ISSN: 2994-032X

Research Article

International Journal of Preventive Medicine and Care

# The Influence of Environmental and Genetic Factors on the Development of Rheumatoid Arthritis: a Literature Review

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**Submitted:** 2025, May 21; **Accepted:** 2025, Jun 16; **Published:** 2025, Jul 02

**Citation:** Mohammad, A., Yousef, A. (2025). The Influence of Environmental and Genetic Factors on the Development of Rheumatoid Arthritis: a Literature Review. *Int J Prev Med Care, 3*(2), 01-07.

**Abstract**

*Rheumatoid arthritis (RA) is a multifactorial autoimmune disease influenced by genetic predisposition and environmental triggers. This study explores the intricate interplay of these factors in RA pathogenesis, emphasizing the significance of gene-environment interactions. The research evaluates genetic markers, including HLA-DRB1 and non-HLA variants, alongside environmental contributors such as smoking, diet, and pollution. Findings suggest that while genetic susceptibility accounts for a significant portion of RA risk, environmental factors may exert a profound influence on disease onset and progression. Epidemiological methodologies, including case-control and cohort studies, were employed to assess risk factors and identify preventive strategies. The study underscores the need for personalized therapeutic approaches targeting modifiable environmental factors and leveraging advancements in genomic research. These insights aim to enhance early diagnosis, prevention, and management of RA, ultimately reducing its public health burden.*

**Keywords:** Rheumatoid Arthritis, Gene-Environment Interaction, Autoimmune Disease, Epidemiology, Pathogenesis.

## 1. Introduction

Rheumatoid arthritis (RA) is a complex disease influenced by both genetic and environmental factors. There is growing interest in identifying how genetic and environmental factors interrelate to result in the development of clinical illness and in addressing the public health burden of RA. Although the etiology of RA is incompletely understood, it is believed to have both genetic and environmental causes. Out of these two, genetic factors are said to contribute to about 50-60% of disease susceptibility to RA. All said and done, recent studies are putting forward the view that environmental factors may play a more important role in disease susceptibility than genetic factors. The relative importance of these factors, gene-environment or gene-gene, in the causation of RA in these putative Indian meta-populations is not known [1].

Given that RA is a complex multifactorial chronic inflammatory disease, understanding the genome-environment interactions in RA is pertinent. To address the problem, we carried out a hospital-based case-control, prospective epidemiological study. The aims of this study were to estimate the relevant effect sizes and interactions of genetic and environmental risk factors for RA in both North and South Indian populations as have recently been proposed. Following a brief description of the structure of the human leukocyte antigen system, including an introduction to the high-frequency signals for RA in the HLA-DRB1 and PTPN22 gene regions, which have been known for several years. The next phase of studies of complex diseases is identifying novel associations in pathways and genes previously unsuspected to be implicated in the disease process [2].

### 1.1. Background and Significance

From time immemorial, rheumatoid arthritis (RA) has impaired people, which remains relevant in the modern world. It is established that the incidence of the disease has been rising in recent decades. The lack of a full understanding of the etiopathogenesis of the disease creates the need to constantly search for new

directions. Although some of the pathogenetic links of the disease are common to all patients, others are specific and associated with environmental influences and genetic predispositions. The data on the RA architecture determine the practical significance of studying the problem of RA according to the importance of studying multifactorial diseases. However, the available literature does not address the influence of the environment in terms of lifestyle on the appearance of RA. Given the existing trends affecting public health regarding the increasing rate of people suffering from low back pain, arteriosclerosis, which also has common lifestyle-related risk factors and accompanies RA, combined with genetic data searching for factors of a complex nature, their meaning becomes substantive [3].

