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Global epidemiology of rheumatoid arthritis

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Abstract | Rheumatoid arthritis (RA) is a systemic autoimmune disease that predominantly affects the joints. The prevalence of RA varies globally, with generally a higher prevalence in industrialized countries, which may be explained by exposures to environmental risk factors, but also by genetic factors, differing demographics and under-reporting in other parts of the world. Over the past three decades, strong trends of the declining severity of RA probably reflect changes in treatment paradigms and overall better management of the disease. Other trends include increasing RA prevalence. Common risk factors for RA include both modifiable lifestyle-associated variables and non-modifiable features, such as genetics and sex. A better understanding of the natural history of RA, and of the factors that contribute to the development of RA in specific populations, might lead to the introduction of specific prevention strategies for this debilitating disease.

Rheumatoid arthritis (RA) is a chronic rheumatic disease, characterized by progressive articular damage and extra-articular manifestations, which can lead to permanent disability and which is associated with a mortality rate higher than that in the general population. RA is the most prevalent systemic autoimmune disease among the rheumatic inflammatory musculoskeletal diseases. RA can be difficult to treat, and it generally necessitates lifelong therapy, but advances in management paradigms and the development of more effective treatments have resulted in considerable progress. Although the disease itself is associated with enormous indirect costs resulting from lost productivity[1], newer treatments also incur a high financial burden[2]. Some of the more recent second-line therapies for RA are not considered to be affordable medications within all health-care systems, further contributing to heterogeneous management and outcomes of the disease worldwide.

In this Review, we focus on the global epidemiology of RA and discuss regional differences in its prevalence. We comment on temporal trends associated with the disease, in terms of both epidemiology and disease impact. Finally, we summarize evidence relating to some of the more established risk factors of RA, which might contribute to the regional differences in the epidemiology of the disease.

Global epidemiology of RA

Methodological considerations

Numerous studies have assessed the prevalence and incidence of RA. Many of the epidemiological estimates from the literature are difficult to compare, given the wide variety of methods used for collection of the information and the variable definitions used for RA. Studies of low-prevalence diseases (that is, ≤1%), such as RA, are vulnerable to methodological pitfalls, including various selection biases and information biases. For example, self-reported RA typically overestimates true disease prevalence, as it can include the reporting of any musculoskeletal pain or other rheumatic disease as RA, resulting in an ascertainment bias[3–5].

Several approaches can be taken to optimize the accuracy of estimates of RA incidence and prevalence. In the reporting of the Global Burden of Disease (GBD) 2017 study, a unified method was proposed to overcome the heterogeneity of the existing literature in estimating the prevalence of RA[6]. The GBD 2017 study incorporates 121 sources for RA, from 42 countries, using the 1987 ACR RA classification criteria as a reference for case definition. These RA sources cover a large time window, from 1950 to 2016, and include published literature, survey data, surveillance data and claims data, but exclude hospital and clinical data because they are not necessarily representative of the general population[7]. GBD prevalence and incidence rates are modelled using a Bayesian meta-regression tool, and provide epidemiological estimates and predictions for all countries. The WHO–ILAR Community Oriented Program in the Rheumatic Diseases (COPCORD) is another global effort to provide standardized epidemiological data relating to musculoskeletal diseases. Notably, most RA–COPCORD publications have been integrated into the GBD sources. Even though a 2019 version of the GBD study exists, the input sources for RA have not been updated[8]; hence, in this Review we rely mostly on the GBD 2017 estimates of

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Key points

- The estimated prevalence and disease burden of rheumatoid arthritis (RA) vary considerably between geographic regions, with generally higher estimates in industrialized countries and urban settings.
- Aspects involved in the disparity in RA prevalence between populations include genetic factors, environmental exposures, demographics, socioeconomics and reporting of the disease.
- Despite rising RA prevalence, the severity, mortality and disease-associated comorbidities seem to be decreasing.
- The aetiopathogenesis of RA involves interaction between predisposing genetic factors and environmental triggers, mostly at mucosal sites (oral cavity, respiratory system and intestinal tract), resulting in the 'mucosal origin' hypothesis.
- Many RA risk factors are modifiable, including dietary habits and inhalation of pollutants such as tobacco smoke; modifications are being incorporated in prevention strategies.

prevalence and incidence of RA[7]. However, when relevant, we refer to country-specific studies published later than 2016 or that were omitted by the GBD.

Prevalence and incidence estimates are often congruent, but they can diverge if population demographics differ. With an ageing population, the prevalence of a chronic disease might be exaggerated relative to its incidence. Examination of the age of onset of RA in a worldwide survey[9] notably indicated that age at onset was about 8 years lower around the Tropic of Cancer than in northern and southern latitudes ($P < 0.001$; 95% confidence interval (CI) 3.5–13 years). However, the interpretation of this finding is not straightforward, as various biases might be involved, including selection biases, access to specialized care and the age structure of the population. Furthermore, incidence studies require longer follow-up or larger samples than studies of prevalence, so they are less frequently available. To address these potential complications, when possible we report age-standardized and/or sex-standardized prevalence and incidence.

