The European Journal of Biomedical and Life Sciences 2025, No 1–2
ISSN 2310-5674

PREMIER Publishing
ppublishing.org

DOI:10.29013/EJBLS-25-1.2-10-16

ASSOCIATION BETWEEN RISK FACTORS AND RHEUMATOID ARTHRITIS: A ANALYSIS FROM NHANES

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Cite: *By Billy Wang. (2025). Association between risk factors and Rheumatoid Arthritis: A analysis from NHANES. The European Journal of Biomedical and Life Sciences 2025, No 1–2* https://doi.org/10.29013/EJBLS-25-1.2-10-16

Abstract

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder and one of the most prevalent forms of inflammatory arthritis. If left untreated, RA can result in irreversible joint damage, loss of function, long-term disability, and various comorbidities. Despite its clinical significance, the precise etiology of RA remains poorly understood, with current evidence suggesting a multifactorial origin involving genetic, environmental, and lifestyle factors. This study aims to investigate the potential risk factors associated with RA by examining demographic characteristics, including race, gender, and age. In addition, the study explores the impact of dietary factors, particularly salt intake and body weight, on the progression and severity of RA.

Keywords: *Rheumatoid arthritis (RA), Autoimmune disease, Chronic joint inflammation, Joint deformity, Comorbidities, Rheumatoid factor (RF), Autoantibodies*

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease in which the immune system erroneously targets healthy joints, tissue cells, and occasionally organs. Globally, RA affects approximately 0.5–1% of the adult population (Almutairi K. B., Nossent J. C., Preen D. B., et al., 2021). If left untreated, RA can lead to joint inflammation, permanent deformity, comorbidities, disabilities, mental health disorders, and a reduced lifespan (Rheumatoid arthritis).

The precise pathogenesis of rheumatoid arthritis (RA) remains elusive, with no singular determinant identified. It is widely accepted that both genetic and environmental factors contribute to its development (Deane K D., Demoruelle M. K., Kelmenson L. B., et al., 2017). Major risk factors for RA include sex, age, and family history. Epidemiological data indicate that women are more susceptible to RA than men, with a female-to-male prevalence ratio of approximately 3:1. This disparity is thought to be influenced by genetic factors and hormonal differences (Smolen J. S., Aletaha D., Barton A., et al., 2018; Mohammed A., Alshamarri T., Adeyeye T., et al., 2020). Genetic (X-linked) factors and hormonal differences are suspected to play a role (Wilder R. L., 1998; O'Brien S. M., Fitzgerald P., Scully P., 2007; Van Vollenhoven R. F., McGuire J. L., 1994). RA onset most commonly occurs between the ages of 40 and 60. A positive family his-

tory is a significant risk factor, though it remains unclear whether this reflects genetic predisposition or shared environmental exposures within familial settings (Smolen J. S., Aletaha D., Barton A., et al., 2018). Notably, the risk of developing rheumatoid factor (RF)-seropositive RA is markedly increased by the interaction between genetic predispositions, such as the shared epitope of HLA–DR, and environmental factors like smoking (Ruiz-Esquide V., Sanmartí R., 2012). RA is associated with several autoantibodies that serve as diagnostic and prognostic markers, with rheumatoid factor (RF) being among the most studied. RF is an antibody that targets the Fc region of immunoglobulin G (IgG). In RA patients, persistent RF production is observed, often throughout the individual's lifetime. It is hypothesized that immune complexes containing RF contribute to a self-perpetuating inflammatory cycle through complement activation and interactions with monocytes. The initial trigger for this process remains unidentified, as no exogenous antigen has been consistently detected in these immune complexes (Smolen J. S., Aletaha D., Barton A., et al., 2018).

The objective of this study is to examine various aspects of individuals' lives, including genetic traits and lifestyle factors, to identify potential risk factors and direct causative elements associated with the development of RA.

Methods

The data for this research were sourced from the National Health and Nutrition Examination Survey (NHANES), a program that collects health information through interviews, physical examinations, and laboratory tests. NHANES employs standardized protocols to ensure data accuracy and comparability across different sites and providers (National Health and Nutrition Examination Survey (NHANES) 2024).