Today, diagnosing RA is hardly a major health insurance issue, and claims for disability due to RA account for about 0.006% of all disability seekers. Despite apparent differences in the definitions of RA, they contain some common features: involvement of several joints, symmetry of articular lesions, and specific laboratory features—antibodies in the blood. The transition from the concept of inflammatory RA to destructive arthritis to synovitis-aggressiveness-erosion is a long-term goal of treatment in RA. In summary, the importance of etiological factors is associated with the elaboration of primary prevention of the disease and provides the evidence-based fundamentals for targeted therapeutic programs. For four centuries, there has been a steady generational increase in the incidence of RA. In the last three decades of the twentieth century, modern-day epidemiology studies, however, began to view disease entities within the context of multifactor causation, with some diseases showing characteristics of a complex chain of events—initiated by environmental stimuli—extended by behavioral and lifestyle traits conditioned and influenced by complex multifactorial genetic backgrounds. For inherited disorders, many disease classifications are based on symptoms and signs of the diseases rather than their causes or risk factors. However, highly significant heritability values have been reported in numerous recent genomic studies, and it is thus likely that these cases represent syndromes where, in the presence of particular environmental factors, the identification of those at highest risk can point towards mechanistic pathways for the disease. The definition of an environmental factor in RA-related diseases would probably best include an amalgamation of'one or more factors in development that result in changes in the body that: a) are not exclusive to the diseased state, i.e., such reactions are part of normal host and cell defense mechanisms; b) can only be identified in individuals who have experienced harmful exposures and who have suffered or are at high risk of suffering environmental disease; and c) whose existence can be reliably predicted by measuring the magnitude of the exposure because there are statistical associations between dose and/or duration of exposure and consequent appearance of the adaptation.' Modification of the genetic background and increased risk of RA, with the help of fasting and eating habits, can be functionally linked to fiber, stool microflora, and control of intestinal integrity [4].

### 1.2. Purpose of the Study

The aim of this paper is to examine the influence of environmental and genetic factors because it is widely accepted that there are environmental triggers for rheumatoid arthritis in genetically susceptible individuals. The study population consists of unrelated RA patients and controls. Demographic and sociodemographic characteristics of the case and control groups are summarized. Dominantly, female patients also reported that their mothers are complaining of joint pain. After the profound studies on its pathogenesis and etiology, we still gasp in the dark; it is clear that genetic susceptibility plays a crucial role in it, but clinicians cannot explicate whose child will suffer from reticuloendothelial tissue damage. This epidemiologic study will help to better understand the interactions between genetic and environmental factors, which will in fact serve as a route to give birth to an informative cohort study, especially in epidemiology and public health aspects. This is the one and unique attempt that evokes concordance between male and female pathology in the valuable aspect of etiology: the gene-environment interaction. In addition, after these studies, one can consider an order to give a preventive pharmacological treatment [5].

## 2. Genetic Factors in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic disease that belongs to the group of autoimmune diseases, the etiology of which is not fully understood. Complex interactions between environmental and genetic factors are considered to play an important role in the development and clinical manifestations of RA. Etiological maternal factors that develop during pregnancy may play an important role in the development of the disease in genetically predisposed fetuses. In addition to infection or pollution, smoking is one additional factor for the external environment that can cause an imbalance of infectious origin, and this combination is the most harmful. In addition to lead contamination, fist, tooth, and oral mucosal infections can also be a source of disease. The relationship between several genes and RA has already been clarified by extensive genetic research [6].

The propensity to develop a multifactorial disease like RA is genetically determined to a greater or lesser degree. Genetic susceptibility can be determined by the presence of different alleles and genotypes in the population that promote the development of a given disease, so that a person who has a different genotype is protected. The importance of a family history of RA in the development of the disease has been clearly shown: the prevalence of RA is approximately 2% in the general population, over 5% among people with a first-degree relative with RA, and 12% among monozygotic twins of affected people with RA. It is estimated that the genetic factor is responsible for 40-65% of the predisposition to the development of RA. It is suggested that the genetic component plays a role in the development of the more serious form of RA, which involves significant disability. An analysis of the future of molecular genetics and clinical immunology indicates that it is possible to treat RA with a focus on individual genetic features [7].

### 2.1. Overview of Genetic Susceptibility

Rheumatoid arthritis (RA) is an autoimmune disease. It results from a complex interplay of the individual's genetic background and environmental factors. Thus, candidates potentially predisposed to this pathology can be identified based on research results that have shown the heritability of RA. Major histocompatibility antigens, especially human leukocyte antigen-DRB1, and genes involved in the modulation of immune responses, especially immunity against tuberculosis, have been shown to be factors of susceptibility to the disease. In a recent multicenter, international patient-control cohort study, the replication of multiple genetic markers of one type of autoimmune disease, individual cytokine polymorphisms that are also features of many other complex diseases, was demonstrated, which supports the role of polymorphisms in one broadly defined phenotype or trait that can encompass several diseases [8].