In the GBD 2017 data, the age-standardized prevalence of RA was higher in North America (0.38%; 95% CI 0.36–0.40%), western Europe (0.35%; 95% CI 0.31–0.38%) and the Caribbean (0.34%; 95% CI 0.30–0.37%) than in Oceania (0.14%; 95% CI 0.12–0.15%), western sub-Saharan Africa (0.13%; 95% 0.11–0.15%) or southeast Asia (0.10%; 95% CI 0.089–0.11%) (FIG. 1)[7]. Similar geographical patterns in disease epidemiology occur with other autoimmune diseases, such as systemic lupus erythematosus[10]. Differences in population characteristics, socioeconomic or environmental risk factors, the methods used for classification of RA and the availability of specialists in rheumatology, related to RA diagnosis and survival, are likely to contribute to the observed heterogeneity in RA prevalence.

A 2021 meta-analysis of 67 RA-cohort incidence and prevalence studies from 41 countries found a pooled prevalence of 0.46% (95% CI 0.37–0.57%) for the period 1986–2014 (REF.[11]). Although this estimate is almost twice the 2017 global prevalence of 0.27% (95% CI 0.24–0.3%) found in the GBD study[7,12], the use of stricter inclusion criteria for the meta-analysis might have reduced potential biases, as half the studies included in the GBD were rated at a high risk of bias.

Epidemiological data

Here, we briefly discuss some of the main epidemiological findings by continent, including specific regional characteristics. On the basis of the 2017 GBD data, the prevalence of RA is highest in developed countries, followed by India and South American countries (FIG. 1). RA prevalence also seems to be lower in rural settings compared with urban settings, although the published data are inconsistent about this issue[13].

Africa. In the 2017 GBD study, regional differences in RA prevalence were found in Africa, in particular higher estimates in North Africa and the Middle East (0.26%) compared with western sub-Saharan Africa (0.14%), with a similar trend in incidence (37 per 100,000 patient-years in North Africa and the Middle East and 23 per 100,000 patient-years in western sub-Saharan Africa)[7]. Higher RA prevalence could reflect urbanization, greater life expectancy, higher average population age, improved awareness of RA (with more health-care workers available to diagnose RA) and/or a greater disease burden. Trends in prevalence were paralleled by similar tendencies in incidence, suggesting that the prevalence estimates did not only represent differences in age demographics[14–18].

Clinical presentation differences noted in studies of RA in Africa include patterns of joint involvement, with less finger and thumb involvement among Black South Africans than among white patients[19]. Notably, in a large, multi-ethnic study, knee and large-joint involvement was more common in South African patients than in those from the Netherlands[20]. Importantly, a diagnostic lag together with delayed initiation of DMARDs contributes to the poor outcomes described in African populations[21,22].

The evaluation of prevalence and incidence of RA in Africa is hampered by the lack of reliable data, in this continent where many countries are among the poorest in the world[23]. In addition, the large burden of infectious diseases (such as AIDS, hepatitis B, hepatitis C, Chikungunya and Ebola)[14–18] could contribute to the difficulty in estimating the true occurrence of RA, given that these conditions can present as inflammatory arthritis mimicking RA.

Asia. In the GDB 2017 study, the estimated prevalence of RA was 0.32% for South Asia, 0.21% for Central Asia, 0.19% for East Asia and 0.10% for Southeast Asia. A similar reported pattern for age-standardized incidence

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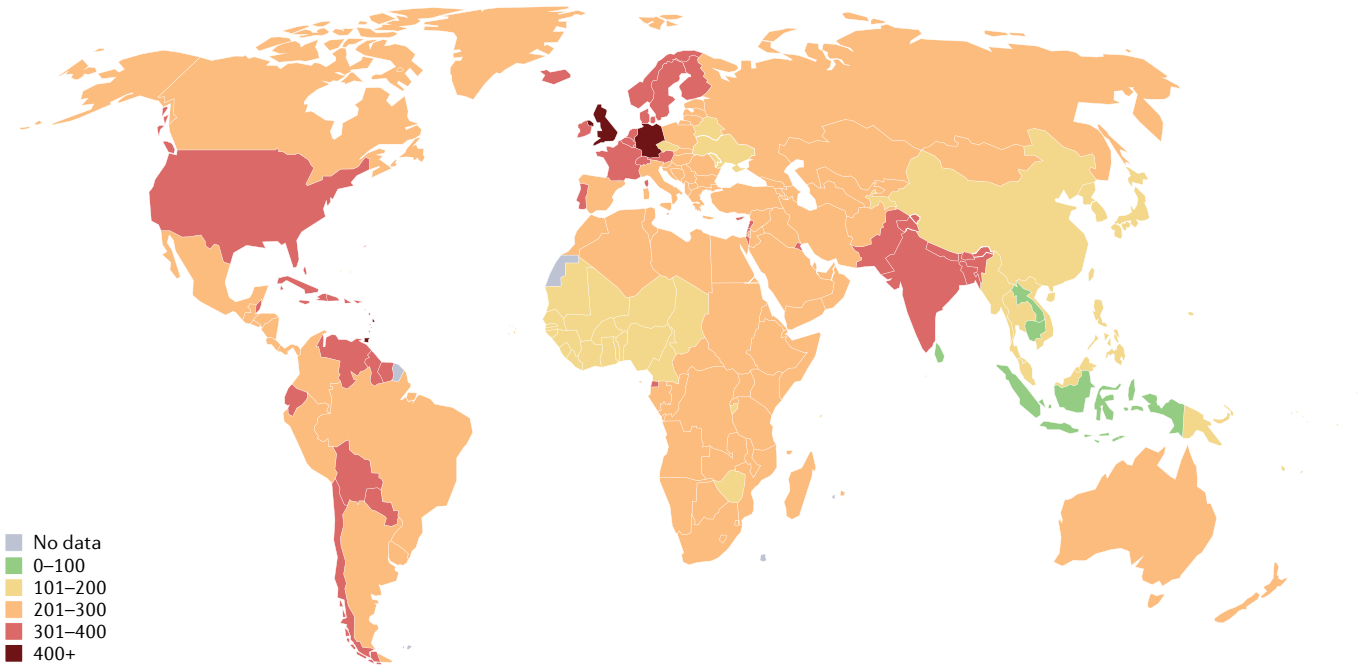

