

The Social Gap Index and the prevalence of osteoarthritis in the community: a cross-sectional multilevel study in Mexico

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Abstract Multilevel studies have gained importance for highlighting social inequalities in health. These associations have been reported previously in diseases such as arthritis and chronic pain. We conducted a cross-sectional study using multilevel analysis to identify individual and contextual factors associated with the variation of prevalence of osteoarthritis (OA) in the Mexican population. The sample included 17,566 individuals of which 10,666 (60.7 %) were women. The relationship between individual and contextual factors and OA were analyzed with a multilevel strategy. From the total population, 1,681 individuals had OA. Multilevel analysis showed that individual variables such as female gender (odds ratio (OR)=1.3, 95 % confidence interval (CI) 1.1, 1.4), age range 55–65 years (OR=1.6, 95 % CI 1.3, 2.0), musculoskeletal pain in the last 7 days (OR=2.6, 95 % CI 2.3, 3.0), and use of pain treatments (OR=1.4, 95 % CI 1.2, 1.7) were associated with OA.

At the regional level, the Social Gap Index (SGIx) was associated with the diagnosis of OA (coefficient 0.5, 95 % CI 0.2–1.1). The SGIx contextual variable was positively associated with the regional prevalence of OA and the variation in prevalence of OA in different regions. The larger the social gap, the greater the variation in OA prevalence. These factors were independently associated with the prevalence of OA: female gender, pain intensity, physical limitation, and the use of pain treatments were individual variables associated with OA. The association between OA prevalence and regional variations with SGIx reflects inequities in health provisions that should be considered in health programs.

Keywords Epidemiology · Health inequity · Multilevel analysis · Osteoarthritis

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Introduction

Educational, economic, and health care inequities characterize human society. In a wide sense, social inequity has been recognized as an important factor in health and disease. Health inequity refers to the moral or ethical dimensions of health inequality. Health inequality refers to variations in health status across individuals in a population [1]. Social inequity plays an important role in the prevalence of chronic diseases [1, 2], but information related to rheumatic diseases is still scarce [3, 4]. Few studies have identified the existence of inequities among patients with rheumatoid arthritis (RA) [4], osteoarthritis (OA) [5], and systemic lupus erythematosus [6] in any country.

Despite the fact that social inequities and consequentially health care inequities may be recognized in developed and underdeveloped nations, the problem is greater in those lacking a health care system that covers the whole population. That is the case in many Latin American, Asian, and African countries, and in the United States of “North” America to some extent. In particular, the Mexican health care system is a mixed or fragmented model, in which around half of the population is not covered by the state and the expenses generate great economic and social inequities. The burden of disease affects the household through out-of-pocket expenses and restrains economic growth and family activities. In contrast, the impact of the disease in the population covered by the national health budget is much less important. The proportion of households having catastrophic expenses resulting from RA as a consequence of impoverishment is much greater than in those covered by the state [7, 8].

We recently reported the results of a large epidemiological study to determine the prevalence of the most important rheumatic diseases in 17,566 individuals distributed in several states. The results showed OA as the most common of the rheumatic diseases with a prevalence of 9.5 % (95 % CI 9.1, 10.0). A more detailed analysis of the data showed wide geographic variations, ranging from 2.5 to 16.3 %, which were not easily explained by methodological and individual characteristics. Nonetheless, because we carried out our study in geographical regions with uneven socioeconomic indicators [9], we hypothesized that social inequity could play a role in the prevalence of OA in each of the geographic areas studied. The approach of these geographic variations was based on a multilevel contextual design, which is able to detect social inequalities in health. Therefore, we aimed to identify individual and contextual factors associated with the prevalence of OA and integrate the level of social and cultural elements influencing health and disease.

