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INEQUITY AND VULNERABILITY IN LATIN AMERICAN INDIGENOUS AND NON-INDIGENOUS POPULATIONS WITH RHEUMATIC DISEASES :A SYNDEMIC APPROACH

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Complete List of Authors:	Granados, Ysabel; Hospital "Dr. Manuel Núñez Tovar," Gastelum Strozzi, Alfonso; Universidad Nacional Autonoma de Mexico, ICAT Alvarez-Nemegyei, Jose; Hospital Star Medica Merida Quintana, Rosana; Hospital Provincial de Rosario, Reumatology Julian-Santiago, Flor; Universidad Nacional Autonoma de Mexico Santos, Ana; Universidad de La Sabana, Rheumatology Guevara-Pacheco, Sergio; Universidad de Cuenca Loyola-Sanchez, Adalberto; University of Alberta Faculty of Medicine & Dentistry Goycochea-Robles, Maria Victoria; Universidad Nacional Autonoma de Mexico, Grupo Cochrane Juarez, Vicente; Hospital Señor del Milagro Garza-Elizondo, Mario Alberto; Hospital Universitario "Dr. José Eleuterio González" de la Universidad Autónoma de Nuevo León, Internal Medicine, Rheumatology Service Rueda, Juan; Universidad de La Sabana, Department of Rheumatology Burgos-Vargas, Ruben; Hospital General de Mexico Dr Eduardo Liceaga, Rheumatology Londoño, John; Universidad de La Sabana, Rheumatology; Hospital Militar Central, Rheumatology Pons-Estel, Bernardo; Centro Regional de Enfermedades Autoinmune y Reumáticas (CREAR) Pelaez-Ballestas, Ingris; Hospital General de México Dr Eduardo Liceaga, Rheumatology
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INEQUITY AND VULNERABILITY IN LATIN AMERICAN INDIGENOUS AND NON-INDIGENOUS POPULATIONS WITH RHEUMATIC DISEASES

A SYNDEMIC APPROACH

1. Ysabel Granados, MD.

ORCID: 000-0002-7148-4060

e-mail: ymgranados@gmail.com

2. Alfonso Gastelum-Strozzi, PhD,

ORCID: 0000-0001-9668-5822

e-mail: alfonso.gastelum@icat.unam.mx

3. José Alvarez-Nemegyei, MD, PhD.

ORCID: 0000-0002-5499-5280

e-mail: nemegyei@yahoo.com.mx

4. Rosana Quintana, MD, PhD.

ORCID: 0000-0003-0643-2755

e-mail: rosanaquintana@gmail.com

5. Flor Julian-Santiago , MD, PhD

ORCID: 0000-0001-6137-045X

e-mail: maifjs@hotmail.com

6. Ana María Santos, PhD

ORCID: ORCID 0000-0002-1973-8043

e-mail: ana.santos@unisabana.edu.co

7. Sergio Guevara, MD, PhD.

ORCID: 0000-0001-5798-6200

e-mail: sergio_guevarap@yahoo.com

8.Adalberto Loyola-Sanchez A, MD, PhD.

ORCID: 0000-0002-0082-2907

e-mail: adalbert@ualberta.ca

9. María Victoria Goycochea-Robles, MD, MSc.

ORCID: 0000-002-92488511

e-mail: mavis.goycochea@gmail.com

10. Vicente Juárez, MD.

ORCID: 0000-0003-3865-087X

e-mail: vtejuarez@gmail.com

11. Mario Garza-Elizondo, MD, PhD

ORCID: 0000-0002-8992-4714

e-mail: mariogarz@hotmail.com

12. Juan Rueda, MD, PhD candidate.

ORCID: 0000-0002-6263-2914

e-mail: juan.rueda@unisabana.edu.co

13. Ruben Burgos-Vargas, MD.

ORCID: 0000-0005-1058-8955

e-mail: burgosv@gmail.com

14. John Londoño, MD, PhD.

ORCID: 0000-0003-1074-644X

e-mail: john.londono@unisabana.edu.co

15. Bernardo A. Pons-Estel, MD.

ORCID: 0000-0003-2518-0266

e-mail: bponsestel@gmail.com

16. Ingris Peláez-Ballestas, MD, PhD[1]

ORCID: 0000-0001-5188-7375

e-mail: pelaezin@gmail.com.

Pons-Estel B.A and Peláez-Ballestas I. on behalf of the Latin American Study Group of Rheumatic Diseases in Indigenous Peoples (GLADERPO).

Affiliations:

1. Hospital "Dr. Manuel Núñez Tovar," Maturín, Monagas, Venezuela.

2. Instituto de Ciencias Aplicadas y Tecnología, Universidad Nacional Autónoma de México, Mexico City, Mexico.

3. Rheumatology Staff. Hospital Star Médica. Mérida, Yucatán, México

4. Centro Regional de Enfermedades Autoinmunes y Reumáticas (CREAR). Rosario, Santa Fe, Argentina.

5. Independent researcher.

6. Grupo Espondiloartropatias .Universidad La Sabana, Bogotá, Colombia.

7. Universidad de Cuenca, Cuenca, Ecuador.

8. Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada.

9. Grupo Cochrane-UNAM- Hospital ABC Santa Fe, Ciudad de Mexico

10. Hospital Señor del Milagro, Salta, Argentina.

11. Hospital Universitario "José Eleuterio Gonzalez," Monterrey, Nuevo León, Mexico.

12. Grupo Espondiloartropatias.Universidad La Sabana, Bogotá, Colombia.

13. Rheumatology Unit, Hospital General de México "Dr. Eduardo Liceaga," Mexico City, Mexico.

14. Grupo Espondiloartropatias. Universidad La Sabana, Bogotá, Colombia.

15. Centro Regional de Enfermedades Autoinmunes y Reumáticas (CREAR). Rosario, Santa Fe, Argentina.

16. Rheumatology Unit, Hospital General de México "Dr. Eduardo Liceaga," Mexico City, Mexico.

Corresponding author

Pelaez-Ballestas I., Ph.D. Rheumatology Unit, Hospital General de México "Dr. Eduardo Liceaga." Dr. Balmis 148, Colonia Doctores, 06726, Mexico City. E-mail: pelaezin@gmail.com. Phone: +52 (55) 5004-3849.

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Abstract.

Syndemics is a framework that documents health inequities and vulnerabilities in populations with rheumatic diseases. Compared to other approaches, syndemics is able to conjunctly consider epidemiological, biological, sociodemographic and economic factors, and their interactions.

Objective. To estimate health inequity and vulnerability among indigenous and non-indigenous populations with rheumatic and musculoskeletal disease (RMD) in Latin America using the syndemic approach.

Methods. This is a secondary analysis of a previously published large-scale study on the prevalence of RMD carried out in five Latin American countries. Health inequity and vulnerability in RMD were identified through a syndemic approach using network and cluster analysis.

Results. A total of 44,560 individuals were studied: 29.78% self-identified as indigenous, 60.92% were female, the mean age was 43.25 years. Twenty clusters were identified in the indigenous population and seventeen in the non-indigenous population.

The variables associated with RMD among indigenous populations were rurality, public health system, high joint biomechanical stress, greater pain, disability and alcoholism; and among non-indigenous people they were being a woman, urban origin, older age, private health system, joint biomechanical stress, greater pain and disability. We identified different health inequities among RMD patients (i.e. lower educational attainment, more comorbidities), associated with factors such as indigenous self-identification and rural residence.

Conclusion. A syndemic approach enables us to identify health inequities in RMD, as shown by higher prevalence of comorbidities, disability and socioeconomic factors like lower educational attainment. These inequities exist for the overall population of patients with RMD, though it is more evident in indigenous groups with added layers of vulnerability.

- **What is already known on this topic**
  Syndemics are a framework that has demonstrated deleterious effects on health when different diseases occur, in contexts of social deprivation and limited health systems. This has been demonstrated mostly in conditions such as HIV-AIDS, Diabetes and in RMDs in indigenous populations.

- **What this study adds**
  This study adds evidence of the variability of health determinants associated with having a rheumatic disease in countries with high health inequity and ethnic diversity. Using the syndemic approach and strategies from artificial intelligence (i.e., network and cluster analysis) is necessary to perform complex analyses that document health inequities comprehensively.