Fig. 1 | **Global prevalence of rheumatoid arthritis.** The figure displays the reported prevalence ranges for rheumatoid arthritis (RA) per country (per 100,000 of the population), as denoted by the key. The plotted data, which are from the Global Burden of Disease (GBD) 2017 study (GBD-2017), can be accessed via the GBD-2017 query tool. Appendix 1 of the 2017 GBD study[6] contains detail about included sources and subsequent modelling strategy. Briefly, after extensive literature searches, population-based studies were selected (hospital or clinic-based studies were excluded) for 42 countries and 23 regions, from 1950 to 2016. Missing data were then modelled with the Bayesian meta-regression tool DisMod-MR 2.1, based on other covariates of the GBD study, assuming a natural (that is, drug-free) remission rate and the absence of RA under 5 years old. ACR 1987 criteria were set as the reference for case definition.

includes a rate of 21 per 100,000 patient-years for South Asia, with lower rates for Central Asia (13 per 100,000 patient-years), East Asia (12 per 100,000 patient-years) and Southeast Asia (6.2 per 100,000 patient-years)[7]. These regional differences in the epidemiology of RA in Asia could be the results of genetic or environmental factors, or of differences in the methodology used for the collection of the information. Asia comprises both low-income countries and high-income countries. RA estimates in lower-income and middle-income countries are almost all based on the COPCORD method[24]. In a national survey, based on self-administered questionnaires, the prevalence of RA in Japan in 2020 was estimated at 0.75% (REF.[25]). In Taiwan and South Korea, the use of claims databases has resulted in RA prevalence estimates of 0.14–0.32%, and incidence estimates of 18.5–28.5 per 100,000 patient-years[26,27]. In China, a two-stage study consisting of a home-administered questionnaire followed by a clinical examination of positive responders found an age-adjusted RA prevalence of 0.28% (REF.[28]).

Europe. According to the estimates obtained from the GBD data, age-adjusted prevalence and incidence of RA are higher in the northern and western European countries (about 0.40% prevalence and 20–30 new cases per 100,000 patient-years) than in southern and eastern European countries (approximately 0.20% prevalence and 7–15 new cases per 100,000 patient-years) (FIG. 1). The GBD-estimated RA prevalence in Europe increased slightly between 1990 and 2015, as did the incidence. However, in another study, contradictory findings were reported with regard to RA incidence in the UK, indicating that it decreased after 2005 (REF.[29]). The latter study also highlighted regional variations in prevalence and incidence, which were suggested to stem mostly from heterogeneity in smoking habits. Some studies have produced prevalence estimates for specific European countries that tend to be higher than those from the GBD study, which could result from methodological variations, age adjustments and RA case definition[29–35]. The reported female-to-male ratios for incidence vary around approximately 2:1 (REFS.[7,36–39]), with female-to-male prevalence ratios ranging from 1.4:1 in Poland to 5.7:1 in France (REFS.[30–32,36,37,40–44]).

Latin America. In the GBD study, the regional prevalence of RA ranges from 0.25% in the Central Latin America region to 0.31% in the Andean Latin America region[7]. However, country-specific age-adjusted prevalence can vary considerably from this range, with published values as low as 0.1% in a particular region of Brazil and as high as 3.2% in an indigenous community in Argentina[45,46]. RA prevalence is generally greater in indigenous communities than in non-indigenous populations in Latin America[47]. In a study of regional variation of RA prevalence in Mexico (using COPCORD methodology), estimates ranged from 0.7% to 2.8% (REF.[48]), whereas in Buenos Aires, Argentina, the prevalence in 2015 was 0.33% and the incidence (calculated

using data obtained from 2000 to 2015) was 18.5 per 100,000 patient-years[49]. Variations within countries or between ethnicities are not well captured by the GBD study, so the generalizability of the GBD estimates is not known. Among the limitations of available epidemiological studies, including the GBD, are a focus on predominantly urban or other specific communities.