Materials and methods

This is a secondary analysis of the database of a previously published study on the prevalence of musculoskeletal (MSK) symptoms and rheumatic conditions, including OA, carried out in the Mexican population [9]. Briefly, the study was cross-sectional and included communities from the states of Nuevo Leon, Sinaloa, Yucatan, and Mexico City. The Community Oriented Program for the Control of Rheumatic Diseases (COPCORD) questionnaire was used to identify patients with nontraumatic MSK pain and collect a number of demographic, clinical, therapeutic, economic, and educational information. Additional questionnaires were administered to obtain clinical, therapeutic, economical, educational, and functional capacity data. A positive MSK case definition was an individual with nontraumatic MSK pain >1 on a visual analog scale (0 to 10) in the last 7 days or in the past. Positive cases were referred to board certified rheumatologists for diagnosis. The diagnosis of OA was established according to American College of Rheumatology criteria [10–12]. We consider “cases” those individuals who had symptomatic OA, which we define as those patients who reported the presence of pain or discomfort and stiffness accompanied by articular crepitus. Only borderline cases were asked to undergo a radiographic study. The sample that underwent analysis included 17,566 individuals (60.7 % women) with a mean age of 43.1 years (17.4 standard deviation [SD]; range 18–99 years). The group of controls in this study included all individuals without OA. The study protocol was previously approved by the Institutional and Ethics Committees of each participating institution. All study participants were informed of the study procedures prior to their participation and voluntarily signed informed consent forms.

Construction of the multilevel model

We included variables related to the individual in the level 1 model whereas the level 2 model comprised all variables related to collective or contextual data (for a complete definition of variables, please see Table 1 and Fig. 1). The level 1 model included the following variables: (1) *socioeconomic variables*: age and gender, economic and educational level, work status, household income, housing facilities, and support for health care access; (2) *individual's lifestyle* (tobacco and alcohol consumption), *clinical* (MSK pain, self-reported comorbidities, previous treatments, and medical and alternative therapy), and *physical disability variables* (Health Assessment Questionnaire-Disability Index [HAQ-DI])[13]. Level 1 variables were all obtained from the COPCORD questionnaire that each individual had already completed.

Level 2 model variables included group information, i.e., state information [14]. The selection of these variables was probabilistic and according to risk factors described in the

Table 1 Definition and sources of ecological variables included in level 2

Ecological Variables	Source	Description
Human Development Index	UNDP (2004)	Combines health variables (life expectancy), education income (1=maximum advance possible, 0=no advance)
Inequality	CONEVAL; Maps of equality (2005)	The Gini coefficient is a measure of concentration. This coefficient uses values of 0 to 1; the higher the value to 1, the greater the inequality that exist with regard income
Level of urbanization	UNDP (2005)	Measures the average difference between the percentages homes in an urban/rural zone with regard to access to public services
Gross national product	INEGI; National Account System: Total economic activity (2009)	Existing macromagnitude that measures the final production of goods and services in a state over a period of time (usually 1 year)
Health care access	INEGI; National Account System (2009)	Percentage of persons who have some type of health insurance (public or private)
Percent of unemployment	INEGI (2011)	Opportune indicators of occupation and work: unemployment rate by state
Migration index	CONAPO; Migration Index (2002)	A measure summarizing nine socioeconomic indicators allow the measuring of forms of social exclusion and are disadvantage or deficit variables very low–very grade (−1.5–2.25)
Marginalization index	CONAPO; Marginalization Index (2000)	A summary measure that differentiates states and municipalities according to the impact of the shortage suffered by the population as a result of a lack of access education and adequate housing and a perception of insufficient cash income
Social gap index	CONEVAL; Social Gap Index (2010)	Adjusted measure that summarizes four indicators of social deficiency (education, health, basic services, and housing) into one index in order to organize the units observed according to their social needs. Lower index means less social disadvantage

UNDP United Nations Development Program-Mexico, CONAPO National Population Council, INEGI National Institute of Statistics and Geography, CONEVAL National Council of Evaluation of Social Development Policy