- **How this study might affect research, practice or policy**
  Through the identification of specific clusters with these methods, we are able to define target populations according to common characteristics, including shared comorbidities and social determinants of health. In this way, we can design interventions and policy that move us towards true health equity, addressing the specific needs of each group instead of population-level interventions that will serve some but not all, or inefficient personalized approaches.

Introduction

Rheumatic and musculoskeletal diseases (RMD) are a significant cause of morbidity and mortality worldwide [1]; they produce substantial socioeconomic impact and deterioration of quality of life in patients, who represent approximately 10% of the general population [2].

Since 2000, the World Health Organization (WHO) has recognized RMD as a relevant health problem, due to the increase in secondary disability and a greater demand for health resources [3].

There is now a greater need to define global strategies for the timely access of patients with RMD to health systems [4], including the evaluation of social determinants, such as gender, education, work, income level, ethnic group and place of residence [5].

Latin America is an extensive geographic area made up of 26 countries, characterized by multiculturalism and great contrasts in political, social and economic aspects [6]. Significant social inequity has been documented, with marked inequality in health coverage for individuals and social groups; these inequities are observed within and among countries in the region [7]. Epidemiological studies have documented a prevalence of RMD between 23% and 46.5% in Latin America, with more aggressive presentations, higher morbidity and mortality among indigenous populations. Genetic predisposition to systemic lupus erythematosus (SLE) has also been identified among indigenous groups [8], as well as a high prevalence of rheumatoid arthritis (RA) among indigenous Mayan groups of Yucatan, Mexico [9] and the Qom of Argentina [10].

Despite the high prevalence of RMDs in the Latin American region, these diseases continue to have a low priority in the planning of health policies [11]. Overall, the healthcare system in Latin America is highly fragmented and disconnected. For rheumatology care specifically, 33.5% of rheumatologists work in public/government hospitals, 28.8% in private practice, 20.8% in private hospitals, and 15.5% in university hospitals, most of them distributed in large urban areas, with a significant lack in small cities and none in rural areas [8].

These differences in disease prevalence and distribution of health resources which limit access to rheumatology care in Latin America can be understood as health inequities. Health inequity is not synonymous with inequality. Inequity implies the idea of injustice and of lack of actions to avoid *preventable* differences. On the other hand, inequality describes differences in health outcomes that are not fundamentally unfair [11]. Health inequity is deeply connected to vulnerability. From a biomedical perspective, vulnerability means being susceptible to certain diseases or to environmental risk. However, vulnerability can also be understood as a product of the interaction between available resources (personal, family, community, cultural, economic, institutional), the sociocultural context of the patient, structural elements, and exposure to risks [12]. Therefore, vulnerability is a result of health inequity.

To document inequity in health, the syndemic model has proven useful to analyze the interaction of disease with social determinants that condition inequality in health, and how these lead to increased physical and environmental vulnerability [8,13,14]. Syndemics aggregate interaction of two or more concurrent diseases, as well as the sociocultural and healthcare contexts which can exacerbate the negative effects of this interaction on the health of individuals, communities, and societies [14,15]. The syndemic framework evaluates the interaction of any type of disease in conditions of health inequality caused by poverty, stigmatization, stress or structural violence [14,16]. Thus, syndemics encompasses social determinants, vulnerabilities, and inequities and inequalities in health as well.

Previous studies have shown that syndemics is a good comprehensive model to document inequity and inequality in health. In a study of RMD in indigenous populations in Latin America, as well as a study of patients with low back pain, disease is associated with being a woman, belonging to an indigenous population, and having low educational attainment. It

is also exacerbated by the presence of comorbidities, especially those within the mental health domain [17,18].

Given the intricacy of a syndemic approach, conventional statistical methodologies are insufficient. Instead, using strategies from artificial intelligence (i.e., network and cluster analysis) is necessary to perform complex analyses that document health inequities comprehensively. The syndemic approach is useful to identify health inequities and vulnerabilities in different population groups.

We hypothesize that the is a syndemic in Latin American populations suffering from rheumatic diseases, associated with comorbidities such as diabetes and hypertension, and living in a fragmented health care context. We also hypothesize that this phenomenon is is more significant in vulnerable populations such as indigenous peoples. Therefore, we proposed the following study to measure syndemics comparatively between indigenous and non-indigenous populations with RMD in Latin America.

MATERIALS AND METHODS

Design

This is a secondary analysis, based on multilevel network analysis using a syndemic framework, of a previously published large-scale cross-sectional study on the prevalence of RMD in five Latin American countries.

Data sources

We used a database compiled by GEEMA (Grupo de Estudios Epidemiológicos de Enfermedades Músculo Articulares), COPCORD-LATAM (Community Oriented Program

for Control of Rheumatic Diseases-Latin America) and GLADERPO (Grupo Latino Americano de Estudios de Enfermedades Reumáticas en Pueblos Originarios).

GLADERPO recorded information on the Qom and Wichí indigenous populations of Argentina [10,19], Saraguro of Ecuador [20], Yucatec-Maya and Mixtec of Mexico [21] and the Chaimas, Kariñas and Warao of Venezuela [22].

COPCORD-LATAM was developed with the results of epidemiological studies conducted on the non-indigenous populations of Colombia [23], Ecuador [24], Mexico [25] and Venezuela [26], using COPCORD (Community Oriented Program for Control of Rheumatic Diseases) methodology, culturally and linguistically adapted to the different communities studied, and subsequently validated in each country.

The COPCORD methodology consists of trained health personnel administering a questionnaire house to house, which identifies patients with pain of non-traumatic origin, historical and in the last seven days. The participation of certified rheumatologists allowed for the diagnosis of RMDs [24–27].

The same measurements were collected in all the studies: sociodemographic variables, joint biomechanical stress, comorbidities, physical disability and accessibility to local health care.

Sociodemographic variables such as age, gender, self-defined ethnicity according to the laws of each country (indigenous and non-indigenous), formal schooling (numbers of years studied in the official education system) and place of residence (urban/rural).

Level of Joint biomechanical stress was classified according to self-reported occupation. Individuals were asked for a visual recreation of their activity, according to the degree of effort and the body regions involved. Following a survey on the level of physical load repetitiveness, each occupation was classified into three levels of joint biomechanical stress

in the workplace: high (e.g. farmers, homemakers, machine operators), medium (e.g. artisans, drivers, technicians) and low (e.g. merchants, professionals, students, teachers, retirees).

Comorbidities were self-reported [28,29], while physical disability was measured with the **Health Assessment Questionnaire-Disability Index** (HAQ-DI), validated for each country and with an established cut-off point of greater than 0.8 [30].

Accessibility to the local healthcare system was classified by conducting an exercise of comparisons and equivalences among the researchers from the five participating countries. Considering all characteristics of the healthcare systems, the three subgroups used to classify accessibility were: partial coverage, involving a public system that covers physician appointments, laboratory tests and basic but not high specialty medications; full coverage, involving a social security system that covers all health expenses; and private coverage, where patients pay fully for their care.

Analysis

A multi-phase analysis was performed.

First, we applied descriptive statistics of sociodemographic characteristics (age, gender, formal schooling, urban/rural residence), rheumatic diagnoses, comorbidities, disability (HAQ-DI) and levels of accessibility (partial, full and private coverage). Reported with totals and percentage of the population by indigenous/non-indigenous classification and by country of origin.

Subsequently, we performed a simple logistic regression using RMD diagnosis as a dependent variable and those described above as independent variables, reported in odds ratio (OR), confidence interval 95% (CI95%) and significance (p).

Two separate logistic regression were implemented, one for the indigenous population and another for the non-indigenous one. For both regressions the dependent variable was having a rheumatic disease. The logistic regression was perform using the logit function from statsmodels 0.14.0 [31]. The selection of the independent variables was done in a recursive way, variables were eliminated from the model when: A singular matrix was obtained, and a test for collinearity was performed to find columns with single values or low variance that could explain the singularity. Logit does not achieve convergence. Then the resulting model was evaluated to find variables with large confidence interval and P values that show non significance. Finally, the Pseudo R-Squared value of the model was evaluated, there is discussion into what is a good fit according to this value, a model was accepted when the value was equal or greater than .3 as a good fit according to McFadden [32,33]

Finally, we used the network analysis technique [34] to evaluate the relations between individuals according to the impact of their work, the place of living and the access to care, using the following variables: accessibility level, level of joint biomechanical stress and urban/rural residence. The relation between individuals was obtained using a similarity measurement calculated using the cosine similarity method [35] and a categorical vector defined by the mentioned variables. The vector and the cosine similarity method were used to calculate the similarity index of each individual with respect to the rest of the population. The index was weighted by the difference of age between everyone to account for the possible relation between age and the level of joint biomechanical stress, the more similar the ages the greater the final weighted index. Finally, to introduce a measurement related to economical level another weight was calculated using the difference of year of education between individuals, For the network representation each individual is a node and a

connection edges is generated when the index of similarity between two individuals is greater than the average of the similarity indices plus standard deviation [36]. The nodes and edges tables are simulated in Gephi [37] in order to obtain a network where each node(individual) location depends on the relationships with the other nodes through the connecting edges, the final nodes position are used to defined cluster of similar nodes using the DBSCAN method [38] to define each cluster.

