# Association of Regional and Cultural Factors With the Prevalence of Rheumatoid Arthritis in the Mexican Population

## *A Multilevel Analysis*

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**Background:** The overall estimated prevalence of rheumatoid arthritis (RA) in Mexico is 1.6%, but there are major variations in different geographic areas of the country.

**Objective:** This study aimed to determine the impact of individual and regional variables on the geographic distribution of RA in Mexico.

**Methods:** This multilevel analysis used data from a cross-sectional study that investigated the prevalence of RA among 19,213 individuals older than 18 years throughout 5 geographic regions in Mexico. Logistic regression models were used to determine predictors of RA, including individual and regional variables as well as cultural factors. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were determined.

**Results:** The prevalence of RA varied from 0.77% to 2.8% across the 5 regions. Individual factors associated with RA were sex (OR, 2.32; 95% CI, 1.74–3.07), previous medical diagnosis of RA (OR, 3.32; 95% CI, 2.19–2.20), disability (OR, 2.07; 95% CI, 1.48–2.93), and the 56- to 65-year age group (OR, 1.95; 95% CI, 1.08–3.74). The regional factor of speaking an indigenous language had an OR of 2.27 (95% CI, 1.13–4.55).

**Conclusions:** Various individual and regional factors were associated with variations in the prevalence of RA in the Mexican population.

**Key Words:** geographic locations, indigenous population, language, multilevel analysis, rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory disease of undetermined etiology that leads to a marked reduction in health-related quality of life. Rheumatoid arthritis also has a highly significant economic and social impact and is associated with increased mortality.[1] Rheumatoid arthritis affects nearly 1% of the adult population worldwide,[2] but its prevalence and incidence differ across geographic areas and countries. The prevalence of RA is higher in Northern Europe and North America than in Southern Europe, Africa, and developing countries.[3–5] In part, such differences have been explained by the younger age of the population in low- to middle-income nations[6] and by variations among ethnic and urban versus rural groups.[7,8]

Geographic differences in the prevalence of RA may result from a combination of individual characteristics as well as socioeconomic, environmental, and cultural factors. Individual factors include smoking,[9] hormonal therapy,[10] diet and obesity,[6] female sex,[10] female reproductive variables,[11] early-age infections, poor hygiene conditions, increased growth in childhood,[12] moderate stress at work,[13] and exposure to insecticides and agricultural pesticides.[14] Interestingly, the effect of these variables in the prevalence of RA does not necessarily result from geographic clustering, but from discrete factors. Environmental factors include those related to industrialization, demographic transition, and urbanization.[15,16]

Despite increasing interest in the geographical distribution of RA, there is a need for further research incorporating more rigorous methodological approaches. In this study, we aimed to identify individual and regional factors associated with the prevalence of RA across various geographic regions in Mexico.

## METHODS

### Survey

This multilevel analysis of RA prevalence in Mexico included individual and regional factors. Information concerning the individual was obtained through a screening survey, whereas data related to contextual variables at the regional level were obtained from secondary regional information.

The population in this analysis comprised 19,213 individuals older than 18 years and included 7611 (39.61%) men and 11,602 (60.39%) women who had participated in a study on the prevalence of rheumatic diseases in Mexico. Briefly, the study comprised a cross-sectional community-based survey in 24 municipalities distributed throughout 5 regions of Mexico, in the north (Chihuahua), the Northeast (Nuevo León), the Northwest (Sinaloa), the South (Yucatán), and the center (Mexico City).[17] In 2005, Mexico's population was reported as 103 million, with 76% living in urban areas. The mean education level was 8.1 years among a population with a 91.6% literacy rate. The educational level ranged from 7.6 years in the south to 10.2 years in the center (mean, 8.82 years; SD, 0.91) of the nation.[18] The mean annual income was US $6316.74.[18] The proportion of people living in urban areas varied from 71% in the northwest region to 100% in the capital (mean, 86.4%; SD, 9.97). At the time of the study, there were 19 million inhabitants in Mexico City, 4 million in Nuevo Leon, 3.5 million in Chihuahua, and close to 2 million in Sinaloa and Yucatan.[18]