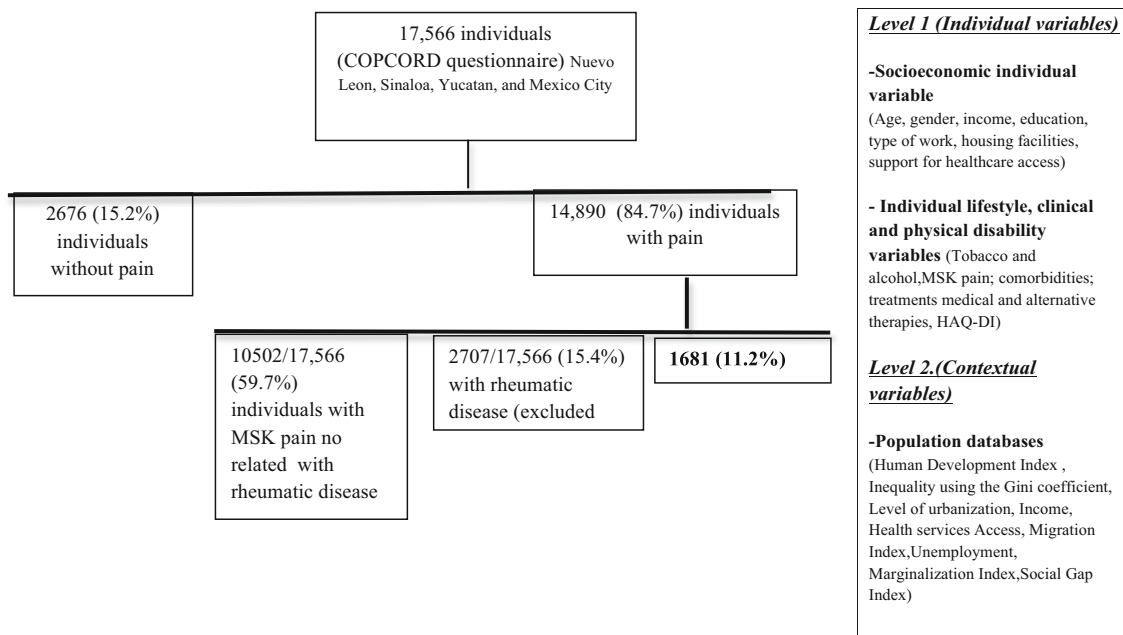


Fig. 1 Participant flow chart and variables considered for the construction of the multilevel model

literature for its association with OA [15–20]. The model included the following instruments and topics: (a) Human Development Index (HDI) [21], (b) Gini coefficient for inequality [22], (c) urbanization [23], (d) gross national product (GNP) [24], (e) health care access [25], (f) the Migration Index (MiI) [26], (g) unemployment [27], (h) the Marginalization Index (MaI) [28], and (i) the Social Gap Index (SGI) [29]. Information was extracted from the National Institute of Statistics and Geography (INEGI), the National Population Council (CONAPO), the National Health Survey (ENUSALUD), and the National Council for the Evaluation of Social Development Policy (CONEVAL), all Mexican electronic databases. Of special interest is the SGI, which is an aggregate of variables extracted from the database of the CONEVAL, which incorporates indicators of education, access to health services, basic services, of housing quality and space, and household assets. This index is scored as very low, medium, and very high social underdevelopment, which is interpreted as those locations that range from lower to higher limitations in the indicators (a higher score means more limitations) [30].

Statistical analysis

In the descriptive analysis, we reported measures of central tendency and dispersion as continuous variables and absolute and relative frequencies in ordinal as well as nominal or categorical variables. For each variable, we performed a bivariate analysis with analysis of variance (ANOVA), one and two-tailed for continuous variables, and the chi-square test for ordinal, nominal, or categorical variables. The presence of each individual variable was evaluated in the model by a stepwise selection methodology; the initial model was a full descriptive model, but additional parameters were deleted in each step. The significance of parameters was evaluated using the Wald test. For the multivariate analysis, we used a two-level logistic model, level 1 for individual variables and level 2 for contextual variables. A multilevel analysis was performed with simultaneous analysis of the influence of individual and community characteristics in relation to variations of OA prevalence [31]. Given the constraints of sample size, we did not add the states as a first-level unit to the model [32], but rather the municipalities (counties) within it. The initial phase of analysis corresponded to raw comparisons using the chi-square test.