Results from population studies in Latin America also highlight the fact that limited access to rheumatological assessment contributes to an important delay to diagnosis[50]. Overall, Latin American countries have an average of 0.93 rheumatologists per 100,000 inhabitants, compared with 1.28–3.07 per 100,000 inhabitants in North America, and ranging from no rheumatology specialist at all in Guyana to 3.6 rheumatologists per 100,000 inhabitants in Uruguay[51–53].

North America. According to the GBD data, an age-standardized prevalence of 0.38% and an age-standardized incidence of 22.5 per 100,000 patient-years can be estimated for North America. A study from the US Centers for Disease Control determined in 2008 that the prevalence of RA in the USA as a whole was about 0.6% (REF.[54]). More recently, analysis of health-care claims among more than 40 million individuals in the USA estimated that RA prevalence was between 0.54% and 0.63% (REFS.[55,56]). Women had a higher prevalence of RA than men (0.73% versus 0.29%)[55,56]. Claims-based studies are limited in that they largely assess individuals with health-care insurance, and the 'diagnosis' of RA is generally made by algorithms that utilize diagnostic codes, which might not accurately reflect the diagnosis of RA according to classification criteria. Estimates of age-standardized and sex-standardized prevalence are slightly higher (0.65–0.78%) in Canada than in the USA[57–59]. Furthermore, within the USA, estimates indicate a younger age at diagnosis and higher prevalence in the east than in the west[60]. Notably, in Canada, incidence among First Nations people in Manitoba is around twice as high as in the area's non-First Nations population[57–59]. Prevalence in some indigenous US populations is also high, with estimates ranging from 1.4% to 7.1%, with the highest rates occurring in the Chippewa population (6.8–7.1% RA prevalence)[61–63]. Furthermore, the average age of indigenous North Americans with RA is lower than that of the non-indigenous population, whereas the female-to-male ratios are similar.

Oceania. In the GBD study, modelling replaced missing epidemiological data from Oceania, which had an overall prevalence estimate of 0.13% (REF.[7]). Prevalence and incidence estimates were higher for Australia and New Zealand (prevalence about 0.27%, 16 new cases per 100,000 patient-years) than for the other islands of Oceania (about 0.15% prevalence, about 7 new cases per 100,000 patient-years). Although the Australian Bureau of Statistics reports a prevalence of 2%, this value is based on self-reported data from 2014–2015 (REF.[64]). A study using the Australian national primary health-care database reported a lower RA prevalence of 0.8% for the period 2000–2016, but this study also mistakenly included patients with a diagnosis of polymyalgia rheumatica among those categorized as having RA[65].

Box 1 | **Global trends in rheumatoid arthritis**

Increasing over time
- Prevalence and incidence
- Age at disease onset

Decreasing over time
- Mortality (including cardiovascular mortality)
- Orthopaedic surgeries
- Time between diagnosis and initiation of anti-rheumatic therapies

Global trends

Trends in RA prevalence and incidence

The results of the 2017 GDB study indicate that the global age-standardized prevalence of RA increased by 7.4% (95% CI 5.3–9.4%) and the incidence by 8.2% (95% CI 5.9–10.5%) between 1990 and 2017 (BOX 1), thereby increasing the number of years lived with disability worldwide attributable to RA (from 0.24% to 0.31% as a percentage of total years lived with disability worldwide between 1990 and 2017), albeit with some regional differences in trends[7]. Interestingly, in a US study with a population-based inception cohort, a differential trend in incidence between 1985 and 2014 was identified according to the type of RA, with a decrease in seropositive RA but an increase in seronegative RA, using the 1987 ACR classification criteria[7,66].

Establishing whether apparent changes in the incidence and prevalence of RA over time are real is difficult, as findings can be confounded by improvements in the awareness and detection of RA, and by increases in life expectancy. Overall, across all countries and regions, accurate epidemiological estimates for RA are limited, although ongoing improvement in access to health care might help to provide more data[23]. Underlying trends in environmental risk factors are likely to affect the incidence of RA, and these trends vary between countries. For instance, as discussed below in greater detail, smoking and occupational exposure to silica have decreased in Westernized countries, such as the USA, Europe and Australia[67–70], whereas in other parts of world exposure to tobacco smoke is predicted to increase, and environmental exposure to arthritogenic substances (such as various forms of air pollution) is an ongoing concern[71].

Trends in mortality

RA is associated with mortality, with as much as a 50% higher risk of cardiovascular mortality compared with the general population[72,73]. Because RA disease activity is strongly associated with mortality[74], survival might have been expected to improve along with the changes in treatment paradigms that have occurred in the past few decades, including early intervention[75,76] and treat-to-target approaches[77]. Data from the GBD identify a decrease, between 1990 and 2017, in age-standardized mortality from RA and other musculoskeletal diseases in western Europe, in high-income Asia Pacific countries and in southern Latin America[78]. However, this trend is reversed in Central Asia, Eastern Europe and tropical Latin America[78]. Notably, data on trends in RA-specific

mortality are not available, making it difficult to evaluate whether the trends described above are associated with RA or with other musculoskeletal conditions. In the UK, three studies, one using administrative health data[79] and two using electronic-medical-record databases[80,81], identified an improvement in overall survival of patients with RA in the 2000s compared with the 1990s[82,83]. In Canada, a similar trend of a decline in the mortality of patients with RA was observed, although the excess risk of mortality compared with the general population (the 'mortality gap') remained unchanged, with 40–50% excess mortality in patients with RA[84]. Likewise, nationwide studies from Sweden and from the Netherlands have identified excess mortality in patients diagnosed with RA compared with the general population[85,86]. In the UK Norfolk Arthritis Register, no improvement in mortality was identified between 1990 and 2011 in patients with early inflammatory arthritis compared with the general population[87].