Multistage random probabilistic sampling was used for the states of Nuevo León, Sinaloa, and Yucatán. The 2005 population census was used to generate a sample of individuals older than 18 years, stratified by region, to obtain a representative proportion

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of adults across all states and regions. A second random sampling was performed in each region to select municipalities by proportional sample size. One or more basic geostatistical areas in each municipality were selected for household interviews.[17] An updated census was used for Mexico City and Chihuahua.[18] A door-to-door survey to identify musculoskeletal complaints over the last 7 days was carried out using the World Health Organization/International League Associations for Rheumatology Community Oriented Program for the Control of Rheumatic Diseases stage 1 questionnaire.[19,20] All individuals reporting joint pain, swelling, or stiffness over the last 7 days and at any point during their lives were evaluated by board-certified rheumatologists, and the RA diagnoses were based on the 1987 American College of Rheumatology standardized medical classification criteria.[21]

## Variables at the Individual Level (Level 1)

These included demographic variables such as age (at the time the survey was completed), sex, lifestyle characteristics, income, educational level, type of job, self-reported comorbidities, and disability. For definition of each variable used see Appendix (available online at http://links.lww.com/RHU/A48).

## Variables at the Regional (Collective) Level (Level 2)

We obtained data on these variables in municipal offices. These were indicators of latent variables (constructs) such as poverty,[22–24] development,[23] urban/rural differences,[25] income,[26] and health services.[27]

Ethnic and cultural aspects were analyzed using native language usage,[28] migration,[29] violence,[30] and nutrition of the population.[31] For itemized descriptions of the variables used see Appendix (available online at http://links.lww.com/RHU/A48).

## Statistical Analysis

Two-level and rare event logistic models were used to concurrently investigate the influence of individual level (first-level variables) and regional characteristics (second-level variables) in RA prevalence.[32] Given the limited number of states included in the study, we could not integrate third-level units to the model[33]; instead each state was represented by selected municipalities. We performed a preliminary evaluation of the effect of the individual-level variables by using independent $\chi^2$ tests and 1-level logistic models.

The suitability of the 2-level approach was assessed with the intraclass correlation coefficient. At the individual level, the associations between the studied variables and RA (and their variance) were evaluated using the odds ratio (OR) and 95% confidence interval (CI) in the fixed-effects part of the models. Regional effects were considered as random effects in order to allow for possible between-population differences in the association between these variables and RA prevalence. On the other hand because estimates related to regional-level variables (Tables 3 and 4) cannot be used to indicate individual odds in the traditional way, they can be viewed as estimates of the variation of the traditional individual odds across states. This way, keeping constant the other variables in the model, the regional-level coefficients can be considered as the variation in "average states when not affected by specific regional effects."

For the individual-level model, variables were selected by stepwise logistic regression analysis. Such variables were then entered in the multilevel model. Changes in model structure were valued with the use of likelihood information criteria.[32,33] A median OR was also calculated as a measure of heterogeneity in RA prevalence across regions. This measure can be understood as the median of the ORs obtained by choosing 2 random persons with the same covariates but from different regions and computing the OR between them.[32] Verification of the results by the multilevel approach was made by means of robust estimation procedures because of the low prevalence of RA. All analyses were carried out with STATA 10 software (StataCorp, College Station, TX).[34]

## Ethical Issues

The study protocol was approved by the Ethics Committee of each center. All participants in the study were informed of the protocol procedures and signed an informed consent form after they agreed to participate.