To verify the suitability of the multilevel approach, we calculated the intra-class correlation coefficient (ICC). The association between such variables and the prevalence of OA (and its uncertainty) were assessed at the individual level

by odds ratio (OR) and 95 % confidence intervals (95 % CI; fixed model effect). To incorporate state variations in the relation between variables and the prevalence of OA, we considered regional variables as random effects. The structure of the covariance matrix used in this study did not allow for a correlation analysis of the levels of information. The final model was achieved after a backward selection process, stage by stage, eliminating one variable by one to obtain first, the individual model, and then the regional and individual variables at the same time. Changes in each model were examined using likelihood criteria [30]. The OR was calculated from the median as a measure of heterogeneity among the different geographic areas. This measure can be defined as the median of the ORs obtained by choosing two random individuals with the same covariates, but from different geographic areas [32]. Unobserved heterogeneity was quantified by considering the median OR for pairs of randomly sampled persons having the same covariate value, i.e., living in the same area. The aim of the median odds ratio (MOR) is to translate the area level variance in the widely used OR scale, which has a consistent and intuitive interpretation. The MOR is defined as the median value of the OR between the area at highest risk and the area at lowest risk when randomly choosing two areas. MOR can be conceptualized as the increased indirect risk that (in a median value) would occur if moving to another area with a higher risk [32]. All analyses were performed using the statistical package STATA v 11 (College Station, Texas, USA [33]).

Results

The diagnosis of OA was established in 1,681 individuals. The prevalence of OA was 9.5 % (95 % CI 9.1, 10.0), higher in women than in men [10.9 % (IC95% 10.3–11.5) vs. 7.3 % (IC95% 6.7–8.0), $p < 0.01$]. By age group, the prevalence of OA was 4.8 % (95 % CI 4.4, 5.2) in individuals ≤ 45 years, 14.0 % (95 % CI 1.0, 15.0) in individuals between 46 and 65 years, and 21.4 % (95 % CI 19.7, 23.2) in those over ≥ 65 years. Interestingly, the prevalence of OA varied from 2.5 % in Sinaloa to 6.7 % in Yucatan, 12.8 % in Mexico City, and 16.3 % in Nuevo Leon. Compared with control individuals, the subjects with OA reported VAS pain in the last 7 days with an intensity ≥ 4 (6.1 vs. 3.4 %, $p < 0.01$), physical limitations (9.6 vs. 4.0 %, $p < 0.01$), and greater use of pain treatments (55.5 vs. 44.4 %). OA prevalence in individuals under 45 years was 4.8 % (95 % CI 4.4, 5.2), in those between 46 and 65 years 14.0 % (95 % CI 1.0, 15.0), and in those over 65 years 21.4 % (95 % CI 19.7, 23.2).

Individual variables Significant differences contextual variables in individuals with and without OA included income

Table 2 Comparison of individual variables in subjects with osteoarthritis and controls

Variable	Without OA N=13,209 %-mean (95 % CI)	With OA N=1681 %-mean (95 % CI)	<i>p</i>
Income ^a	25.8 (26.1, 27.4)	17.2 (15.5, 18.8)	0.000 ^c
Education ^a	8.5 (8.5, 8.6)	7.9 (7.6, 8.3)	0.000 ^c
Type of work (physical burden)	61.4 (60.6, 62.2)	55.9 (53.5, 58.3)	0.000 ^c
Previous treatments	22.9 (22.3, 23.6)	50.0 (47.8, 52.2)	0.000 ^c
History of pain	17.3 (16.7, 17.9)	26.3 (24.4, 28.2)	0.000 ^c
Pain in the last 7 days	30.1 (29.4, 30.8)	64.1 (62.0, 66.2)	0.000 ^c
Disability HAQ (Y/N)	11.1 (10.6, 11.6)	26.3 (24.4, 28.2)	0.000 ^c
Comorbidities			
Type 2 diabetes	8.9 (8.4, 9.3)	17.5 (15.6, 19.3)	0.000 ^c
HT	15.0 (14.4, 15.5)	30.0 (27.6, 32.0)	0.000 ^c
Cardiopathy	2.4 (2.2, 2.7)	6.9 (5.7, 8.1)	0.000 ^c
Peripheral vascular disease	12.2 (11.7, 12.7)	22.5 (20.5, 24.5)	0.000 ^c
Gastritis	18.6 (18.0, 19.2)	23.9 (21.9, 26.0)	0.000 ^c
Anxiety	4.9 (4.6, 5.28)	8.0 (6.7, 9.3)	0.000 ^c
Depression	6.2 (5.8, 6.5)	10.5 (9.0, 12.0)	0.000 ^c
Obesity	9.1 (8.7, 9.6)	14.7 (13.0, 16.3)	0.000 ^c
Hyperlipidemia	7.6 (7.2, 8.0)	13.1 (11.5, 14.7)	0.000 ^c