In relation to specific causes of mortality, studies conducted in the USA and in Norway have identified reduction of numbers of cardiovascular events and cardiovascular mortality in patients with RA in the 2000s, suggesting that the previously described excess cardiovascular mortality is no longer observed[82,83]. Interstitial lung disease is strongly associated with RA disease activity and is another common cause of increased mortality in patients with RA. Results from a US study using death certificates suggested a trend for decreased age-standardized mortality attributable to interstitial lung disease between 1999 and 2018 (REF.[88]). The decrease in mortality caused by interstitial lung disease was most pronounced in women[88], and in the age group 65–74 years[89]. Similar findings were suggested in a study of a cohort from Minnesota, USA[90], which demonstrated a trend for lower mortality attributable to RA-related interstitial lung disease in the period 1999–2014, compared with 1955–1994.

Taken together, available data suggest that overall mortality, cardiovascular mortality and possibly interstitial lung disease mortality associated with RA have decreased in recent decades in high-income countries. These trends may reflect better management of comorbidities. At the same time, however, mortality has fallen in the general population, so that the mortality gap for patients with RA in these countries has remained largely unchanged. In other parts of the world, trends in overall mortality and cause-specific mortality in RA are scarce, and difficult to interpret[88,89].

Trends in disease severity

A systematic review evaluating trends in RA severity over time identified a trend for decreasing disease activity at RA onset, with lower disease activity at presentation in two European studies, suggesting a trend towards earlier diagnosis[91]. For extra-articular manifestations, despite improvement in treatments, no change in incidence was observed in a Minnesota cohort with RA diagnosed between 1955 and 1995 and followed up to 2000 (REF.[92]). However, in a UK study the incidence of rheumatoid vasculitis decreased between 1988 and 2002, and in a Finnish study a decrease in the incidence of renal failure resulting from amyloidosis was observed between 1988 and 1997 (REFS.[93,94]). More recent studies or studies of other trends in extra-articular manifestations are lacking.

Surprisingly, despite progressive improvement in the management of RA and a reduction in the radiographic progression of structural joint damage, the prevalence of functional disability does not seem to have decreased over time[95,96]. A possible explanation is that some confounding by age is occurring, as patients with RA now have greater life expectancy, and loss of function is strongly associated with ageing. Indeed, although estimates of the crude disability-adjusted life years (DALY) lost in patients with RA showed an increase over time in the 2017 GBD study, the age-standardized DALY rate did not substantially change from 1990 to 2017 (REF.[7]).

Improvements in the treatment of RA should affect the progression of joint damage and rates of orthopaedic surgery. In an English cohort study published in 2019, lifetime risks of knee and hip replacement following a diagnosis of RA were estimated to be 22% and 17%, respectively, which are around double the risks in the general population[97], but rates of prosthetic joint replacement seem to be declining in patients with RA since the beginning of the century[98]. Likewise, in a Norwegian study, a general decline in the rates of arthroplasties, arthrodesis and synovectomies was observed among patients with RA between 1997 and 2011 (REF.[99]). Notably, these trends differ according to the joint location. In a nationwide US study, a reduction in the proportion of patients with RA needing total elbow or shoulder arthroplasty, but not those needing total hip or knee arthroplasty, was observed between 2002 and 2012 (REF.[98]). A retrospective medical-record review of patients in Minnesota also found a reduction in small-joint surgery, but not in large-joint surgery, between 1980 and 2013, with the latter even trending upwards[100]. Similarly, in the UK, a trend for the reduction of small-joint (foot and ankle) surgery, but not large-joint surgery, was found between 1986 and 2012 (REF.[101]). In Brazil, a decrease in the number of hospital admissions for orthopaedic surgical procedures related to RA was observed between 1996 and 2009 (REF.[102]), while at the same time the rates of total hip and knee arthroplasty increased in the general population[103,104].

Altogether, it seems as though newer and more potent antirheumatic therapies and aggressive approaches to the management of RA have resulted in a measurable improvement in the severity of RA, although perhaps not in functional disability in large joints.

Risk factors for RA

Progressive changes and regional differences in the prevalence of RA might be related, at least in part, to variation in risk factors. Many risk factors for RA have been described (FIG. 2), and a detailed discussion of them all is beyond the scope of this Review. Instead, we focus here on female sex and on some environmental risk factors for which there is evidence relating to the epidemiological findings described above. Our hope is that further understanding of the environmental factors that affect the development of RA can lead to actionable prevention of the disease in the future.