Due to the complexity of representation of the clusters, a procedure was conducted to select the most relevant ones, according to group consensus on the three most important variables per the study objectives. The variables included in the model, in hierarchical order of importance, are: prevalence of RMD, prevalence of rheumatoid arthritis (RA) specifically, and number of individuals comprising the cluster. Every cluster was assigned a weighted score for each of the three selected variables by all the researchers. Finally, the six clusters included per group (indigenous and non-indigenous) were those with the highest total sum by consensus.

In order to confirm there were no biases, a sub-analysis was performed based on a weighted sample, randomly selected from indigenous/non-indigenous populations from the three countries that studied both at the same time and in the same region (Ecuador, Mexico and Venezuela); two countries only had samples of indigenous (Argentina) or non-indigenous (Colombia) populations.

The clusters obtained through this analysis are defined by factors such as living in a rural setting, lower health coverage and greater disability, which go beyond our initial indigenous/non-indigenous classification, and which impact the management of rheumatic

diseases. These emerging differences can be used to document inequity insofar as they highlight the variables which negatively impact the health of people with RMD.

Patient and Public Involvement

Patients and members of the public were involved at original stages of each study including as cultural liaisons. We disseminated the main results to all participants and health authorities to improve health conditions.

RESULTS

A total of 44,560 individuals from five Latin American countries (Argentina, Colombia, Ecuador, Mexico and Venezuela) were studied. Of these, 29.78% (13,269) self-identified as indigenous and 27,145 (60.92%) were female, with the average age of 43.25 (SD = 18.02) years and a mean of 8.06 (SD = 5.02) years of schooling. RMD was diagnosed in 13,528 (30.36%) individuals. Rheumatic regional pain syndromes (RRPS) was the rheumatic diagnosis with the highest prevalence (6100, 13.69%) followed by osteoarthritis (3690, 8.28%), while RA was reported in (877,1.97%) individuals (Table 1).

Table 1. Comparison of sociodemographic characteristics, country, health coverage, rheumatic diagnosis, pain, disability and comorbidities between indigenous and non-indigenous groups.

	Indigenous n = 13269 (29.78)	**Non-indigenous n = 31291 (70.22)**	**Total n = 44560 (100.00)**	**p**
Gender (female)	8010 (60.37)	19135 (61.15)	27145 (60.92)	0.123
Age (years), mean (SD)	42.23 (18.17)	43.69 (17.94)	43.25 (18.02)	<0.001
Urban setting	3877 (29.22)	24331 (77.76)	28208 (63.30)	<0.001
Educational level, mean number of years (SD)	7.13 (5.07)	8.46 (4.95)	8.06 (5.02)	<0.001
Countries				
Argentina	2295 (17.30)	0 (0.00)	2295 (5.15)	<0.001
Colombia	234 (1.76)	6454 (20.63)	6688 (15.01)	<0.001
Ecuador	2682 (20.21)	4858 (15.53)	7540 (16.92)	<0.001

Mexico	6525 (49.17)	16085 (51.40)	22610 (50.74)	<0.001
Venezuela	1533 (11.55)	3894 (12.44)	5427 (12.18)	<0.01
Health coverage *				
Full	3481 (26.23)	4493 (14.36)	7974 (17.89)	<0.001
Partial	7441 (56.08)	18314 (58.53)	25755 (57.80)	<0.001
Private	795 (5.99)	1741 (5.56)	2536 (5.69)	0.079
Other**	330 (2.49)	221 (0.71)	551 (1.24)	<0.001
Joint biomechanical stress ***				
High	5000 (37.68)	10199 (32.59)	15199 (34.11)	<0.001
Medium	1538 (11.59)	4720 (15.08)	6258 (14.04)	<0.001
Low	4014 (30.25)	9213 (29.44)	13227 (29.68)	0.090
Unspecified	1815 (13.68)	2784 (8.90)	4599 (10.32)	<0.001
Rheumatic disease				
Totals	4012 (30.24)	9516 (30.41)	13528 (30.36)	0.721
Osteoarthritis	1433 (10.80)	2257 (7.21)	3690 (8.28)	<0.001
Rheumatoid arthritis	278 (2.10)	599 (1.91)	877 (1.97)	0.223
Back pain	1548 (11.67)	1281 (4.09)	2829 (6.35)	<0.001
RRPS	505 (3.81)	5595 (17.88)	6100 (13.69)	<0.001
Musculoskeletal disorders	521 (3.93)	664 (2.12)	1185 (2.66)	<0.001
Fibromyalgia	181 (1.36)	212 (0.68)	393 (0.88)	<0.001
Other ****	45 (0.34)	118 (0.38)	163 (0.37)	0.602
Pain				
Historical pain	5408 (40.76)	11780 (37.65)	17188 (38.57)	<0.001
Non-traumatic pain (7 days)	2258 (17.02)	8024 (25.64)	10282 (23.07)	<0.001
Physical disability (Health Assessment Questionnaire-Disability Index (HAQ-DI)				
HAQ-DI ≥ 0.8	761 (5.74)	2558 (8.17)	3319 (7.45)	<0.001
Comorbidities				
Diabetes mellitus	814 (6.13)	2279 (7.28)	3093 (6.94)	<0.001
High blood pressure	1649 (12.43)	5613 (17.94)	7262 (16.30)	<0.001
Cardiovascular disease	415 (3.13)	1106 (3.53)	1521 (3.41)	0.033
Smoking	1138 (8.58)	4996 (15.97)	6134 (13.77)	<0.001
Alcoholism	1751 (13.20)	1068 (3.41)	2819 (6.33)	<0.001
Anxiety/depression	2304 (17.36)	3727 (11.91)	6031 (13.53)	<0.001
No comorbidities	6391 (48.16)	14450 (46.18)	20841 (46.77)	<0.001

* Missing data: 1222 (9.21%) indigenous and 6522 (20.84%) not indigenous, total 7744 (17.38%)

** Other: Traditional healthcare

*** Missing data: 902 (7.01%) indigenous and 4375 (13.80%) not indigenous.

**** Others: *Indigenous*: 29 ankylosing spondylitis, 9 gout, 4 scleroderma and 3 psoriasis. *Non-indigenous*: 39 ankylosing spondylitis, 74 gout, 1 scleroderma and 4 psoriasis.

A lower urban origin (18.71%) and less years of formal schooling (6.74, SD = 5.71) were observed in the indigenous population, while the non-indigenous population had a predominance of private coverage (10.89%). High joint biomechanical stress (47.01%) and historical pain (39.99%) were more frequent in indigenous populations. The prevalence of RMD was similar between populations studied; RA was more prevalent in indigenous people (2.26% vs 1.74%), but not significantly. Non-indigenous people had greater disability (8.15% with HAQ ≥0.8) and higher prevalence of diabetes mellitus, high blood pressure and smoking

(7.09%, 18.59% and 15.16%). Among indigenous people, alcohol consumption and anxiety/depression were more prevalent (13.98% and 19.55%) (see supplementary table).

In terms of the sub-analysis by country, Argentina had the youngest individuals (35.98, SD:=14.25); Ecuador and Colombia recorded a higher level of schooling (9.31, SD= 5.49) and a higher prevalence of RMD (47.69% and 40.76%); Argentina and Mexico had the highest prevalence of RA (3.01% and 2.22%); Colombia had a higher prevalence of historical and non-traumatic pain (73.95% and 43.94%); and Ecuador had the highest number of disabled people (8.70% with HAQ ≥0.8) (Table 2).

Table 2. Comparison of sociodemographic characteristics, health coverage, rheumatic diagnosis, pain, disability, and comorbidities between populations of five Latin American countries.