OA osteoarthritis, HT hypertension, HAQ Health Assessment Questionnaire

^a Proportion of individuals with an income of \$ 192 USD per month or less: equivalent to legal minimum wage

^b Number of years completed

^c Significant differences with 95 % confidence

25.8 (95 % CI 26.1, 27.4) vs. 17.2 (95 % CI 15.5, 18.8); education 8.5 (95 % CI 8.5, 8.6) vs. 7.9 (95 % CI 7.6, 8.3) (Table 2).

The group of individuals with OA had greater pain intensity (OR=2.6, 95 % CI 2.5, 3.0), physical limitation (OR=1.6, 95 % CI 1.5, 1.8), paid work (OR=0.7, 95 % CI 0.7, 0.8), HAQ_DI score greater than 1.0 (OR=3.3, 95 % CI 2.9, 3.7), and increased use of therapies for pain (OR=4.3, 95 % CI 3.8, 4.7) compared with controls.

Contextual variables The GNP and the SGIX were significantly different across states. All other regional differences of contextual variables are shown in Table 3.

Multilevel analysis

Multilevel model 1 The inclusion of regional variables in the analysis confirmed the existence of significant variations in the prevalence of OA even after controlling for individual factors ($\chi^2=549.69, P<0.001$). The

multilevel model, including all regional and individual effects, showed statistically significant differences regarding the prevalence of OA associated with female gender (OR=1.3, 95 % CI 1.1, 1.4), higher age (OR=1.6, 95 % CI 1.3, 2.0), MSK pain in the last 7 days (OR=2.6, 95 % CI 2.2, 3.0), pain treatments (OR=1.4, 95 % CI 1.2, 1.7), and SGIX (OR=0.3, 95 % CI 0.2, 0.6). All other variables were marginal or not significant (see Table 4).

Multilevel model 2 SGIX was the unique variable showing significant effect at the regional level (see Table 5). The model showed significant variation in the OR by SGIX level. Thus, an increase of 1 SGIX unit in a specific state implied an increase of 1 standard deviation in the OR resulting from comparison of OA and the reference value. However, the estimate of this effect was so variable that the magnitude of the standard error of the coefficient represents 46 % of its value (SE=0.2). Thus, the states with high SGIX (i.e., Yucatan, mean -1.2, SD 0.4) were characterized by a greater social underdevelopment in comparison with the state with the lowest SGIX (Mexico City, mean -2.0, SD 0), which is one standard deviation below the overall mean (-1.3 SD 0.8)(see Table 3).

Interaction between level 1 data and level 2 was not statistically significant, though we found considerable variation in the presence of pain in the last 7 days, marital status, use of pain treatments, physical limitation, decreased ability to bend over and squat, and age (see Table 5).

The interpretation of the hypothesis is that the effects associated with each of the individual variables are not significant. The chi-square test indicated that the variation in the prevalence of OA, once adjusted for the effect of individual variables, was significantly heterogeneous in terms of the values of the index of the social gap.