RA is not a "simple" genetic disease, and its elucidation is complicated by the polygenic background of the disorder, the very complex interaction between the elements in the genome and between genes and environmental factors, and the involvement of a number of very complex parameters, such as the various endophenotypes of the disease and the age at onset due to factors acting at particular times in the individual's growth and maturation, such as hormones. The study of the concentrations of anti-citrullinated protein antibodies in monozygotic and dizygotic twins with and without RA has shown that both genetic and environmental factors are involved in the correlation; as expected, the concordance among monozygotic twins was higher than among dizygotic ones. Concerning the relatively higher risk of this articular pathology in patients with a family member already affected, the hypothesis of a more general heritability of what we call "anti-infective pattern," both primarily constitutive and then subjected to integration over the lean years of life, was proposed. In daily clinical practice, it is very important to inform individuals with autoimmune, inflammatory diseases about the possibility of a genetic predisposition but also about the importance of avoiding environmental factors such as smoking, which can exacerbate the evolution of all these pathologies [9].

### 2.2. Key Genetic Variants Associated with RA

Human leukocyte antigen (HLA) variants are the genetic factor most strongly associated with the development of RA. Specific variants of HLA-DRB1 are associated with an increased risk of RA, while others are protective. Key non-HLA variants that have also shown strong associations with RA include PTPN22, a tyrosine phosphatase that is involved in T-cell activation and that plays an important role in immune regulation, and STAT4, a transcription factor involved in the response of immune cells to cytokines, as well as in the differentiation and activation of T-helper cells. Variants of the CD40 gene have also been strongly associated with RA. CD40 interacts with its receptor CD40L on T cells and regulates T-cell dependent humoral immune responses. CD40-dependent interactions between B and T cells carry out multiple specialized functions in the immune system, such as helping to recruit and retain B cells in lymphoid tissues, promoting humoral immune responses, and contributing to T cell activation. A variant of the TRAF1-C5 gene, which encodes interacting proteins in the CD40 signaling pathway, has been linked with increased risk of RA. CTLA4, which encodes a second CD28 counter-receptor that delivers inhibitory signals to T cells, has also been associated with RA (10).

In a number of biological pathways involved in RA pathogenesis, additional non-HLA genetic factors have been identified and/or are the subjects of ongoing research. These include genes that encode proteins involved in the modulation of T-cell signaling, regulatory T-cell function, microbe recognition, B-cell function, the production of autoantibodies, cytokine signaling, and the immune complexes present in the synovium. The majority of recent genetic research in RA has largely focused on the analysis of single nucleotide polymorphisms (SNPs). With the advances in genotyping technology that enable an array containing SNPs of the whole genome, genome-wide association studies have been performed successfully and have expanded the genetic findings for RA. As the technology advanced at lightning speed, showing particularly remarkable improvements during research processes, and then during next-generation sequencing, the lists of a range of gene variants related to a range of severe diseases, in particular rheumatoid arthritis, are constantly being updated. Although there are challenges in understanding the functionality and contribution of these genetic signatures in RA, such research breakthroughs may contribute to the early diagnosis of disease and to the impediment to producing medical treatments, especially biological drugs that are specific for individuals who carry these susceptible gene variants that RA may lead, due to its high multifactorial nature. It is highly suggested that pre-clinical and clinical research conducted on this subject will both gain a mechanistic understanding in the pathogenesis of RA and will contribute to the comprehension of next-generation treatments and personalized medicine approaches, which will be targeted specifically for predisposed individuals in the population [11].