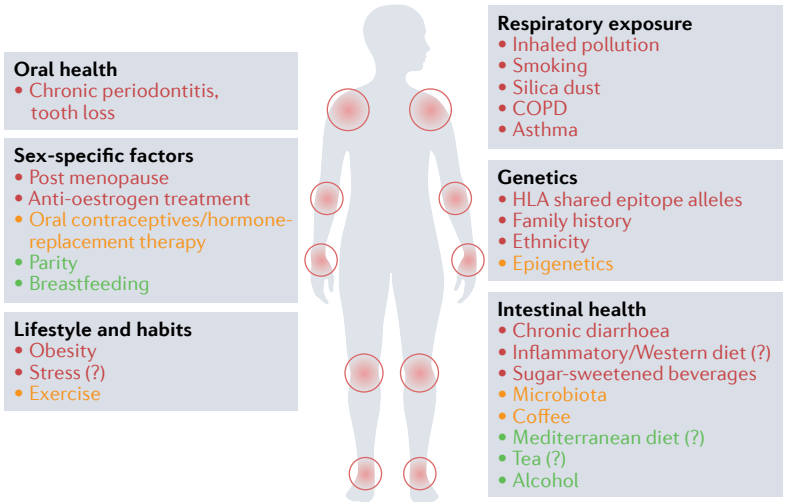

Fig. 2 | **Known risk factors for rheumatoid arthritis.** Many factors can contribute to the risk of developing rheumatoid arthritis (RA), including genetic factors, respiratory exposure, hormonal factors, dietary factors, oral health and lifestyle. These factors can be protective or detrimental, and varying levels of evidence are available to link them to RA. In this Figure, green text indicates protective factors; red indicates detrimental factors and orange indicates conflicting or weak evidence. Several of these risk factors may interact together, and with genetic predisposition, to affect the risk of disease. COPD, chronic obstructive pulmonary disease.

Female sex and hormonal factors

Globally, RA is more prevalent in women than in men[105–108], with a female-to-male sex ratio ranging from 4:1 in younger individuals to less than 2:1 in older populations with the disease[109]. Results from several studies have indicated that a sudden decline of oestrogenic function (seen in menopause, or with the use of anti-oestrogenic therapies) might be a risk factor for the development of RA, and that factors related to high oestrogen exposure may be protective. In the Nurses' Health Study cohort, post-menopausal status was associated with a higher risk of developing seronegative RA than pre-menopausal status, particularly for women with an early menopause (occurring at <44 years of age)[110,111]. The use of anti-oestrogenic agents such as selective oestrogen-receptor modulators or aromatase inhibitors was also associated with a cumulative, dose-dependent increase in the incidence of RA[112].

Oral contraceptives are a source of oestrogens, but their effect on the risk of RA is still being debated[113]. Older studies tend to show a stronger protective effect against RA than more recent studies, which suggests a potential dose dependence, on account of the higher oestrogen doses that were originally provided by oral contraceptives. In a large Swedish cohort, users of oral contraceptives had a lower risk of anti-citrullinated-protein antibody (ACPA)-positive RA than never-users[114]. Similarly, a protective association of hormone-replacement therapy with ACPA-positive RA was identified in a Swedish case–control study, but not for oestrogen-only therapy[115].

Pregnancy is associated with high levels of oestrogens, although the effect of these oestrogens is modified by other hormonal changes. In a prospective, case–control study of women in Washington, USA, a negative association between parity and risk of RA was identified[116]. By contrast, the postpartum period, which is characterized by a decline in concentrations of oestrogens (and other hormonal changes), is consistently associated with elevation of the risk of RA[117]. A case–control study in an indigenous North American population demonstrated a high risk of developing RA during the first postpartum year[118]. However, evidence relating to breastfeeding consistently indicates a negative association with the risk of RA[119]. For example, results from a study in China identified decreasing RA risk in association with increasing duration of breastfeeding, up to 36 months[120]. A similar association was also found in the Nurses' Health Study cohort[121].

Modifiable and environmental factors

The population-attributable risk of RA associated with known modifiable environmental risk factors (smoking, BMI, alcohol, parity and breastfeeding) in the Nurses' Health Study was 41%, implying that a considerable number of RA cases could be preventable with lifestyle intervention in people at risk[122]. Trials of interventions to reduce cardiovascular risk in the general population have demonstrated associated reductions in incident RA cases in the intervention arms, thereby demonstrating the influence of lifestyle factors on the development of RA[123].

The current understanding of the aetiopathogenesis of RA hypothesizes a 'mucosal origin', in which the autoimmune processes that lead to the development of RA are triggered in the mucosa-associated lymphoid tissues in the lung, the oral cavity and the gut, prior to systemic spread[124]. Notably, most of the environmental risk factors listed below imply the involvement of chronic mucosal inflammation, but more research is needed to understand the mechanisms that are involved.

Inhaled factors and lung disease as risk factors for RA. Results from multiple studies suggest that RA-related autoantibodies may be generated in the lung mucosa and in draining lymph nodes prior to the onset of clinically apparent RA[125–127]. Individuals who are exposed to tobacco smoke have a higher risk of RA than those with no exposure[128]. Smoking represents up to 25% of the population-attributable risk for seropositive RA[129,130]. This risk is particularly high in individuals who are homozygous for HLA shared epitope alleles and who are heavy smokers (OR 52.6; 95% CI 18.0–154), emphasizing a strong gene–environment interaction[131,132]. The effect of smoking is dose-dependent and decreases slowly after cessation[129].