# RESULTS

The overall prevalence of RA was 1.6% (95% CI, 1.42%–1.78%), 2.09% (95% CI, 1.83%–2.35%) in women and 0.85% (95% CI, 0.64%–1.06%) in men (Table 1). The mean (SD) age was 42.89 (17.34) years; 40.64% of the subjects were older than 45 years, and 20.42% were older than 55 years. After adjustment according to age and sex distribution in Mexico in 2010,[18] the overall prevalence was 1.49% (95% CI, 1.39%–1.6%), ranging from 0.78% (95% CI, 0.56%–0.6%) in Nuevo León to 2.66% (95% CI, 2.41%–2.92%) in Yucatán (Table 1).

The crude initial bivariate analysis showed significant differences in the prevalence of RA across states ($\chi^2$ = 68.74; $P$ = 0.000). Previous treatments and comorbidities, as well as socioeconomic indicators, also showed significant differences between subjects with and without RA (Table 2). All crude comparisons among individual characteristics achieved a statistical power higher than 80% with prevalence rates as low as 3%. The prevalence of high blood pressure, peripheral vascular disease, and hyperlipidemia was significantly higher among subjects diagnosed with RA, as was the proportion of people with pain indicators, use of previous treatments, and higher levels of disability. The role of illegal drug use was estimated with a very low precision level because of the low response rate (n = 51) (Table 2).

**TABLE 1.** Demographic Characteristic by Region of Residence

| State | Sample Size, n (%) | Age, Mean (SD) | % Women | RA Prevalence (95% CI), % | Adjusted RA Prevalence (95% CI)[a] |
|---|---|---|---|---|---|
| Chihuahua | 1647 (8.57%) | 40.35 (17.03) | 56.83 | 1.94 (1.27–2.6) | 1.95 (1.61–2.29) |
| México City | 4059 (21.13%) | 44.64 (16.81) | 68.86 | 1.08 (0.76–1.4) | 0.92 (0.77–1.08) |
| Nuevo León | 4713 (24.53%) | 43.61 (17.35) | 55.91 | 0.77 (0.47–0.98) | 0.78 (0.56–0.8) |
| Sinaloa | 4879 (25.39%) | 41.72 (17.39) | 57.68 | 1.8 (1.43–2.17) | 1.63 (1.45–1.81) |
| Yucatán | 3915 (20.38%) | 42.71 (17.73) | 61.86 | 2.81 (2.29–3.32) | 2.66 (2.41–2.92) |
| Total | 19213 (100%) | 42.88 (17.34) | 60.39 | 1.60 (1.42–1.78) | 1.49 (1.39–1.6) |

[a]Adjusted to the age and sex.