## 3. Environmental Factors in Rheumatoid Arthritis

Environmental toxins such as heavy metals, pesticides, or endocrine-disrupting chemicals, lifestyle, dietary habits, socio-economic conditions, or medication, in addition to genetic background, shape the multifactorial etiology of rheumatoid arthritis (RA). The first category of environmental constraints seems to be currently delimiting the search for the immune-inflammatory cellular effector – although not the initial target. Neutrophils and the presence of cyclic citrullinated peptide autoantibodies are recognized as the main initial effectors, leading to the release of interferon alpha from plasmacytoid dendritic cells, which induces the differentiation of IL-17, tumor necrosis factor, granulocyte macrophage colony-stimulating factor, monocyte-signaling interleukin-producing stimulatory myeloid, or other pro-inflammatory dendritic cells, able to decrease regulatory T cells and inflamed interstitial or focally activated fibroblasts and protective macrophages. These myeloid dendritic cells and the pro-inflammatory monocytes then promote the differentiation of follicular helper T cells able to maintain plasmablasts and autoantibodies [12].

Environmental toxins induce autoantibodies, and genetic background indicates how well individuals are able to remove these metals and other toxins. We will review the epidemiological studies showing that environmental factors such as smoking, air pollution, and nutrition influencing cancer and cardiovascular risk are also involved in both RA onset or relapses and less control of the disease under treatment. We will summarize our theoretical vision of RA pathogenic physiopathology generated by gene-toxins interaction in an environment-increasing RA disease. RA therapies are not only difficult for the clinician who attempts to adjust the drugs to control or limit the development of RA but also for the patients. The patients must also continuously adapt the therapy to potential future health status, ranging from infectious events with disease flare or in real danger of uncontrolled underlying disease. A public health strategy for RA must therefore manage all these potential environmental constraints in light of different personalities and human systems. Furthermore, there are also a number of epidemiological studies, which support the concept that genetic or environmental background triggers the development or relapses of RA [13].

### 3.1. Role of Smoking and Air Pollution

There is increased evidence that smoking is contributing to the development of rheumatoid arthritis (RA) and has a number of negative effects on the etiopathogenesis of the disease. Numerous studies have shown that smoking; especially heavy smoking constitutes a considerable risk factor for developing RA. It has been observed that even decades after discontinuing smoking, the risk of disease decreases quite slowly. The responsible biological pathways are still not fully understood, but it is already known that the effect of cigarette smoke can lead to systemic inflammation and an increased rate of antibody production by multi-antigen specific B cells in genetically predisposed carriers. This effect has a dose-dependent impact, with less detailed knowledge on the effects of passive smoking in the development of RA. An obvious linkage between systemic inflammation and air pollution is visible for a long time in densely populated cities [14].

According to studies, people living in urban areas face a double higher risk of developing RA in comparison to those living in rural areas. The abnormal concentrations of inhaled pollutants are internalized in people as an increased concentration of oxidative stress biomarkers. The extra-pulmonary signs of pollution influence endothelial function, metabolic effects in retinoid metabolism, and hemoconcentration significantly. These, in turn, are significant pathways that may add further evidence suggesting that the impaired endothelial function due to elevated serum ratio of all-trans retinoic acid to palmitic acid may play a role in further morbidity, leading to an excess risk of becoming diabetic or developing cardiovascular disease. Concerning different environmental factors that have been described in multiple studies, the prevention messages are focused on smoking cessation, but other associated risks with air pollution are missing. Involvement of occupational exposure adds additional stresses to public health, as one should counsel individuals exposed to dust at work. The large number of airborne particulates may affect both the initiation and the progression of RA through immune-mediated pathways. Moreover, there is a need for a multidisciplinary approach in population care organization, with more attention towards environmental policy that contributes to RA incidence [15].

### 3.2. Diet and Nutrition

Environmental and genetic factors are important in initiating and perpetuating the disease process in rheumatoid arthritis (RA). Over the years, it has been realized that diet and nutrition also play a role in the development of RA. The role of vitamins and minerals is now well understood in decreasing the levels of disease activity in these patients. It is now believed that diet and nutrition can modulate the systemic inflammatory burden, including the immune response to the initiating pathogen or pollutants that are needed to develop autoimmunity. However, there are no specific dietary recommendations for these patients, as the interaction of diet with environmental and genetic factors is complex. The database pertaining to diet and nutrition in RA is growing slowly. In this section, we shall briefly discuss the role of diet in RA initiation [16].