A growing body of evidence links air pollution or inhaled particulates (such as those encountered following the 11 September 2001 terrorist attack in New York) with the risk of RA[133–136]. Silica, asbestos and textile-dust inhalation are all associated with the development of RA[137,138]. Studies in the USA and Canada have found higher incidence and prevalence of RA in areas geographically located near major roadways[133,134,139]. Occupational exposures to factors inhaled by miners, pottery workers and dental technicians also increase the risk of RA[140–142]. In addition, household air pollution produced by indoor cooking with the use of fuels derived from crops, animal dung, shrubs or grass was associated

with an increased risk of arthritis in a study conducted in low-income and middle-income countries[143]. Given that in 2010 it was estimated that approximately 40% of households used solid fuels for cooking, particularly in Africa and Southeast Asia[144], a large number of people are exposed to this risk factor. The potential role of inflammation of respiratory mucosa in the development of RA is also suggested by results from prospective cohort studies that demonstrate associations between pre-existing chronic airways disease, such as asthma, and future onset of RA[145–147].

Although the specific mechanisms of the pulmonary triggers of RA are not completely understood, these findings should raise questions about the long-term effects of the increase in exposure to particulates in association with climate change and rising population density.

Nutritional factors, gut microbiota and RA. A growing body of evidence suggests that a healthy diet may be protective against the development of RA. In the Nurses' Health Study, a broadly defined 'healthy' diet was associated with a lower risk of RA (particularly for seropositive RA) than a less healthy diet[148]. However, insufficient evidence is available in support of a specific diet in this regard. For instance, the Mediterranean diet, assessed in the Nurses' Health Study, was not associated with a reduction in the risk of RA development[149]. Other case–control or cohort studies have provided evidence to support a role for the Mediterranean diet, with modest protective effects in particular subgroups, such as men with seropositive RA[150] or women who have ever smoked[151]. An 'inflammatory diet' pattern has long been alleged to influence RA development, but only weak evidence exists to support this hypothesis[152]. Some evidence suggests an association between intake of red meat and total protein and the development of inflammatory polyarthritis[153], but other studies have not reproduced these findings[154,155]. Daily consumption of sugar-sweetened sodas is associated with an increased risk of RA[156,157], whereas alcohol consumption might be inversely associated with the risk of RA in a dose-dependent manner[158], in particular for ACPA-positive RA[159] (although some evidence suggests that there is no association with alcohol consumption)[160]. Results from several studies implicate high sodium intake as a risk factor for RA, but only in smokers[161,162]. Obesity has also been reported to increase the risk of RA in women[163], mostly for seronegative RA[164,165]. Nevertheless, in seropositive individuals without a diagnosis of RA, incident arthritis is associated with body fat, and this effect is additive to other risk factors, so that, for instance, in one small study of seropositive individuals, the overall risk of RA at a median of 27 months follow-up was 28%, but the risk in overweight smokers was 60% (REF.[166]). Surprisingly, among men, a high BMI instead results in a protective effect on RA risk, in particular regarding ACPA-positive RA[164,167].

With regard to specific nutrients, consumption of omega-3 fatty acids has repeatedly shown a modest and dose-dependent negative association with the risk of RA[168–170]. However, a prospective study involving two Nurses' Health Study cohorts found no association between intake of omega-3 fatty acids and RA development[171]. Evidence supporting a protective effect of omega-3 fatty acids relates to RA-associated autoimmunity[172,173]. A secondary analysis of the Vitamin D and Omega-3 Trial (a US nationwide, randomized, double-blind, placebo-controlled trial) demonstrated that long-term supplementation with omega-3 fatty acids and/or vitamin D_3 resulted in a 25–30% lower incidence of autoimmune diseases (compared with no supplementation) in older adults (mean age 67 years)[174]. The effect size was larger for RA than for autoimmune disease in general, but was not statistically significant; for individuals who received vitamin D_3 supplementation, the hazard ratio versus placebo was 0.58 (95% CI 0.30–1.13; $P = 0.11$). In the Nurses' Health Study, using a healthy-lifestyle index that included the five modifiable risk factors of smoking, alcohol consumption, body weight, physical activity and diet, the risk of incident RA was lower (HR 0.42; 95% CI 0.22–0.8) in women with all five healthy lifestyle factors, compared with those with none[175]. Overall, 34% of RA in this study was determined to be preventable by adherence to at least four of these healthy-lifestyle characteristics[176]. Thus, diet experiments have recently regained interest in the context of active RA, even though clinical outcomes in such trials do not seem to be significantly improved[177,178].

