as shown by cross-sectional and longitudinal studies [33]. Smoking is associated with RF and ACPA production. In addition, smoking multiplies the adverse effect of the HLA-DRB1 shared-epitope alleles. Heavy cigarette smoking has been linked to a substantial increase in the susceptibility to RA. The risk of RA increases after 10 pack-years of smoking and remains elevated up to 20 years after smoking discontinuation. The effect of smoking may be related to tetrachlorodibenzo-p-dioxin (TCDD), which up-regulates the expression of IL-1beta, IL-6, and IL-8 by binding to the arylhydrocarbon receptor, whose effect is transmitted via the nuclear factor-kb and extracellular signal-regulated kinase signalling cascades. TCDD induces inflammatory cytokines and may therefore exacerbate the pathophysiological mechanisms involved in RA [34]. Other potential factors include silica dust, mineral oils, and other airborne exposures.

3.6.2. Infections

Several microorganisms have been implicated in the development of RA (Table 3) based on higher titres of the relevant antibodies in patients with RA. One possibility is that these microorganisms trigger the development of RA in individuals who carry genetic susceptibility factors to the disease.
Infectious agents reported to trigger rheumatoid arthritis.

- Human parvovirus B19
- Rubella virus
- Human retrovirus 5
- Alphaviruses
- Hepatitis B virus
- Epstein–Barr virus
- Borrelia burgdorferi
- Mycoplasma
- Mycobacterium tuberculosis
- Escherichia coli
- Proteus mirabilis
- Porphyromonas gingivalis

All unsubstantiated based on evidence-based research.

However, the role for microorganisms as initiating factors of RA remains controversial. Clearly, no single microorganism is responsible for the development of RA. Evidence supporting a role for parvovirus B19 includes the presence of viral DNA in the synovial fluid, synovial cells, and/or synovial tissue of RA patients. Sera from RA patients contain high titres of Epstein–Barr virus (EBV) antigens and of antibodies to latent and replicative EBV antigens. In addition, EBV RNA has been identified in B cells in synovial tissue from RA patients [35]. Despite these findings, the evidence that microorganisms are involved in the development of RA remains inconclusive.

### 3.6.3. Dietary factors

A diet rich in fish, olive oil, and cooked vegetables has been shown to protect against RA, an effect ascribed to the high content in these foods of omega-3 fatty acids. Several studies found that populations of southern Europe had milder forms of RA, with fewer extra-articular and radiological manifestations, compared to other populations. This difference may be ascribable in part to the Mediterranean diet.

A high vitamin D intake has been associated with lower risk of RA. Vitamin K, which is found primarily in legumes and other vegetables, may inhibit the proliferation of fibroblast-like synoviocytes, thereby diminishing the severity of inflammation in RA.

A recent systematic review of the literature evaluated the effects of dietary manipulation in patients with RA [36]. The interventions included vegetarian, Mediterranean, elemental, and elimination diets. The results were inconclusive, because the studies were small and had substantial risks of bias. In addition, there was often a single study available for a given intervention. Weight loss was an adverse effect in the dietary intervention groups [36].

### 3.6.4. Pollutants

Pollutants may affect the risk of developing RA. As with cigarette smoke, inhaled particulate matter may induce both local lung inflammation and systemic inflammation. Indirect support for this hypothesis comes from the established link between air pollution and diseases involving pulmonary and systemic inflammation such as asthma and chronic bronchitis, cardiovascular disease, and lung and laryngeal cancers. A recent study [37] nested in the Nurse’s Health Study examined the distance between the place of residence in 2000 and the nearest road, which served as an indicator of exposure to traffic pollution. The required data were available for 90,297 nurses. The statistical models were adjusted for age, calendar year, race, cigarette smoking, parity, lactation, menopausal status and hormone use, oral contraceptive use, body mass index, physical activity, and census-tract-level median income and house value. Women living within 50 m of a road had an increased risk of RA (hazard ratio, 1.31; 95% CI, 0.98–1.74), compared to women living 200 m or farther from a road. Thus, exposure to traffic pollution in adulthood may be a newly identified environmental risk factor for RA.

### 3.6.5. Urbanization

Urbanization has been associated with an increased prevalence of RA. For example, in the Xhosa tribe of South Africa, the prevalence of RA is higher among individuals living in an urban rather than a rural environment. Similar findings have been obtained in urban, suburban, and rural populations in Taiwan [38]. These results suggest that environmental factors may affect RA susceptibility in individuals who share the same genetic background.