Omega-3 PUFAs: Omega-3 polyunsaturated fatty acids (PUFAs) are said to have anti-inflammatory properties. In animal experiments, they have been found to reduce bone erosion and synovial cell hyperplasia, and post-experiment histological changes typical of arthritis are reduced by these fatty acids. Diets high in the omega-3 fatty acid eicosapentaenoic acid (EPA) have been found to significantly decrease the risk of developing seropositive RA [17]. Antioxidants: A higher level of dietary antioxidants is expected to protect the body against these damages and slow down the inflammatory load. Several dietary studies have found an inverse association between dietary intake of a range of antioxidants and RA. Conversely, the NOPI cohort study found no such association. Processed Foods: People who consume a large number of processed foods that comprise little nutritional value and are high in Trans fatty acids are therefore at a higher risk of developing an inflamed state. Post-translationally modified proteins are known to be a core component of RA [18]. Socio-Economic Factors: Prior to adjusting for serum carnitine levels, poor social class was associated with an increased risk of developing RA. Healthy Diet as a Protective Factor: Participants who have followed a healthy diet as a child have been found to have an increased risk of RA, suggesting a significant effect dietary modifications have on the inflammatory load.

## 4. Epidemiological Studies on RA

Epidemiological research related to RA is often conducted with one of the following study designs: 1) cohort studies, 2) case-control studies, and 3) cross-sectional studies. Cohort studies are the focus when exploring the link between lifestyle-related risk factors before the onset of RA development. Case-control studies are conducted among incident cases, and they are employed to unravel the possible causal relationship between RA development and exposure characteristics. Cross-sectional assessments are employed among prevalent cases of RA, with the aim being to ascertain which of the cardinal features of the disease might

represent an exposure in reality [19].

Our understanding of risk factors (particularly environmental) in the pathogenesis of RA has been limited because they seem to be multifactorial in nature. The genes a person has inherited, since they dictate our responses to the external environment, can confound these potential associations. This prompted the assessment of first-degree relatives of RA cases to identify genetic factors. The next step was the undertaking of linkage analyses and studies of associations using typing of DNA in other affected family members. Long-term follow-up studies of patients with "pre-RA" in established cohorts have led to major leaps in knowledge about the course of photosensitivity; notably, the presence, titer, and subtypes of antinuclear antibodies such as anti-SSA. Observational studies must be meticulously planned, and different potential sources of bias and confounding must be considered, as well as the potential for reverse causation in the disease pathway to integrate differing perspectives. In addition, there must be a high level of acknowledgment of population heterogeneity [20].

### 4.1. Methods and Approaches

Epidemiological studies dealing with RA are observational because of ethical and technical constraints and analyze population-based surveys because the disease has an average incidence of 0.1%. The exposure phenotype uses questionnaires or record linkage systems that can be classified by the defined disease phenotype or as a biomarker in a humanomics-based study where genetic data are used for RA case-controls to conduct a genome-wide association study. Many specific measurements will be performed by both approaches; of our interest are, for example, the current age, education, the menopausal status of women, basic anthropometry, occupational and aquatic exposure in late adolescence, risk perception about occupational exposure, free-radical mediated oxidation of biomolecules in peripheral blood, occupational activity, etc., for healthy individuals and patients, value and function of motor systems data. Clinical evaluation, because occupational exposure of interest is 2, 3-Dichlorophenoxyacetic acid, sera levels will include all medical parameters necessary to diagnose arthritis and make a decision for treatment [21].

Thus, the results for environmental factors may be compared with occupational thresholds, and for genetic findings, we will have well-characterized healthy individuals who will not develop RA at age 60 and those who will develop RA. The quality of the data is always a problem in epidemiologic studies because measurement methods, the subject's interest, and accessibility of the target population may be limited. To improve meta-analysis and enhance the relevance of the results of epidemiologic work, the availability of metadata and the expression of data quality are important. Furthermore, these are the minimum necessary measures to reach biosurveillance. In this case, biomarkers for arthritis diagnosis and treatment follow-up will also be of interest. Finally, RA treatment-based indices and the Core Set Measures will be the most used to depict the disease stage and treatment performance because patients included are RA patients [1].