Table 3 Description of contextual variables by states

Variable	Nuevo Leon	Sinaloa	Mexico City	Yucatan	<i>p</i>	Total
OA prevalence, %	16.3	2.5	12.8	6.7		
HDIx, M(SD)	0.8 (0)	0.8 (0)	0.8 (0)	0.8 (0)	<0.001	0.80
GCoe, M(SD)	0.4 (0.0)	0.5 (0.0)	0.5 (0)	0.5 (0.0)		0.48
Level of urbanization, M(SD)	70.4 (15)	64.3 (11.9)	88.3 (0)	68.8 (5.8)	<0.001	
GNP, %	5.2	3.8	2.0	3.0		4.4
Average % of health coverage, M(SD)	45.7(21.6)	50 (15.4)	36 (0)	49 (18.1)		
Unemployment rate,%	0.9	0.9	0.8	0.81		
MiIx, Me (IQR)	0 (0–0)	0 (0–3)	0(0–0)	2 (0–3)		
SGIx, M(SD)	–1.3 (0.8)	–1.6 (0.7)	–2.0 (0)	–1.2 (0.4)		
Low–very low	3036 (64.4)	4107 (84.1)	4059 (100)	868 (22.1)	<0.001	
Medium	414 (8.7)	0	0	3047 (77.8)		
High–very high	1263 (26.8)	772 (15.8)	0	0		

OA osteoarthritis, GCoe Gini coefficient, GNP Gross National Product, HDIx Human Development Index, MiIx Migration Index, SGIx Social Gap Index

Discussion

We found individual and contextual factors associated with the variable prevalence of OA in the Mexican population. The implementation of two multilevel models to determine the influence of social and cultural elements in this study followed today’s global initiatives to identify health disparities as well as to prevent and reduce the impact of MSK diseases in the general population [34]. In this sense, our study is consistent with the research proposal of the CONEVAL [35], which refers to the identification of global factors affecting health equity, defined “as the absence of systematic differences in health, between and within countries that are avoidable by reasonable action” [36].

Regarding individual variables in the level 1 model, we found significant associations between the prevalence of OA and female gender as well as older age and at least three related variables: pain of great intensity, use of pain treatments, and functional limitations for which temporality should be analyzed in detail. A community study of hip OA found a significant association between HAQ_DI score and levels of education and poverty [37]. That association could result in

Table 5 Multilevel model 2. Association of significant regional and individual variables

Individual variable	OR (95 % CI) ^c	<i>p</i>	<i>z</i>
Pain in the last 7 days	2.0 (1.9, 2.3)	< 0.001	11.9
History of pain	1.1 (1.0, 1.3)	0.001	2.2
Marital status, separated or divorced ^d	1.6 (1.2, 2.0)	< 0.001	3.8
Previous treatments	1.5 (1.3, 1.7)	< 0.001	6.7
Some limitation ^b	0.8 (0.7, 0.9)	< 0.001	–3.4
HAQ-DI, can bend over (Y/N) ^c	0.8 (0.7, 0.9)	0.003	–3.6
HAQ-DI, can squat (Y/N) ^c	1.2 (1.0, 1.3)	0.001	2.8
HAQ-DI, can kneel (Y/N) ^c	1.2 (1.0, 1.3)	0.030	2.6
Age (18–25) ^d	0.3 (0.2, 0.4)	< 0.001	–7.7
Age (26–35) ^d	0.3 (0.2, 0.4)	< 0.001	–8.5
Age (36–45) ^d	0.5 (0.4, 0.6)	< 0.001	–5.4
Age (46–55) ^d	0.6 (0.5, 0.8)	< 0.001	–3.8
Age (56–65) ^d	0.8 (0.6, 1.0)	< 0.001	–2.0
Regional variable	OR (95 % CI)		
SGIx	0.5 (0.2, 1.1)		NA

^a Reference category: bachelor/bachelorette

^b Currently with limitations or with past limitations

^c Yes, included the following: with some difficulty, with much difficulty, and unable to do

^d Reference category: over 65 years

^e Due to uneasy interpretation of the coefficient related to the regional variable, we do not offer an OR directly of its effect; instead, the table only shows its coefficient as an indicator of its variation. The use of the term median OR is an attempt to better explain its interpretation

Random-effects parameters: SGIx 0.45 (SE 0.21 [0.1-1.1]). | Estimate Std. Err. [95 % Conf. Interval]LR test vs. logistic regression: chi2(2)=549.69 Prob>chi2=0.0000Wald chi2=1073.03. LR test vs. Log likelihood=–5461.2412. Prob>chi2=0.0000