In this study, we examined various factors potentially associated with the pathogenesis of rheumatoid arthritis (RA), including age, gender, race, salt intake, body mass index (BMI), and health insurance status. RA status was determined based on self-reported responses to specific questionnaire items. Socioeconomic status was assessed using the poverty-income ratio, calculated by NHANES based on household income and size. Participants were categorized into four racial/ethnic groups: non-Hispanic white, non-Hispanic black, Hispanic, and other ethnicities. Age was stratified into four groups: under 30, 30–50, 50–65, and over 65 years. Health insurance coverage was dichotomized into insured and uninsured categories. Dietary salt intake was self-reported and classified into three categories: rarely, occasionally, and very often. BMI was measured and categorized into four classes: underweight, normal weight, overweight, and obese.

Descriptive analyses were conducted using weighted percentages and raw counts for each variable category. Associations between RA and each variable were assessed using Pearson's chi-squared tests. To evaluate the strength of associations between predictors and RA status, logistic regression models were employed, accounting for survey weights. Both univariate models (including a single variable) and multivariate logistic regression models (adjusting for all covariates) were constructed. A p-value of less than 0.05 was considered statistically significant. All analyses were performed using R software (Team R. C., 2020).

Results

Table 1 presents the sample characteristics of participants based on their arthritis status. The prevalence of arthritis among female participants was significantly higher at 28.6%, compared to 21.1% among males ($p < 0.0001$). Arthritis prevalence also varied by race. Non-Hispanic White participants exhibited the highest prevalence at 28.2%, which was significantly greater than that of non-Hispanic Black participants (21.2%, $p < 0.0001$), Mexican Americans (12.1%, $p < 0.0001$), other Hispanics (15.3%, $p < 0.0001$), and individuals from other or multiracial backgrounds (18.6%, $p < 0.0001$). Age was a critical factor, with arthritis prevalence increasing dramatically with age. Participants aged 65 and older had the highest prevalence at 54.8%, significantly higher than those aged 50–65 (38.7%, $p < 0.0001$), 30–50 (13.9%, $p < 0.0001$), and under 30 (3.6%, $p < 0.0001$). Lifestyle factors also demonstrated significant associations with

arthritis prevalence. Participants who reported frequent salt intake had a 30% prevalence rate, slightly higher than those with occasional salt intake (25.2%, $p < 0.0001$) and significantly higher than those with rare salt intake (22.2%, $p < 0.0001$). Health insurance status also showed a notable disparity, with 27.4% of insured individuals having arthritis compared to only 13.1% of uninsured individuals ($p < 0.001$). Obesity was strongly associated with arthritis, with 32.3% of obese participants affected, compared to 23.5% of overweight individuals, 19.7% of underweight individuals, and 17.5% of those with normal weight ($p < 0.0001$).

Table 1.

Variable name	Arthritis				
	No		Yes		
	N	%	N	%	p value
Gender					
Male	8390	78.9	2433	21.1	
Female	7792	71.4	3207	28.6	<0.001
Race					
Mexican American	2913	87.9	608	12.1	
Non-Hispanic Black	3182	78.8	1103	21.2	
Non-Hispanic White	6905	71.8	3227	28.2	
Other Hispanic	1422	84.7	376	15.3	
Other Race	1760	81.4	326	18.6	<0.001
Age Group					
<30	4072	96.4	134	3.6	
30–50	6625	86.1	1044	13.9	
50–65	3352	61.3	2043	38.7	
65+	2133	45.2	2419	54.8	<0.001
Salt Intake					
Occasionally	74.8	4930	25.2	1806	
Rarely	77.8	7775	22.2	2418	
Very Often	70	3477	30	1416	<0.001
Have Health Insurance					
No	86.9	4216	13.1	607	
Yes	72.6	11966	27.4	5033	<0.001
Body Mass Index					
Normal weight	82.5	5013	17.5	1151	
Obesity	67.7	5450	32.3	2661	
Overweight	76.5	5450	23.5	1749	
Underweight	80.3	269	19.7	79	<0.001

Table 2 displays the results from univariate and multivariate logistic regression models. In the univariate models, each predictor variable was regressed independently on arthritis status, while in the multivariate model, all variables were included simultaneously. Age showed a clear trend in increasing odds of arthritis with advancing age, consistent across both models. Compared to participants under 30 years old, individuals aged 30–50 were 3.93 times more likely to have arthritis (OR = 3.93, 95% CI [3.15, 4.91]).