**TABLE 2.** Individual-Level Variables and Comorbidities and Crude Comparisons

| Individual Variables/Comorbidities | Total (n = 19213) Mean (95% CI) | With RA (n = 308) Mean (95% CI) | Without Rheumatologic Diagnosis (n = 14,599) Mean (95% CI) | *P* |
|---|---|---|---|---|
| Smoking | 7.54 (7.15–7.93) | 3.98 (1.67–6.29) | 7.01 (6.56–7.45) | 0.040[a] |
| Alcohol use | 4.07 (3.78–4.36) | 2.89 (0.91–4.87) | 4.00 (3.66–4.34) | 0.351 |
| Income[b] | 25.77 (25.15–26.39) | 25.65 (25.03–26.27) | 33.11 (27.86–38.27) | <0.001[a] |
| Education level[c] | 8.51 (8.43–86) | 7.86 (7.15–8.57) | 8.71 (8.60–8.80) | 0.009[a] |
| Type of job (heavy loads) | 54.09 (53.34–54.75) | 55.51 (49.96–61.06) | 53.91 (53.09–54.73) | 0.576 |
| Type 2 diabetes | 9.72 (9.29–10.16) | 12.68 (8.73–16.63) | 8.39 (7.91–8.87) | <0.001 |
| High blood pressure | 16.48 (15.93–17.02) | 23.91 (18.88–28.94) | 13.59 (13.00–14.19) | <0.001[a] |
| Heart disease | 2.93 (2.68–3.18) | 3.62 (1.41–5.82) | 2.22 (1.96–2.48) | 0.121 |
| Peripheral vascular disease | 13.11 (12.61–1361) | 19.02 (14.55–23.84) | 10.02 (9.50–10.54) | 0.000[a] |
| Gastritis | 18.93 (18.35–19.51) | 22.82 (17.87–27.77) | 16.06 (15.42– 16.69) | <0.001[a] |
| Anxiety | 5.19 (4.86–5.51) | 6.52 (3.60–9.43) | 3.76 (3.43–4.09) | 0.018 |
| Depression | 6.51 (6.14–6.87) | 8.69 (5.37–12.01) | 4.65 (4.28–5.02) | 0.018 |
| Drug use | 0.03 (0.02–0.04) | — | — | — |
| Obesity | 9.47 (9.03–9.9) | 11.95 (8.12–15.78) | 7.75 (7.28–8.21) | 0.010[a] |
| Hyperlipidemia | 8.11 (7.71–8.52) | 14.85 (10.65–19.05) | 6.38 (5.95–6.80) | <0.001[a] |
| Previous treatments | 25.66 (25.04–26.27) | 43.47 (37.62–49.32) | 7.45 (6.99–7.91) | <0.001[a] |
| Historical MSK pain | 18.27 (17.72–18.82) | 37.01 (31.62–42.41) | 14.76 (14.81–15.34) | <0.001[a] |
| Concurrent MSK pain | 33.23 (32.57–33.9) | 52.27 (46.69–57.85) | 21.52 (20.85–22.81) | <0.001[a] |
| Previous diagnostics | 12.79 (12.29–13.28) | 43.47 (37.62–49.32) | 7.45 (6.99–7.91) | <0.001[a] |
| Health Assessment Questionnaire Disability (yes/no) | 12.93 (12.45–13.41) | 35.38 (30.04–40.72) | 8.15 (7.71–8.60) | <0.001[a] |

All *P* values correspond to the comparisons between the RA group versus the group with no rheumatologic diagnosis.

[a]Significant differences at 95% confidence level.

[b]Proportion of people earning US $3.5 daily or less, or less than the 2 minimum daily legal Mexican salaries.

[c]Number of year completed.

MSK indicates musculoskeletal.

That finding is consistent with RA prevalence variations found through the multilevel modeling after controlling for individual-level variables. ($\chi^2$ = 445.71; $P < 0.001$; intraclass correlation coefficient = 0.23). All estimations were stable and confirmed the absence of bias in the backward selection process (Table 3).

The adjusted analysis (Table 4) showed that the individual variables that most influenced the prevalence of RA were sex (OR, 2.32; 95% CI, 1.74–3.07), previous medical diagnosis other than RA (OR, 3.32; 95% CI, 2.19–2.22), previous medical treatments for conditions other than RA (OR, 2.22; 95% CI, 1.34–3.66), disabilities (OR, 2.07; 95% CI, 1.48–2.93), and age 56 to 65 years (OR, 1.95; 95% CI, 1.08–3.74).

The percentage of persons speaking a native indigenous language was the only group-level variable with a significant effect. Neither income, urban/rural area, development, poverty, nor health service variables had a significant role in the model. The estimates show that the risk of RA doubled on average with every percentage point increase in the use of native languages at a state level (2.27). Inclusion of the cross-level interaction terms had minimal effects on the contribution of individual-level and regional-level variables and was very limited because of the small sample sizes in the first-level analysis. Finally, the inclusion of the first-level (regional) variables had minimal effects on the ORs estimated for individual-level variables (Table 4). This supports the nonexistence of cross-level interactions in the model and also the association of the regional effect (monolingualism) with variations in the prevalence of RA across the studied states.