Mechanisms linking dietary risk factors to RA are still being uncovered. For instance, the results of experiments in an animal model illustrated how acetate (metabolized from alcohol) could impair the function of T follicular helper cells that support autoantibody production[179]. The effects of dietary factors, and also of smoking and obesity, might be mediated by their influence on the digestive microbiome, gut permeability or the local immune system. Next-generation sequencing of gut and oral microbiota has been used to investigate their potential as risk factors for RA. Expansion of intestinal bacteria in the family Prevotellaceae is associated with early RA[180–183], but is not found in patients with established, treated RA[184–186]. In particular, expansion of *Prevotella* species is associated with RA-related autoimmunity and nonspecific articular symptoms in preclinical stages of RA[187]. Although *Prevotella copri* expansion seems to contribute to arthritis in mouse models[180,181], it is unclear whether microbiota alterations have an active role in humans, or if they merely reflect changes in the microbial microenvironment in response to systemic inflammation. *Prevotella* species are not the only bacteria that are potentially involved in RA onset, and preliminary evidence suggests that dysregulation of bacteria from a number of genera is associated with the onset of RA. For example, some evidence indicates that the *Bacteroides* genus is under-represented in patients with new-onset RA[181,188], and the *Eggerthella* genus[184,185] and *Collinsella aerofaciens*[185,186] have also been associated with human RA. Interestingly, *Collinsella aerofaciens* notably worsens arthritis in mouse models[185,186], and is highly coated by intestinal IgA in patients with inflammatory bowel disease, suggesting it is targeted by an adaptive reaction of the immune system[189]. Still, the hypothesis of a cross-reaction between human and bacterial antigens remains to be proved in RA.

No prospective cohort study has yet demonstrated that gut microbiota dysbiosis is associated with subsequent RA. However, in a population study conducted in the Netherlands, gut microbiomes were profiled in more than 8,000 individuals in a three-generational cohort, and were found to be shaped predominantly by environmental exposures and cohabitation[190]. In addition, microbiome characteristics were strongly associated with common non-communicable diseases and their medications. Various individual species were associated with clusters of diseases, including several oral species in RA, as previously identified. The potential role of inflammation of the gut mucosa on the development of RA was also suggested by results in the French E3N-EPIC cohort, which demonstrated an association between chronic diarrhoea and the risk of subsequent RA[191].

Results from both cross-sectional[184,192] and prospective[193] studies have identified associations between periodontitis and RA. Similar findings in the preclinical RA population[194,195] have led to hypothesizing of a causal role of particular oral microbes such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, which might trigger ACPA production[196,197]. Other microbial species might also be involved, as, for instance, Streptococcaceae are major contributors to oral dysbiosis in RA, and cell walls from *Streptococcus parasalivarius* isolates can induce chronic small-joint arthritis in mice[198].

The available evidence suggests that any direct influence of the microbiome on RA will be difficult to tease apart from environmental exposures that influence the microbiome and/or tissue inflammation using classical epidemiological methods. However, the mucosal origin hypothesis provides a mechanistic framework within which to investigate the effects of socioeconomic and lifestyle-related exposures on the subsequent development of RA.

Disease management

Over the past few decades, the treatment of RA has evolved to emphasize the importance of early initiation of treatment[75,76] and use of a treat-to-target strategy[77], with a recognition that these strategies limit disease activity, radiographic progression and loss of function[199]. However, the implementation of these management recommendations seems to remain suboptimal. In 2017, a US study found that as many as 64.3% of visits did not include any of the components needed for a treat-to-target strategy[76]. In Greece in 2020, only 20% of patients not reaching treatment targets initiated or switched treatments[200]. In 2015, 59% of Japanese rheumatologists reported setting clinical remission as their target and only 45% were using composite measures of disease activity[201]. But, if we look at the glass as half-full, >50% of patients are treated according to the treat-to-target strategy. Additionally, progression to earlier initiation of anti-rheumatic therapies has been described in several European countries[202–206].

In low-income countries, additional challenges of treating RA exist[207], including unreliable drug availability, financial restrictions, patient hesitancy and both the availability and the costs of tests used for monitoring. A large proportion of patients with RA rely on ineffective or unverified complementary and alternative medicines[208]. There are inadequate numbers of physicians, rheumatologists and rheumatology nurses to diagnose and manage rheumatic diseases, including RA. In addition, prevalent infections (especially hepatitis B virus, tuberculosis and HIV) complicate the management of RA, as many biologic DMARDs need to be used with caution in this setting[209]. Patients exposed to effective biologic DMARDs have a higher incidence of tuberculosis than the general population in a tuberculosis-endemic region[210,211]. In addition, most of these drugs are financially out of reach for many patients with RA in low-income countries, and better access is urgently needed[212,213].

Conclusions

Available prevalence estimates for RA indicate that it is more common in developed countries and in urban settings than in developing countries and rural settings, which suggests that environmental exposures may be involved. Although the prevalence of RA might be increasing, the severity and some of the long-term consequences of the disease are decreasing. However, access to diagnostic testing (such as autoantibody tests and imaging, which are used in RA classification) and specialized care remains an important challenge in developing countries[207,208].

New insights into the aetiology of RA suggest that complex interactions occur at the mucosal level, between environmental exposures, the microbiome and host immune cells. A future task for researchers in the field will be to identify how these parameters interact to trigger an autoimmune inflammatory response and the development of RA. A better understanding of the natural history of RA will help to anticipate how changes in global cultures and climate will affect the epidemiology of RA in the future. Further insight into the aetiopathogenesis of RA should also lead to specific prevention strategies to reduce the development or progression of this debilitating disease.

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