	Argentina n (%) n = 2295 (5.15)	**Colombia n (%) n = 6688 (15.01)**	**Ecuador n (%) n = 7540 (16.92)**	**Mexico n (%) n = 22610 (50.74)**	**Venezuela n (%) n = 5427 (12.18)**	**Totals* n (%) n = 44560 (100.00)**	**p**
Ethnicity (indigenous)	2295 (100.00)	234 (3.50)	2682 (35.57)	6525 (28.86)	1533 (28.25)	13269 (29.78)	<0.001
Gender (female)	1393 (60.70)	4280 (64.00)	4590 (60.88)	13634 (60.30)	3248 (59.85)	27145 (60.92)	<0.001
Age (years), mean (SD)	35.98 (14.25)	46.41 (18.35)	43.39 (18.60)	43.08 (17.93)	42.98 (17.63)	43.25 (18.02)	<0.001
Urban setting	0 (0.00)	6688 (100.00)	3384 (44.88)	14242 (62.99)	3894 (71.75)	28208 (63.30)	<0.001
Educational level, mean number of years (SD)	5.43 (3.60)	9.19 (4.00)	9.31 (5.49)	7.41 (4.98)	8.77 (5.27)	8.06 (5.02)	<0.001
Health coverage *							
Total	2295 (100.00)	6527 (97.60)	5453 (72.32)	17114 (75.70)	5427 (100.00)	36816 (82.62)	
Full	29 (1.26)	1920 (28.71)	3148 (41.75)	2877 (12.72)	0 (0.00)	7974 (17.89)	<0.001
Partial	2053 (89.46)	4465 (66.76)	405 (5.37)	13674 (60.48)	5158 (95.04)	25755 (57.80)	<0.001
Private	183 (7.97)	39 (0.58)	1482 (19.66)	563 (2.49)	269 (4.96)	2536 (5.69)	<0.001
Other**	30 (1.31)	103 (1.54)	418 (5.54)	0 (0.00)	0 (0.00)	551 (1.24)	<0.001
Joint biomechanical stress ***							
Totals	1698 (74.00)	6686 (99.97)	7440 (98.67)	20253 (89.58)	3206 (59.08)	39283 (88.16)	
High	420 (18.30)	3511 (52.50)	3382 (44.85)	6667 (29.49)	1219 (22.46)	15199 (34.11)	<0.001
Medium	159 (6.93)	1569 (23.46)	516 (6.84)	3438 (15.21)	576 (10.61)	6258 (14.04)	<0.001
Low	120 (5.23)	1604 (23.98)	3510 (46.55)	6684 (29.56)	1309 (24.12)	13227 (29.68)	<0.001
Unspecified	999 (43.53)	2 (0.03)	32 (0.42)	3464 (15.32)	102 (1.88)	4599 (10.32)	<0.001
Rheumatic disease							
Totals	705 (30.72)	2726 (40.76)	3596 (47.69)	5092 (22.52)	1409 (25.96)	13528 (30.36)	<0.001

Osteoarthritis	88 (3.83)	521 (7.79)	470 (6.23)	1797 (7.95)	814 (15.00)	3690 (8.28)	<0.001
Rheumatoid arthritis	69 (3.01)	84 (1.26)	120 (1.59)	501 (2.22)	103 (1.90)	877 (1.97)	<0.001
Back pain	460 (20.04)	237 (3.54)	474 (6.29)	1357 (6.00)	301 (5.55)	2829 (6.35)	<0.001
RRPS	41 (1.79)	2726 (40.76)	2671 (35.42)	461 (2.04)	201 (3.70)	6100 (13.69)	<0.001
Musculoskeletal disorders	50 (2.18)	0 (0.00)	62 (0.82)	1013 (4.48)	60 (1.11)	1185 (2.66)	<0.001
Fibromyalgia	3 (0.13)	27 (0.40)	214 (2.84)	126 (0.56)	23 (0.42)	393 (0.88)	<0.001
Other ****	2 (0.09)	26 (0.39)	32 (0.42)	80 (0.35)	23 (0.42)	163 (0.37)	0.179
Pain							
Historical pain	938 (40.87)	4946 (73.95)	3420 (45.36)	6141 (27.16)	1743 (32.12)	17188 (38.57)	<0.001
Non-traumatic pain (7 days)	402 (17.52)	2939 (43.94)	1525 (20.23)	4204 (18.59)	1212 (22.33)	10282 (23.07)	<0.001
Physical disability (Health Assessment Questionnaire-Disability Index (HAQ-DI)							
HAQ ≥ 0.8	95 (4.14)	400 (5.98)	656 (8.70)	1741 (7.70)	427 (7.87)	3319 (7.45)	<0.001
Comorbidities							
Diabetes mellitus	125 (5.45)	428 (6.40)	382 (5.07)	1898 (8.39)	260 (4.79)	3093 (6.94)	<0.001
High blood pressure	379 (16.51)	1591 (23.79)	1046 (13.87)	3078 (13.61)	1168 (21.52)	7262 (16.30)	<0.001
Cardiovascular disease	144 (6.27)	435 (6.50)	250 (3.32)	471 (2.08)	221 (4.07)	1521 (3.41)	<0.001
Smoking	497 (21.66)	2409 (36.02)	1587 (21.05)	1080 (4.78)	561 (10.34)	6134 (13.77)	<0.001
Alcoholism	379 (16.51)	0 (0.00)	470 (6.23)	1523 (6.74)	447 (8.24)	2819 (6.33)	<0.001
Anxiety/depression	123 (5.36)	1463 (21.88)	1843 (24.44)	2185 (9.66)	417 (7.68)	6031 (13.53)	<0.001
No comorbidities	882 (38.43)	2483 (37.13)	2460 (32.63)	12471 (55.16)	2545 (46.90)	20841 (46.77)	<0.001

* Missing data: 7744 (17.38)

**Other: Traditional healthcare

*** Missing data: 5277 (11.84)

**** Others: Ankylosing spondylitis, gout, scleroderma, psoriasis.

A logistic regression analysis was performed by ethnicity. In the indigenous population, the variables significantly associated with RMD diagnosis were living in a rural setting, younger age, relying on the public health system for treatment, high levels of joint biomechanical stress, greater pain and greater disability. In turn, the variables associated with RMD diagnosis in the non-indigenous population were being a woman, living in an urban setting, older age, relying on the private sector for treatment, more frequent joint biomechanical stress regardless of the level, greater pain, greater disability and less association with having diabetes mellitus (Table 3).

Table 3. Logistic regression. Dependent variable: a rheumatic disease. Independent variables: gender, place of residence, age, schooling, health coverage, biomechanical stress, pain, functional capacity, and comorbidities.

	Indigenous		Non-indigenous	
	OR (95% CI two-sided)	p	OR (95% CI two-sided)	P
Intercept	0.02 (0.01 - 0.03)	< 0.01	0.10 (0.08 - 0.12)	< 0.01
Gender (female)	1.10 (0.96 - 1.25)	0.164	1.19 (1.11 - 1.27)	< 0.01
Age (years)	0.49 (0.41 - 0.59)	< 0.01	1.49 (1.37 - 1.62)	< 0.01
Urban setting	1.02 (1.02 - 1.02)	< 0.01	1.00 (1.00 - 1.01)	< 0.01
Educational level	0.99 (0.97 - 1.00)	0.051	1.01 (1.00 - 1.01)	0.081
Health coverage				
Full	1.46 (1.11 - 1.91)	< 0.01	0.82 (0.74 - 0.91)	< 0.01
Partial	1.15 (0.88 - 1.50)	0.322	0.59 (0.55 - 0.64)	< 0.01
Private	1.55 (1.10 - 2.19)	0.013	1.43 (1.25 - 1.64)	< 0.01
Other	1.36 (0.87 - 2.13)	0.172	0.98 (0.70 - 1.36)	0.900
Level of joint biomechanical stress				
High	1.18 (1.00 - 1.40)	0.054	1.55 (1.41 - 1.69)	< 0.01
Medium	1.22 (0.96 - 1.56)	0.110	1.31 (1.17 - 1.46)	< 0.01
Low	1.17 (0.97 - 1.42)	0.101	1.52 (1.38 - 1.66)	< 0.01
Pain				
Historical pain	27.77 (24.09 - 32.01)	< 0.01	3.84 (3.59 - 4.11)	< 0.01