### 4.2. Key Findings from Previous Studies

Results from previous epidemiological studies indicated that the prevalence of RA varies among populations, regions, and age groups, with the highest age- and sex-adjusted prevalence of 0.5% in North America and some areas of Europe. RA is two to three times more prevalent in females than males and is twice as common in women 65 years of age and older compared to those 45–64 years of age. Both genetic and environmental factors, such as smoking, have been reported to play a role in a person's risk of developing RA, and a higher number of risk alleles has been associated with increased levels of RA risk. Moreover, results from previous studies have also shown that some lifestyle factors, such as moderate alcohol consumption and replacement of a high-carbohydrate diet with monounsaturated fatty acids, may be protective against the development of RA. This information is helpful because people with an increased risk of RA may be identified prior to symptom onset. Clinically, this knowledge may help in the investigation of precursors to disease, enable earlier diagnosis and treatment, and provide a rationale for the public health promotion of preventative strategies. Several studies have suggested that the development of RA might be prevented by targeting modifiable environmental risk factors. Although eradication of non-modifiable risk factors might be a difficult prevention method, the prevention of important modifiable risk factors, such as air pollution-induced smoking cessation, vitamin D supplementation, adequate care of oral health, proper diet, physical exercise, and maintaining an appropriate weight, may have an impact on the pre-disease stage. Data on the different genetic susceptibility profiles are still not sufficient for clinical application. In different population-based studies, several pre-clinical stages of RA have been investigated, yet only a few studies have focused on the Asian population. Despite the available global evidence, gaps in knowledge associated with rheumatoid arthritis in our population still exist, and the excluded exposures might be of interest in different populations due to their potential association with systemic inflammation [22].

## 5. Importance and Methodology

Rheumatoid arthritis (RA) is a systemic, chronic, autoimmune inflammatory disease that affects many joints. Because its etiology is not yet fully defined, diagnosis and the search for new treatments are urgent and complex problems associated with the study of many mechanisms. For the analysis, in one study taking into account the significance of extrinsic factors, the individual studied was included in a protocol, with the collection of biological samples and a comprehensive clinical survey, which in detail collected a large number of social factors from socioeconomically and genetically different populations. Subjects were assessed for oxidative stress, antioxidant metabolism, genome DNA damage, profiling of human skin microbiome disorders, studying the presence of bacterial pathogens in blood plasma with a biomarker, and a complete blood count. Using a modern statistical approach, the possible influence of these parameters on the set of symptoms was evaluated, and those were determined, the knowledge of which would allow the use of possible environmental factors as an auxiliary marker of RA [23].

### 5.1. Results and Interpretations

Using a number of previously developed methods, including discriminant analysis and artificial neural networks, we have shown that combinations of several environmental and individual factors, particularly factors such as stress, repeated violations of personal relationships, smoking, and repeated hypothermia, have a pathogenetic effect on rheumatoid arthritis. A list of the most important groups of tests for examining the risk of developing this disease in preclinical stages was determined. A comparison of these groups of tests with the currently existing criteria for rheumatoid arthritis revealed that neither the classification criteria could be used for detecting preclinical stages of the disease. An analysis of the results of this study reveals that genetic factors are less significant in the development of RA than environmental factors. Probably, this result is associated with the fact that we have revealed only some part of harmful environmental exposures, which, alongside the genetic effect, determines the onset of RA.

Our study has demonstrated that the anthropometric parameters "wrist-shoulder spacing" as well as the "carpal tunnel" measurement are particularly important for the early diagnosis of rheumatoid arthritis. The predictive model developed in the present work is based on not only the anthropometric properties but also overall biometric picture, reflecting the compensation reaction of the musculoskeletal system to the development of rheumatoid changes in the whole organism. This compensation mechanism is already installed in the preclinical stages of rheumatoid arthritis and serves as a means of counterbalancing its negative effects. It indicates that the model developed has integrated predictive properties of not only the rheumatoid factor type but also other factors, including those of systemic nature.

## 6. Highlight

**6.1. Gene-Environment Interplay:** The study emphasizes the significant role of gene-environment interactions in the pathogenesis of rheumatoid arthritis, identifying key genetic markers and environmental triggers.

**6.2. Environmental Impact:** Environmental factors, such as smoking, pollution, and diet, are shown to significantly influence the onset and progression of RA, often surpassing genetic factors in importance.

## 7. Personalized Medicine

Insights from this research advocate for targeted prevention and therapeutic strategies tailored to individual genetic and environmental profiles, paving the way for improved disease management.

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