### 3.6.6. Early environmental factors and birth weight

The risk of developing RA may be influenced by early environmental factors such as growth and diet. In one study, high birth weight was positively associated with RA (OR, 3.3), whereas breast feeding was protective (OR, 0.2). The risk of RA associated with high birth weight was evaluated in 87,077 women followed prospectively as part of the Nurses’ Health Study [39]. RA was diagnosed in 619 women between 1976 and 2002. After adjustment for age and potential confounders, birth weight greater than 4.54 kg was associated with a 2-fold increase in the risk of RA compared to birth weight in the 3.2–3.85 kg range (relative risk, 2.1; 95% CI, 1.4 to 3.3).

Studies suggest that a history of infections in infancy may protect against RA in adulthood.

Another factor that may influence the risk of RA is microchimerism, which is the persistence in the body of cells and/or DNA that travelled from the foetus to the mother during pregnancy. These cells can persist in the mother for several decades and may contribute to the development of autoimmunity. In one study, DRB1*01 or DRB1*04 microchimerism was looked for in 33 women with RA and in 46 healthy women who had no RA-associated genes such as HLA-DRB1*01 (n = 33 and n = 46, respectively) and/or HLA-DRB1*04 (n = 48 and n = 64, respectively) [40]. Compared to the control groups, the RA groups had significantly higher rates of DRB1*04 microchimerism (8% vs. 42%; P = 0.00002) and DRB1*01 microchimerism (4% vs. 30%; P = 0.0015). Thus, RA patients had higher rates of microchimerism with RA-associated HLA alleles, but not with non-RA-associated HLA alleles, compared to healthy women.

### 3.7. Gene–environment interactions

One of the most important findings from epidemiological and risk factor studies of RA is the interaction between the HLA shared-epitope and smoking. In a population-based case–control study, the risk of developing RF-positive RA was substantially higher in smokers carrying two copies of shared-epitope genes (RR, 15.7) than in smokers with no copies of shared-epitope genes (RR, 2.4) [33]. Studies have also shown an additive interaction between PTPN22 and smoking [33]. These studies establish that both genetic and environmental factors are important to the development and clinical outcome of RA.

### 4. Conclusions

Epidemiological studies have found substantial variations in the incidence and prevalence of RA across time periods and geographic regions. A substantial decline in RA incidence over time, with a shift toward an older age at onset, was found in several studies. There are virtually no epidemiologic data from developing countries. ACPA-positive patients with RA differ from ACPA-negative patients regarding genetic (HLA-DRB1 and PTPN22) and environmental (smoking) risk factors for RA.

### Take-home messages

- The incidence and prevalence of rheumatoid arthritis (RA) vary across populations, methodologies, and case-ascertainment criteria.

The incidence and prevalence of RA are higher in North America and Northern Europe than in Southern Europe and developing countries. Both the prevalence and the incidence of RA have declined over the last four decades. RA is a multifactorial disease that involves both genetic and environmental factors.

**HLA-DRB1** and **PTPN22** are the main genetic factors associated with the development of RA. RA patients who carry these genes are likely to produce anti-cyclic citrullinated peptide antibodies. Environmental factors whose potential role in RA has been investigated include infections, smoking, pollutant, and dietary factors. Smoking is the main environmental factor associated with RA.

### References


[14] Salliot C, Bombardier C, Saura A, Combe B, Dougados M. Hormonal replacement therapy may reduce the risk for RA in women who carry HLA-DRB1 *01 and or *04 alleles by protecting against the production of anti-CCP. Results from the ESPOIR cohort. Ann Rheum Dis 2009 (in press).


[23] Begovich AB, Commalierini D, Saura A, Combe B, Dougados M. Hormonal replacement therapy may reduce the risk for RA in women who carry HLA-DRB1 *01 and or *04 alleles by protecting against the production of anti-CCP. Results from the ESPOIR cohort. Ann Rheum Dis 2009 (in press).


[32] Begovich AB, Commalierini D, Saura A, Combe B, Dougados M. Hormonal replacement therapy may reduce the risk for RA in women who carry HLA-DRB1 *01 and or *04 alleles by protecting against the production of anti-CCP. Results from the ESPOIR cohort. Ann Rheum Dis 2009 (in press).