Non-traumatic pain (7 days)	2.51 (2.18 - 2.89)	< 0.01	2.26 (2.11 - 2.43)	< 0.01
Physical disability (Health Assessment Questionnaire-Disability Index (HAQ-DI)				
HAQ ≥ 0.8	1.25 (1.00 - 1.56)	0.045	1.37 (1.23 - 1.52)	< 0.01
Comorbidities				
Diabetes mellitus	0.95 (0.75 - 1.20)	0.653	0.82 (0.73 - 0.93)	< 0.01
High blood pressure	0.98 (0.82 - 1.18)	0.842	0.95 (0.87 - 1.03)	0.226
Cardiovascular disease	0.83 (0.62 - 1.12)	0.219	1.06 (0.91 - 1.24)	0.433
Smoking	0.93 (0.74 - 1.16)	0.504	1.06 (0.97 - 1.16)	0.217
Alcoholism	0.78 (0.64 - 0.94)	< 0.01	1.15 (0.97 - 1.37)	0.107
Anxiety/depression	0.99 (0.84 - 1.17)	0.926	1.05 (0.96 - 1.16)	0.266
No comorbidities	0.87 (0.74 - 1.03)	0.111	0.73 (0.67 - 0.80)	< 0.01

Twenty clusters were identified in the indigenous population and seventeen in the non-indigenous population. In order to best represent the results, six clusters were selected for each group, using consensus and weighing as described in the methodology.

The six clusters selected from the indigenous population were: Cluster 1 was represented by individuals with partial coverage, younger, with lower educational attainment, higher prevalence of RA and low back pain, and higher pain and smoking. Cluster 11 included individuals with full coverage, greater functional limitation, and higher prevalence of RA and anxiety/depression. Cluster 13 was represented by individuals with less schooling and a high percentage of smoking and alcoholism. Cluster 14 was represented by individuals with full coverage, high prevalence of RMD, and higher percentage of anxiety/depression and pain. Cluster 15 was the largest, with partial coverage, high level of joint biomechanical stress, and higher prevalence of RMD and associated pain. Lastly, Cluster 16 was the smallest and included individuals with private coverage, high level of joint biomechanical stress, older

age, anxiety/depression and alcoholism, and the highest prevalence of RMD and associated pain out of all the clusters (Figure 1).

In the non-indigenous population, the six selected clusters were: Cluster 4 was the largest, represented by individuals with partial coverage, high level of joint biomechanical stress, higher percentage of pain, and higher prevalence of RMD, high blood pressure and anxiety/depression. Cluster 7 was the smallest, with a low percentage of pain and RMD, but greater physical disability. Cluster 8 included individuals with less years of formal schooling, partial health coverage, higher prevalence of RMD and anxiety/depression, medium level of joint biomechanical stress, and high physical disability.

Cluster 9 included individuals with higher educational attainment, full coverage, higher prevalence of RRPS, greater pain, greater level of smoking and less disability. Cluster 10 was represented by individuals with partial coverage, and lower prevalence of RMD and associated pain, but with greater limitation. Cluster 17 included only Mexican individuals with partial coverage, high level of joint biomechanical stress, lower educational attainment, and higher prevalence of RA, diabetes mellitus and high blood pressure (Figure 2).

DISCUSSION

The syndemic approach analyzes the synergistic interrelationship between different biological and non-biological factors that lead to disease. The application of this approach to the area of health is relatively recent. Multiple studies describe how epidemiological and socioeconomic factors are related to disability and inequity in patients with RMD [39]. However, there are few publications that evaluate inflammatory joint diseases and other chronic musculoskeletal conditions from a broader social and biocultural context, taking into

consideration how the socioeconomic characteristics of the environment interact with the disease.

In the present study, a syndemic approach was used to identify factors associated with health inequity [18,40]. The results obtained through a complex analysis of networks showed a greater clustering of patients with rheumatic diseases who shared common social determinants, such as rural setting and lower schooling. This coincides with the results published by Norton et al, who have described that the greater the comorbidities, the greater the risk of a negative impact on the evolution of RMD [41] and, consequently, the greater the difficulty to adequately control the disease [42].

Commented [AMdLyR1]: Asociación de qué?

This study identified factors associated with inequity in individuals with RMD in five Latin American countries with a syndemic approach. The clusters obtained through our analysis show differential negative impacts in the groups that were formed. The relevant emerging factors are living in rural communities, having lower educational attainment, and depending on the public healthcare system, described as fragmented in all participating countries. Comorbidities such as smoking, alcoholism and those related to mental health (anxiety/depression) are most prevalent overall, and greater in the indigenous population. The differences detected through the clusters can be considered health inequities, since they constitute avoidable differences such as low schooling and a health care system without full coverage. Furthermore, the clusters that have greater impact are those which include indigenous people. All of the above attests to the inequity in RMD in low- and middle-income countries in general, and even more so in historically vulnerable populations, such as indigenous groups.

Multiple reports describe disparity and inequity among patients with RMD. Though they contemplate the interaction of disease with epidemiological, biological and socioeconomic factors, most of the research of this phenomenon does not include a conjunct and comprehensive analysis of all factors as is achieved by syndemics [43,44].

Another important finding of the study is the clusters with higher prevalence of comorbidities, particularly high blood pressure, tobacco, and alcohol consumption, and those related to mental health (anxiety/depression). As previously reported, the greater the comorbidity, the greater the risk of negative impact on the evolution of RMD [45]. The coexistence of two or more conditions prevents the proper control of disease activity, hindering the achievement of therapeutic goals like those proposed by the treat to target recommendations [46].

The coexistence of several chronic conditions involving systemic inflammatory processes and deterioration in functional capacities, leads to a greater impact on the quality of life and greater demand of health services, to which many populations in Latin America have no universal access. Indeed, the results of this analysis identified several clusters with partial or no access to medical care coinciding with greater comorbidity (cluster 1, 10,11). The association between RMD severity and comorbidities as biological interactions is clear, but it is important to correlate these at a social level, since not having access to timely diagnoses or specialized care increases the possibility of greater comorbidity and complications. Additionally, it is important to address the interaction of certain prevalent comorbidities—smoking, alcoholism, and mental health struggles—which contribute to the syndemic as both social and biological factors. While there is sufficient evidence to suggest the possibility of common pathophysiological mechanisms with inflammatory joint diseases, it has also been

shown that states of anxiety and depression can be triggered by non-biological factors such as social isolation, poverty, mental health worldview or cultural stigmatization, and/or lack of access to healthcare [39].

When comparing inequity between population groups, the poverty rate in indigenous and rural communities is higher, as reported in this study: 29.78% of the population self-identified as indigenous, with a higher level of individuals from rural areas and fewer years of schooling. The prevalence of RA specifically was more pronounced in the indigenous population, with the highest rates in Argentina and Mexico (3.01% and 2.22%) (17, 20). Previous research has similarly found that RMD are more frequent in the indigenous populations than in the non-indigenous populations of Canada, Australia, New Zealand and the United States [10].

The indigenous population had a lower prevalence of disability despite presenting greater high level of joint biomechanical stress, historical pain and RA, which may be related to a worldview favoring normalization or underestimation of symptoms. In addition, the interpretation of these symptoms may be one of the causes of delay in seeking specialized care [41]. The relationship between ethnicity and health outcomes seems to be influenced by acculturation; that is, when one ethnic group is forced to adopt the beliefs and practices of another, the members develop negative health behaviors as coping mechanisms [47].

Health systems in Latin America are diverse and complex. Individuals in this study are distributed among the spectrum of public (partial or full) and private systems. Most indigenous communities have public health coverage, though this does not guarantee access or continuity of care and treatment. Limited access is not merely due to economic barriers, but also related to ethnic, cultural and geographical factors, among others [17,18,42,43].

Indigenous communities are among the most vulnerable groups and, due to the conditions described above, their inclusion into the healthcare system is complex [41,42,48].

The inaccessibility of the healthcare system, socioeconomic conditions, presence of comorbidities involving mental health, and RMD disease activity, are all factors that exist in interacting layers to create specific conditions of vulnerability for different patient populations. A model of vulnerability in layers, called a palimpsest design [12], analyzes how the determinants of health at different levels—genetic, biological, psychological, social and political—interact over time, creating barriers that lead to health inequity. The syndemic approach, in taking into consideration all factors and their interactions conjunctly, corresponds with a palimpsest model, providing evidence for the vulnerability of RMD patients associated with social factors such as rurality, low educational attainment, and greater reliance on the public health system (Figure 3).