The odds increased significantly for older groups, with participants aged 50–65 having over 14 times the odds of arthritis (OR = 14.32, 95% CI [11.54, 17.77]) and those over 65 having 28 times the odds (OR = 28.45, 95% CI [23.07, 35.09]).

Table 2.

	Univariate		**Multivariate**	
Variables	OR[LCL, UCL]	P value	OR[LCL, UCL]	P value
Age Group				
< 30	Reference			
30–50	4.37[3.5,5.44]	<0.001	3.93[3.15,4.91]	<0.001
50–65	17.11[13.58,21.56]	<0.001	14.77[11.72,18.61]	<0.001
65 +	32.81[26.35,40.85]	<0.001	28.58[22.83,35.79]	<0.001
Gender				
	Reference			
Male	0.67[0.61,0.72]	<0.001	0.61[0.56,0.67]	<0.001
Race				
Hispanic	Reference			
Black	1.96[1.66,2.31]	<0.001	1.63[1.42,1.87]	<0.001
White	2.84[2.46,3.29]	<0.001	1.89[1.66,2.15]	<0.001
Other Hispanic	1.31[1.07,1.6]	0.0098	1.29[1.05,1.59]	0.0167
Other Race+Multiracial	1.66[1.32,2.08]	<0.001	1.61[1.28,2.02]	0.0001
Salt Intake				
Occasionally	Reference			
Rarely	0.85[0.77,0.94]	0.002	0.97[0.87,1.08]	0.5829
Very Often	1.27[1.14,1.42]	<0.001	1.42[1.27,1.59]	<0.001
Health Insurance				
No	Reference			
Yes	2.5[2.16,2.9]	<0.001	1.3[1.11,1.51]	0.0011
Body-Mass Index				
Normal Weight	Reference			
Obese	2.26[2.01,2.54]	<0.001	2.17[1.93,2.45]	<0.001
Overweight	1.45[1.29,1.64]	<0.001	1.3[1.13,1.5]	0.0003
Underweight	1.16[0.82,1.63]	0.4046	1.25[0.84,1.86]	0.2743

Gender was a significant predictor in the models, with males 39% less likely to have arthritis compared to females (OR = 0.61, 95% CI [0.54, 0.68]). This indicates that females are approximately twice as likely to be diagnosed with arthritis, highlighting a notable gender disparity in disease prevalence. Race and ethnicity also played a role in arthritis risk. Using Hispanic participants as the reference group, other Hispanic participants had 1.29 times the odds of having arthritis (OR = 1.29, 95% CI [1.10, 1.52]), while non-Hispanic Black participants had 1.63 times the odds (OR = 1.63, 95% CI [1.42, 1.88]). Non-Hispanic White participants exhibited the highest odds at 1.89 times (OR = 1.89, 95% CI [1.65, 2.17]), followed by participants of other or multiracial backgrounds, with 1.61 times the odds (OR = 1.61, 95% CI [1.32, 1.97]).

In terms of lifestyle factors, salt intake was a significant predictor of arthritis. Compared to participants who occasionally consumed salt, those who rarely consumed salt

had slightly lower odds of arthritis (OR = = 0.97, 95% CI [0.86, 1.09]). However, participants who frequently consumed salt had a 42% higher likelihood of having arthritis (OR = 1.42, 95% CI [1.24, 1.63]). Body mass index (BMI) categories revealed an association between weight status and arthritis prevalence. Underweight individuals had 1.25 times the odds of having arthritis compared to those with normal weight (OR = =1.25, 95% CI [1.02, 1.54]), while overweight individuals had 1.30 times the odds (OR = = 1.30, 95% CI [1.16, 1.46]). Obese individuals, however, were more than twice as likely to have arthritis compared to those with normal weight (OR = 2.17, 95% CI [1.91, 2.47]), demonstrating a strong association between obesity and arthritis.

In summary, this study found that older age, female gender, non-Hispanic White ethnicity, frequent salt intake, and obesity were all significant risk factors for arthritis. These findings suggest that both demographic and lifestyle factors contribute to the likelihood of developing arthritis and highlight the importance of targeted interventions for at-risk populations.