Table 4 Multilevel model 1. Regional effects and significant individual effects

Individual variables	OR ^a /Coef. (95 % CI) ^b	<i>p</i>
Gender ^a	1.3 (1.1, 1.4)	<0.001
Age (55–65, years) ^a	1.6 (1.3, 2.0)	<0.001
Current MSK Pain ^a	2.6 (2.3, 3.0)	<0.001
Pain treatments ^a	1.5 (1.3, 1.7)	<0.001
SGIx ^b	0.3 (0.2, 0.6)	<0.001
HDIx ^b	1.0 (–0.6, 2.4)	0.05

SGIx Social Gap Index, HDIx Human Development Index

limited access to public transportation as well as exercise facilities and result in individuals being less responsible and less conscious about their own health. The association implies a considerable impact of disease in the health community environment.

In this study, the contextual variable SGIX was significantly associated with the variability of OA prevalence in the community. SGIX is an aggregation of variables extracted from the CONEVAL, a decentralized public database that produces information about social policies, including the measurement of poverty. The association between SGIX and the prevalence of OA in the community was not homogeneous. There was a significant variation in the prevalence of OA after adjusting by individual variables. The prevalence of OA was higher in communities with lower SGIX. This finding of the effect of the variable social underdevelopment in the presence of OA leads us to hypothesize that the effect of social underdevelopment is less in places where social underdevelopment is very high. Reasons include high social underdevelopment, less education, less access to health services, and poor housing. People living in such conditions seem to be more aware of health problems, including MSK diseases and therefore seek medical care early. Alternatively, it is possible that social poverty, among other factors would mask health problems, including OA, as consequence of limitations in education, access to health care, and proper housing. This interpretation is consistent with the fact that in our study, the level of education and household income in patients with OA were much lower than in the control group.

In contrast to our findings, some studies have shown that the prevalence of chronic pain was higher in individuals that live in urban areas characterized by poor education, social networks, and income [16, 20], but high SGIX [15]. On the other hand, a multilevel model study developed in Australia showed a higher prevalence of arthritis in communities with a high SGIX [16]. Explanations for this include the case definitions based on self-reports, the fact that these studies were conducted in developed countries where socioeconomic inequalities are not as marked as those in developing countries, and the use of different social indicators in each study.

Our study has some limitations. The cross-sectional measurement of the data does not allow for the identification of causal inferences that in some cases may be bidirectional. The sample size was different for each state and some of the estimates might vary. The statistical technique used in the study might have some limitations on the model's ability to assign contextual effects to individuals (ecological fallacy) [38]. Additionally, residual confounding may be a problem due to the omission of individual variables related to the characteristics of the group under study and to the prevalence of OA [39]. Nevertheless, we think that such shortcomings did not affect the analysis performed in this study.

Conclusion

The SGIX was positively associated with OA regional prevalence. Female gender, pain intensity, physical limitation, and the use of pain treatments were individual variables associated with OA. These factors were independently associated with the prevalence of OA. The association of SGIX with variations in the prevalence of OA in this study suggests that health inequity in populations with greater social underdevelopment have a higher prevalence of OA and therefore secondary disability. This situation is associated with limited access to healthcare, low educational level, and social disadvantage. It is therefore advisable to design and implement interventional programs aimed primarily at individuals with scarce resources and management tools to improve the health of rheumatic patients in the population.

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Contributors RA-J and PB-I were involved in the conception and design of the study, acquisition of data and/or analysis and interpretation of data; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published. MM-J, AN-J,GR-MV,SL-H, BV-R,GE-M,MM, CM-H were involved in the conception of the study; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published. MMJ, PB-I performed the biostatistical analysis.

Conflict of interest Dr. Burgos-Vargas has received grant/research support from Abbvie; has been a consultant for Abbvie, Bristol Myers Squibb, Janssen, Pfizer, Roche, UCB; and participated as a speaker for Abbvie, BMS, Janssen, MSD, Pfizer, Roche, UCB. Dr. Cardiel has received honoraria for consultations and/or speaking for Pfizer, Lilly, Bristol Myers Squibb, and GSK. Dr. Garza-Elizondo has been a consultant and/or speaker for MSD, Pfizer, Bristol Myers Squibb, and UCB.

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