Limitations

The cross-sectional nature of this study is a limitation to establish causality. However, the analysis of clusters and networks groups individuals by variables to document inequity—the principal objective of this study.

Another limitation is the documentation of comorbidities by self-reporting, which can condition a measurement error. However, in most studies an attempt was made to verify the comorbidities through the medications/prescriptions individuals showed researchers.

In conclusion, the complex analysis from a syndemic approach allowed us to identify the greatest inequity in the clusters that group younger individuals, residents of rural areas, those who self-identify as indigenous, have lower educational attainment, higher prevalence of

RMD and RA specifically, greater comorbidities especially related to mental health and high blood pressure, and partial coverage in the public healthcare system. Given the above we can assume that these social vulnerabilities and comorbidities lead to health inequities for populations living in countries in which RMD are not considered a priority, resulting in lack of coverage for prevention, diagnosis and management.

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Ethics approval

As the present investigation involves data collected as a part of prior studies, no specific study protocol approval was needed, as all Institutional and Ethics Committees of each participating institution (Argentina:1619/2010 and 0127/2011; Ecuador: 2016-129IN, and Mexico: DI/11/4044B/3/123) had already approved pertinent studies and authorities from participating indigenous communities [18].

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Figure Legend

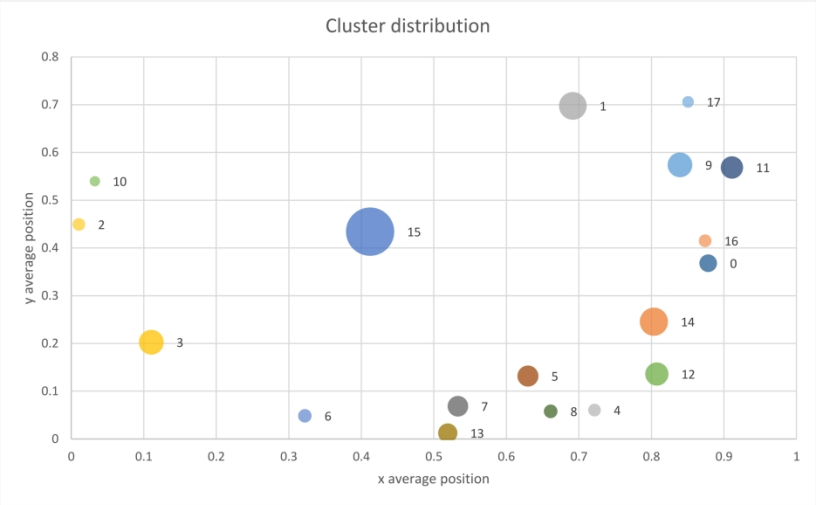
Figure 1. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the indigenous population. (Title)

Figure 2. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the non-indigenous population. (Title).

Figure 3. Inequities and vulnerabilities in RMDs: a palimpsest model (Title)

A model of vulnerability in lavers analyzes how the determinants of health at different levels -genetic, biological, psychological, social and political- interact over time, creating barriers that lead to health inequity. (Figure caption)

Figure 1. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the indigenous population



Cluster	1	11	13	14	15	16
Total	1062	694	514	1097	3234	224
Health coverage	Partial	Full	Partial	Full	Partial	Private
Joint biomechanical stress	Unspecified	High	Medium	High	High	High
Gender	60.36	63.83	57.39	64.18	65.31	57.14
Age*	37.32 (15.00)	41.10 (21.68)	39.26 (15.52)	45.58 (18.60)	44.68 (17.61)	50.40 (17.39)
Formal schooling*	5.10 (3.56)	9.32 (5.52)	4.83 (4.39)	6.11 (4.55)	4.92 (3.74)	5.88 (4.63)
Argentina	82.86	0.00	28.40	0.00	11.87	8.04
Colombia	0.00	0.00	0.00	0.00	0.00	0.00
Ecuador	0.00	84.15	3.11	93.16	5.04	75.45
Mexico	7.72	15.85	19.07	6.84	60.36	16.52
Venezuela	9.42	0.00	49.42	0.00	22.73	0.00
Rheumatic disease (any)	31.83	32.28	29.57	41.66	40.45	47.32
Osteoarthritis	6.21	14.12	7.39	18.87	12.83	23.21
Rheumatoid arthritis	3.01	3.17	2.72	1.73	2.94	2.68
Backpain	19.02	10.66	14.98	18.60	15.34	15.18
RRPS	1.98	4.18	2.53	7.29	2.29	5.36
Musculoskeletal disorders	2.17	4.90	2.72	3.65	8.94	5.36
Fibromyalgia	0.09	3.46	0.58	4.92	1.67	5.80
Others	0.09	0.29	0.78	0.18	0.43	0.45
Historical pain	44.82	40.63	36.19	49.95	52.26	54.91
Non-traumatic pain (7 days)	20.72	7.49	17.32	10.12	27.40	13.84
Physical disability (HAQ-DI)	3.48	12.82	4.28	11.39	3.96	7.14
Diabetes mellitus	5.18	5.04	3.89	5.10	6.77	7.14
High blood pressure	15.35	10.23	7.78	12.94	13.42	17.41
Cardiovascular disease	5.74	1.30	2.72	3.01	3.34	4.02
Smoking	18.74	3.46	16.15	4.19	9.86	7.14
Alcoholism	14.69	10.95	19.84	14.77	23.13	23.66
Anxiety/depression	4.14	39.77	4.09	49.59	22.70	43.75
No comorbidities	42.09	34.44	53.89	27.53	35.44	23.21

RRPS: Rheumatic regional pain syndromes. Health Assessment Questionnaire-Disability Index (HAQ-DI) cut-off point of greater than 0.8.

* Age and formal schooling show mean value (standard deviation)

Figure 1. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the indigenous population

215x279mm (300 x 300 DPI)

Figure 2. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the non-indigenous population

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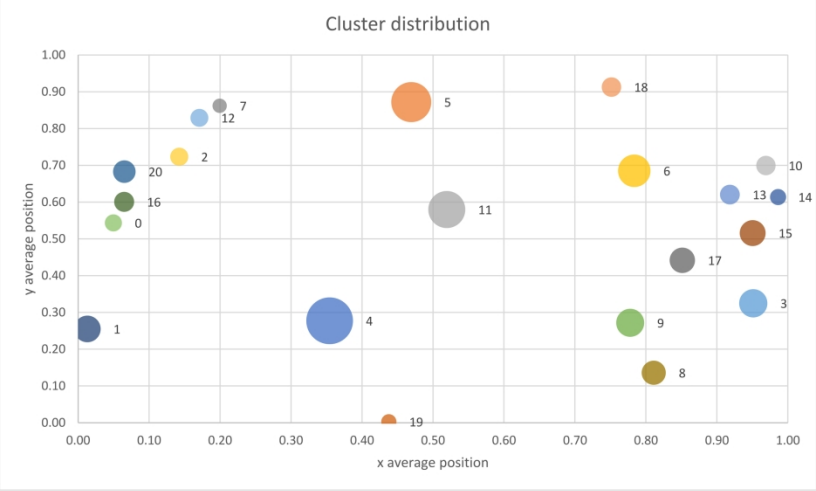

Cluster	4	7	8	9	10	17
Total	4586	429	1223	1647	789	1353
Health coverage	Partial	Public Full	Partial coverage	Full coverage	Partial coverage	Private
Joint biomechanical stress	Unspecified	High	Medium	High	High	High
Gender	78.28	59.67	78.00	50.27	61.22	87.66
Age*	46.99 (17.78)	40.82 (16.70)	44.45 (17.07)	44.11 (18.83)	41.36 (17.53)	47.33 (17.15)
Formal schooling*	7.78 (4.08)	7.85 (4.29)	7.92 (4.53)	11.38 (5.14)	8.69 (4.65)	7.50 (5.09)
Argentina	0.00	0.00	0.00	0.00	0.00	0.00
Colombia	50.81	0.00	4.17	34.30	0.13	0.00
Ecuador	0.00	0.70	36.96	42.74	0.00	0.00
Mexico	39.77	99.30	58.87	22.95	99.62	100.00
Venezuela	9.42	0.00	0.00	0.00	0.25	0.00
Rheumatic disease (any)	40.49	29.84	42.44	41.89	20.41	13.90
Osteoarthritis	11.32	9.09	7.44	5.59	7.48	4.95
Rheumatoid arthritis	2.46	2.80	1.88	1.82	3.55	4.07
Backpain	6.56	9.09	4.74	3.10	4.94	1.85
RRPS	23.92	2.80	26.17	34.00	1.14	0.89
Musculoskeletal disorders	4.49	5.36	2.04	2.43	2.92	2.00
Fibromyalgia	0.41	1.17	1.88	0.67	0.76	0.07
Others	0.37	0.23	0.25	0.79	0.13	0.30
Historical pain	57.78	20.51	35.32	47.54	23.32	17.44
Non-traumatic pain (7 days)	38.60	28.67	33.69	27.26	23.19	15.08
Physical disability (HAQ-DI)	7.76	15.15	14.23	6.44	13.05	12.34
Diabetes mellitus	8.26	7.93	8.91	6.86	9.38	10.20
High blood pressure	22.68	13.75	19.46	18.40	17.87	20.40
Cardiovascular disease	4.93	3.26	3.92	4.80	3.68	2.14
Smoking	17.84	10.26	16.11	32.54	7.48	0.81
Alcoholism	4.91	6.76	3.19	2.37	4.31	0.59
Anxiety/depression	3.92	7.46	12.43	6.07	9.76	8.50
No comorbidities	38.03	43.36	34.10	38.13	46.01	58.39