Discussion

This study examines the impact of genetic and environmental factors on the risk of developing Rheumatoid Arthritis (RA), with a particular focus on whether dietary habits contribute to this risk. The analysis reveals that women are slightly more likely to develop RA compared to men. Additionally, Non-Hispanic Black and Non-Hispanic White individuals have a higher likelihood of having RA compared to Mexican Americans and other Hispanic or multi-racial groups. The study also highlights that RA prevalence increases with age, and the condition is exceedingly rare among individuals under 30 years old.

Our study suggests that changes in the female hormonal environment may contribute to the increased risk of developing RA (Oliver J. E., Silman A. J., 2006), aligning with our findings that females are significantly more likely to be diagnosed with the disease. These results are consistent with the study by Yinke Xu and Qing Wu, which examined RA prevalence trends and disparities among U.S. adults from 2005 to 2018. Their research found that the number of RA cases per 1,000 women was consistently higher than that of men across all years, except for the 2017–2018 period (Xu Y, Wu Q., 2005–2021). This evidence further supports the conclusion that RA prevalence differs significantly by sex.

Additionally, the study showed that ethnicity is also a risk factor. Based on the same study by Yinke Xu and Qing Wu, the number of RA cases are more common in non-Hispanic African Americans (Xu Y, Wu Q., 2005–2021). The amount of RA cases per 1000 men between Non-Hispanic Caucasians and Hispanics are generally similarly common. But there are more Hispanics than Non-Hispanic Caucasians for the amount of RA cases per 1000 women. Compared to our study, which shows Non-Hispanic Black and White groups having a higher percentage of RA cases among the selected population compared to multi racial groups, Mexican Americans, Hispanics, and other races. It is shown that African Americans being more likely to have RA is constant, while Hispanics are less likely to have it.

When examining the relationship between Body Mass Index (BMI) and the risk of developing RA, our data suggests that maintaining a normal weight – defined as a BMI between 18.5 and 25-minimizes the likelihood of RA. Conversely, being underweight, overweight, or obese increases the probability of developing the condition. Although our study focuses on BMI rather than specific dietary factors, our findings align with the research conducted by Crowson et al. (2013), which analyzed RA incidence in residents of Olmsted County, Minnesota. Their study reported an average of 82.7 RA cases per 100,000 people in 2007, with 8.3 cases linked to obesity. While this proportion may appear small, the researchers observed a significant increase in RA incidence among women between 1985 and 2007, rising by 9.2 cases per 100,000. Notably, when excluding individuals with obesity, the increase was only 4.4 cases per 100,000. These findings suggest that approximately 52% of the rise in RA incidence among women during this period is attributable to obesity. Despite the relatively low percentage of obesity among RA patients, the study demonstrates a sub-

stantial correlation between obesity and the likelihood of developing RA.

This study highlights the significant relationship between body mass index (BMI) and the risk of developing rheumatoid arthritis (RA), emphasizing that deviations from a normal BMI range can increase the likelihood of RA. Our findings suggest that maintaining a normal weight, defined as a BMI between 18.5 and 24.9, is associated with a lower risk of RA, while both underweight and overweight individuals are more susceptible to the disease. In particular, obesity showed a strong association with increased RA risk. These results align with previous research conducted by Crowson et al. (2013), which demonstrated that rising RA incidence among women between 1985 and 2007 was partly attributable to obesity. Their study, based on data from Olmsted County, Minnesota, found that while only 8.3% of RA cases were attributed to obesity, this accounted for over 50% of the increase in RA incidence among women during that period. These findings suggest that while obesity may not account for a majority of RA cases, it remains a significant contributor to the growing prevalence of RA, reinforcing the need for public health measures to address weight management as a modifiable risk factor for the disease.

Conclusion

The development of Rheumatoid Arthritis (RA) is associated with multiple factors, including genetic, demographic, and lifestyle influences, all of which can significantly impact an individual's risk of developing the disease. Our analysis of NHANES data, in conjunction with findings from other studies, indicates that inherent factors such as sex and ethnicity play a substantial role in RA risk, with women and certain racial groups showing higher prevalence rates. While these factors are non-modifiable, maintaining a healthy lifestyle, particularly achieving and sustaining a normal BMI, appears to be an effective strategy to reduce the risk of RA. Encouraging weight management and balanced dietary habits may serve as preventive measures, highlighting the importance of lifestyle modifications in mitigating the onset of RA and improving overall health outcomes.

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submitted 12.06.2025;
accepted for publication 26.06.2025;
published 29.07.2025

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