## DISCUSSION

This study showed that the regional variation in the prevalence of the RA in Mexico may be partly explained by the ethnic/cultural composition of the populations, in particular, the proportion of persons who are native-language speakers. This result was consistent with previous findings in studies of predictors of RA in different populations.[8,35] In our case, the south region, with a larger prevalence of RA (2.81%), also had the largest proportion of people who were native speakers (40.13%). Meanwhile, the northeast region, with the lowest prevalence of RA in the study (0.77%), had a low proportion of native speakers (0.4%).

Other regional variables, such as those related to poverty, development, urban/rural differences, income, or access to health services, were not significant in the final model. However, it is likely that the percentage of people using native languages as their mother tongue in some way explains the variations associated with the poverty or level of development in each region. The most frequent use of native languages tends to occur in regions populated by indigenous or endogamic people, thus protecting some cultural and genetic characteristics.[8,35–38]

Explanations for the differences associated with the use of native languages may be related to differential exposures to

**TABLE 3.** Preliminary Multilevel Model With Regional-Level Effects and Significant Individual-Level Effects

| Individual-Level Effects | OR (95% CI) | *P* |
|---|---|---|
| Sex | 2.47 (1.79–3.41) | <0.001 |
| Age (55–65) | 1.88 (1.01–3.49) | 0.043 |
| Type of job (heavy loads) | 0.71 (0.54–0.94) | <0.001 |
| Concurrent ME pain | 1.83 (1.28–2.63) | <0.001 |
| Previous diagnostics | 3.47 (2.46–4.89) | <0.001 |
| Previous treatments | 2.32 (1.55–3.46) | <0.001 |
| HAQ Disability (yes/no) | 2.04 (1.5–2.77) | <0.001 |
| Percentage of people speaking natives languages | 2.23 (1.07–4.64) | 0.032 |
| Deprivation index | 1.12 (0.99–1.26) | 0.052 |
| Human development index | 0.2 (0.00–4.47) | 0.311 |
| Gini coefficient | 2.36 (0.01–3.19) | 0.766 |
| Urbanization level[a] | 0.99 (—) | (—) |
| Gross internal product | 1 (0.99–1.01) | 0.369 |
| Health insurance | 1 (0.98–1.01) | 0.972 |
| Migration | 0.93 (0.71–1.22) | 0.638 |
| Religion | 3.57 (0.1–12.17) | 0.477 |
| Violence | 1.12 (0.99–1.26) | 0.053 |
| Nutritional risk index | 1.14 (0.97–1.33) | 0.08 |
| **Regional-level effects** | **Coefficient (95% CI)** | ***P*** |
| Percentage of people speaking natives languages[b] | 1.01 (0.5–2.05) | 0.006[c] |
| Deprivation index[b] | 0.061 (0.00–0.76) | 0.438 |
| Human development index[b] | 0.71 (0.1–4.75) | 0.303 |
| Gini coefficient[b] | 5.57 (0.26–11.8) | 0.522 |
| Health insurance[b] | 0.008 (0.002–0.29) | 0.110 |
| Migration[b] | 0.23 (0.05–0.97) | 0.174 |
| Religion[b] | 0.99 (0.26–3.75) | 0.140 |
| Violence[b] | 0.06 (0.00–0.76) | 0.442 |
| Nutritional risk index[a,b] | 0.02 (—) | 0.944 |

Urbanization level and gross internal product omitted at collective level because of no convergence in the estimation of its coefficients.

The model includes the effect of speaking native languages as an individual variable as indicator of the related OR on an average state; its variation across states is represented by the regional estimation of the same variable. This is the only variable with significant variation among regions.

[a]No convergence results in the model.

[b]Variables at regional level.

[c]Significant at ecological level.

nonanalyzed variables (eg, infectious agents), regional lifestyles and work activities, and in differences in the accessibility to primary preventive health services and variations in the rates of successful screening and diagnosis. Based on the widely recognized relationship between genetic characteristics and the development of RA,[38,39] it may be hypothesized that the variations in prevalence found in this study could result from an overrepresentation of associated genetic characteristics.