RRPS: Rheumatic regional pain syndromes. Health Assessment Questionnaire-Disability Index (HAQ-DI) cut-off point of greater than 0.8.

* Age and formal schooling show mean value (standard deviation)

Figure 2. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the non-indigenous population

215x279mm (300 x 300 DPI)

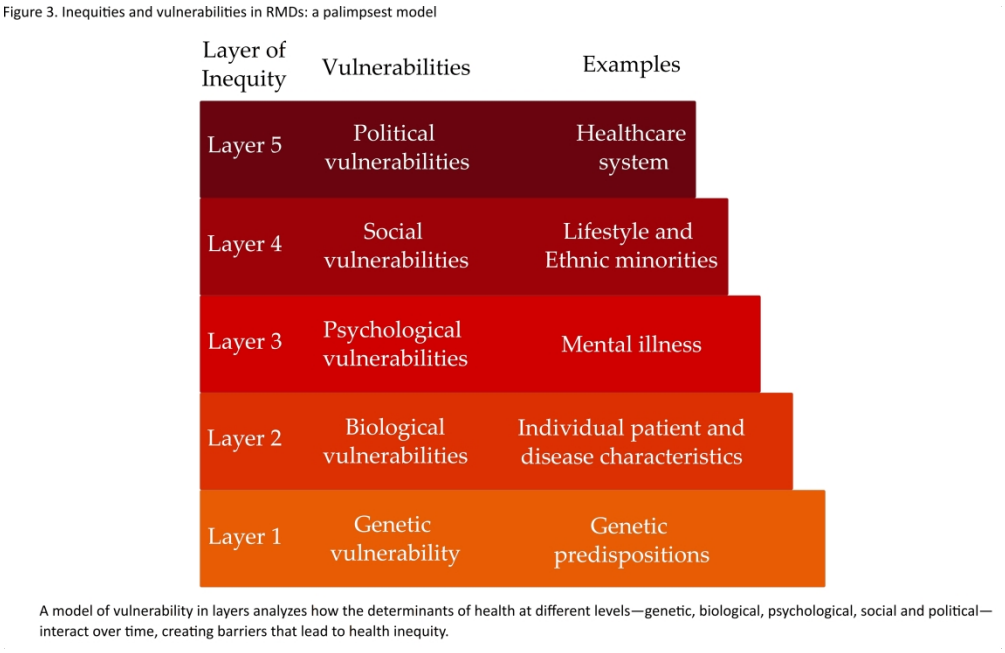

Figure 3. Inequities and vulnerabilities in RMDs: a palimpsest model

452x290mm (236 x 236 DPI)

Supplementary Table. Comparison of sociodemographic characteristics, health coverage, rheumatic diagnosis, pain, disability and comorbidities between indigenous and non-indigenous groups from Ecuador, Mexico and Argentina

	Indigenous n (%) 4599 (50.00)	**Non-indigenous n (%)** 4599 (50.00)	**Totals n (%)** 9198 (100.00)	**p**
Gender (female)	2788 (60.62)	2729 (59.34)	5517 (59.98)	0.217
Age (years), mean (SD)	42.90 (18.71)	42.98 (17.58)	42.94 (18.16)	0.163
Urban setting	832 (18.09)	3624 (78.80)	4456 (48.45)	<0.001
Educational level, mean number of years (SD)	6.74 (5.17)	9.17 (5.15)	7.95 (5.30)	<0.001
Health coverage *				
Full	1351 (29.38)	551 (11.98)	1902 (20.68)	<0.001
Partial	2536 (55.14)	2401 (52.21)	4937 (53.67)	<0.01
Private	245 (5.33)	501 (10.89)	746 (8.11)	<0.001
Other**	171 (3.72)	34 (0.74)	205 (2.23)	<0.001
Joint biomechanical stress ***				
High	2162 (47.01)	1176 (25.57)	3338 (36.29)	<0.001
Medium	534 (11.61)	503 (10.94)	1037 (11.27)	0.323
Low	1472 (32.01)	1574 (34.22)	3046 (33.12)	0.025
Unspecified	254 (5.52)	267 (5.81)	521 (5.66)	0.588
Rheumatic disease				
Totals	1428 (31.05)	1521 (33.07)	2949 (32.06)	0.040
Osteoarthritis	616 (13.39)	334 (7.26)	950 (10.33)	<0.001
Rheumatoid arthritis	104 (2.26)	80 (1.74)	184 (2.00)	0.087
Back pain	521 (11.33)	138 (3.00)	659 (7.16)	<0.001
RRPS	142 (3.09)	895 (19.46)	1037 (11.27)	<0.001
Musculoeskeletical disorders	170 (3.70)	83 (1.80)	253 (2.75)	<0.001
Fibromyalgia	89 (1.94)	50 (1.09)	139 (1.51)	<0.01
Other ****	26 (0.57)	21 (0.46)	47 (0.51)	0.559
Pain				
Historical pain	1839 (39.99)	1487 (32.33)	3326 (36.16)	<0.001
Non-traumatic pain (7 days)	819 (17.81)	1012 (22.00)	1831 (19.91)	<0.001
Physical disability (Health Assessment Questionnaire-Disability Index (HAQ-DI)				
HAQ ≥ 0.8	308 (6.70)	375 (8.15)	683 (7.43)	<0.01
Comorbidities				
Diabetes mellitus	236 (5.13)	326 (7.09)	562 (6.11)	<0.001
High blood pressure	528 (11.48)	855 (18.59)	1383 (15.04)	<0.001
Cardiovascular disease	142 (3.09)	150 (3.26)	292 (3.17)	0.677
Smoking	332 (7.22)	697 (15.16)	1029 (11.19)	<0.001
Alcoholism	643 (13.98)	198 (4.31)	841 (9.14)	<0.001
Anxiety/depression	913 (19.85)	501 (10.89)	1414 (15.37)	<0.001
No comorbidities	2261 (49.16)	1991 (43.29)	4252 (46.23)	<0.001

* Missing data: 296 (6.44%) indigenous and 1112 (24.18%) non-indigenous (total 1408 (15.31%))

** Other: Traditional healthcare

*** Missing data:177 (3.85%) indigenous and 1079 (23.46%) non-indigenous (total 1256 (13.65%))

**** Others: *Indigenous*: 18 ankylosing spondilytis, 4 gout, 1 sclerodermia and 2 psoriasis. *Non-indigenous*: 2 ankylosing spondilytis, 14 gout, and 1 psoriasis.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	6,7
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8,10
Objectives	3	State specific objectives, including any prespecified hypotheses	10
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10,11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11,12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*12*
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12,13,14
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	13

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	17
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*15-16*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17,18,19
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	19
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20,21
Discussion			
Key results	18	Summarise key results with reference to study objectives	21,22,23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	23
Generalisability	21	Discuss the generalisability (external validity) of the study results	24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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INEQUITY AND VULNERABILITY IN LATIN AMERICAN INDIGENOUS AND NON-INDIGENOUS POPULATIONS WITH RHEUMATIC DISEASES :A SYNDEMIC APPROACH

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Epidemiology, Global health, Public health
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, RHEUMATOLOGY, STATISTICS & RESEARCH METHODS

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INEQUITY AND VULNERABILITY IN LATIN AMERICAN INDIGENOUS AND NON-INDIGENOUS POPULATIONS WITH RHEUMATIC DISEASES: A SYNDEMIC APPROACH

1. Ysabel Granados, MD.

ORCID: 000-0002-7148-4060

e-mail: ymgranados@gmail.com

2. Alfonso Gastelum-Strozzi, PhD,

ORCID: 0000-0001-9668-5822

e-mail: alfonso.gastelum@icat.unam.mx

3. José Alvarez-Nemegyei, MD, PhD.

ORCID: 0000-0002-5499-5280

e-mail: nemegyei@yahoo.com.mx

4. Rosana Quintana, MD, PhD.

ORCID: 0000-0003-0643-2755

e-mail: rosanaquintana@gmail.com

5. Flor Julian-Santiago , MD, PhD

ORCID: 0000-0001-6137-045X

e-mail: maifjs@hotmail.com

6. Ana María Santos, PhD

ORCID: ORCID 0000-0002-1973-8043

e-mail: ana.santos@unisabana.edu.co

7. Sergio Guevara, MD, PhD.

ORCID: 0000-0001-5798-6200

e-mail: sergio_guevarap@yahoo.com

8.Adalberto Loyola-Sanchez A, MD, PhD.