At the individual level, our results are consistent with previous findings[10–12]; however, tobacco use did not have a significant association with the risk of RA. Several issues could explain this. First, in our study, smoking was established by means of yes/no self-reported use. Second, the prevalence of tobacco use was significantly lower than in the general population, probably because of an effect of reverse causality in this estimation; that is, people with any manifestation of RA may deliberately have stopped smoking.

As expected, the risk of RA increased with age and was higher in women. No individual socioeconomic gradient was identified in our adjusted model. Other individual factors associated with manifestations of morbidity, such as pain, disability, and previous medical diagnosis and treatments, were also significant. Age was also an important risk factor, especially for those between 55 and 65 years of age, which has been reported as the age when the disease becomes evident.[1,2] Regarding obesity, contrary to the association with RA reported in other studies,[1–4] the adjusted analysis showed no significant association in our study. It is possible that any association may have been masked as more adults undertake weight-loss measures across the nation. Moreover, variables such as high blood pressure and hyperlipidemia were not significant after adjustment.

This study has some limitations. The cross-sectional nature of the data limits our ability to draw causal inferences as it does not allow identification of preceding exposures and consequent outcomes. Furthermore, the numbers pertaining to the first-level factors in each state could affect the precision of the estimates, as was the use of self-reporting. In addition, our results relate to the Mexican population in 5 states and may not fully reflect the situation in all 31 states in Mexico. Regarding the statistical analysis, there was very careful use of inferences, especially related to the model's capacity to assign contextual effects to individuals (ecologic fallacy). Residual confounding could be a problem because of the omission of individual-level variables related to the RA and to the group characteristics investigated.[40]

The statistical approach did provide a wider overview of the problem of RA in the Mexican population and incorporated the effects of regional variables into the model in accordance with the need for further explanations about the dynamics and variations in RA prevalence.[4,41] The analysis also provided a means to link traditionally distinct ecological- and individual-level RA studies[42] and to overcome the limitations inherent in focusing only at the individual level by recognizing populations (or groups) as entities with properties that may affect individuals within them.[42,43] From this perspective, evidence of regional differences in RA prevalence provides valuable information for planners who determine the allocation and provision of medical services, with identification of populations that may need to be particularly targeted in prevention and/or management programs.[44]

Even though recent evidence shows an association between RA prevalence and underprivileged social conditions, including a multilevel perspective,[36] there is a lack of information about this relationship in the developing world or in areas with a significant presence of native groups. Similarly, although the influence of the area where a person lives has been recognized as having an impact on the quality of life and pain levels of RA patients, there is practically no knowledge about how environmental factors affect the likelihood of developing RA or its course. Despite the consensus

**TABLE 4.** Association of Regional and Individual Variables

| Individual-Level Variables | OR (95% CI) |
|---|---|
| Sex | 2.32 (1.74–3.07) |
| Age (55–65 y) | 1.95 (1.08–3.74) |
| Previous diagnostics | 3.32 (2.19–2.22) |
| Previous treatments | 2.22 (1.34–3.66) |
| HAQ disability (yes/no) | 2.07 (1.48–2.93) |
| % People speaking natives languages | 3.27 (1.59–6.69) |

Finalmultilevel model.

that socioeconomic, cultural, and environmental factors can operate as health determinants at any level,[36,43] RA has been traditionally associated mainly with individual lifestyle and genetic risk factors; however, the low penetrance of the disease underscores the potential influence of environmental factors and gene-environment interactions on its etiology.[38,39]

In this study, we found a significant association between the prevalence of RA and the speaking an indigenous language through a multilevel approach methodology. The findings of the current study may enhance our understanding of RA and the role of ecological variables in its development. Further research is needed to better understand the mechanisms that underlie these regional variations and to identify other factors that contribute to the variation in the prevalence of RA, especially in developing countries where knowledge about the etiology of RA is sparse.

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