ORCID: 0000-0002-0082-2907

e-mail: adalbert@ualberta.ca

9. María Victoria Goycochea-Robles, MD, MSc.

ORCID: 0000-002-92488511

e-mail: mavis.goycochea@gmail.com

10. Vicente Juárez, MD.

ORCID: 0000-0003-3865-087X

e-mail: vtejuarez@gmail.com

11. Mario Garza-Elizondo, MD, PhD

ORCID: 0000-0002-8992-4714

e-mail: mariogarz@hotmail.com

12. Juan Rueda, MD, PhD candidate.

ORCID: 0000-0002-6263-2914

e-mail: juan.rueda@unisabana.edu.co

13. Ruben Burgos-Vargas, MD.

ORCID: 0000-0005-1058-8955

e-mail: burgosv@gmail.com

14. John Londoño, MD, PhD.

ORCID: 0000-0003-1074-644X

e-mail: john.londono@unisabana.edu.co

15. Bernardo A. Pons-Estel, MD.

ORCID: 0000-0003-2518-0266

e-mail: bponsestel@gmail.com

16. Ingris Peláez-Ballestas, MD, PhD[1]

ORCID: 0000-0001-5188-7375

e-mail: pelaezin@gmail.com.

Pons-Estel B.A and Peláez-Ballestas I. on behalf of the Latin American Study Group of Rheumatic Diseases in Indigenous Peoples (GLADERPO).

Affiliations:

1. Hospital "Dr. Manuel Núñez Tovar," Maturín, Monagas, Venezuela.

2. Instituto de Ciencias Aplicadas y Tecnología, Universidad Nacional Autónoma de México, Mexico City, Mexico.

3. Rheumatology Staff. Hospital Star Médica. Mérida, Yucatán, México

4. Centro Regional de Enfermedades Autoinmunes y Reumáticas (CREAR). Rosario, Santa Fe, Argentina.

5. Independent researcher, Oaxaca, Mexico

6. Grupo Espondiloartropatias .Universidad La Sabana, Bogotá, Colombia.

7. Universidad de Cuenca, Cuenca, Ecuador.

8. Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada.

9. Grupo Cochrane-UNAM- Hospital ABC Santa Fe, Ciudad de Mexico

10. Hospital Señor del Milagro, Salta, Argentina.

11. Hospital Universitario "José Eleuterio Gonzalez," Monterrey, Nuevo León, Mexico.

12. Grupo Espondiloartropatias.Universidad La Sabana, Bogotá, Colombia.

13. Rheumatology Unit, Hospital General de México "Dr. Eduardo Liceaga," Mexico City, Mexico.

14. Grupo Espondiloartropatias. Universidad La Sabana, Bogotá, Colombia.

15. Centro Regional de Enfermedades Autoinmunes y Reumáticas (CREAR). Rosario, Santa Fe, Argentina.

16. Rheumatology Unit, Hospital General de México "Dr. Eduardo Liceaga," Mexico City, Mexico.

Corresponding author

Pelaez-Ballestas I., Ph.D. Rheumatology Unit, Hospital General de México "Dr. Eduardo Liceaga." Dr. Balmis 148, Colonia Doctores, 06726, Mexico City. E-mail: pelaezin@gmail.com. Phone: +52 (55) 5004-3849.

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Abstract.

Syndemics are a framework that documents health inequities and vulnerabilities in populations with rheumatic diseases. Compared to other approaches, syndemics are able to conjunctly consider epidemiological, biological, sociodemographic and economic factors, and their interactions.

Objective. To estimate health inequity and vulnerability among Indigenous and non-Indigenous populations with rheumatic and musculoskeletal disease (RMD) in Latin America using the syndemic approach.

Design: This is a secondary analysis of a previously published large-scale study on the prevalence of RMD.

Setting: Studies carried out in five Latin American countries (Argentina, Colombia, Ecuador, Mexico and Venezuela). Health inequity and vulnerability in RMD were identified through a syndemic approach using network and cluster analysis.

Participants. A total of 44,560 individuals were studied: 29.78% self-identified as Indigenous, 60.92% were female, the mean age was 43.25 years. Twenty clusters were identified in the Indigenous population and seventeen in the non-Indigenous population.

Results. The variables associated with RMD among Indigenous populations were rurality, public health system, high joint biomechanical stress, greater pain, disability and alcoholism; and among non-Indigenous people they were being a woman, urban origin, older age, private health system, joint biomechanical stress, greater pain and disability. We identified different health inequities among RMD patients (i.e. lower educational attainment, more comorbidities), associated with factors such as Indigenous self-identification and rural residence.

Conclusions. A syndemic approach enables us to identify health inequities in RMD, as shown by higher prevalence of comorbidities, disability and socioeconomic factors like lower educational attainment. These inequities exist for the overall population of patients with RMD, though it is more evident in Indigenous groups with added layers of vulnerability.

Strengths and limitations of this study

- Syndemics are a framework using strategies from artificial intelligence to perform complex analyses that document health inequities.
- The analysis of clusters and networks groups individuals by variables to document inequity, the principal objective of this study.

- The cross-sectional nature of this study is a limitation to establish causality.

Introduction

Rheumatic and musculoskeletal diseases (RMD) are a significant cause of morbidity and mortality worldwide [1]; they produce substantial socioeconomic impact and deterioration of quality of life in patients, who represent approximately 10% of the general population [2]. Since 2000, the World Health Organization (WHO) has recognized RMD as a relevant health problem, due to the increase in secondary disability and a greater demand for health resources [3].

There is now a greater need to define global strategies for the timely access of patients with RMD to health systems [4], including the evaluation of social determinants, such as gender, education, work, income level, ethnicity and place of residence [5].

Latin America is an extensive geographic area made up of 26 countries, characterized by multiculturalism and great contrasts in political, social and economic aspects [4,6]. Significant social inequity has been documented, with marked disparities in health coverage for individuals and social groups; these inequities are observed within and among countries in the region [7]. Epidemiological studies have documented a prevalence of RMD between 23% and 46.5% in Latin America, with more aggressive presentations (higher morbidity and mortality) among Indigenous populations. Genetic predisposition to systemic lupus erythematosus (SLE) has also been identified among Indigenous groups [8], as well as a high prevalence of rheumatoid arthritis (RA) among Indigenous Mayan groups of Yucatan, Mexico [9] and the Qom of Argentina [10,11].

Despite the high prevalence of RMD in the Latin American region, these diseases continue to have a low priority in the planning of health policies [4]. Overall, the healthcare system in

Latin America is highly fragmented and disconnected. For rheumatology care specifically, 33.5% of rheumatologists work in public/government hospitals, 28.8% in private practice, 20.8% in private hospitals, and 15.5% in university hospitals, most of them distributed in large urban areas, with a significant lack in small cities and none in rural areas [12–16].

These differences in disease prevalence and distribution of health resources which limit access to rheumatology care in Latin America can be understood as health inequities. Health inequity is not synonymous with inequality. Inequity implies the idea of injustice and of lack of actions to avoid *preventable* differences. On the other hand, inequality describes differences in health outcomes that are not fundamentally unfair [12]. Health inequity is deeply connected to vulnerability. From a biomedical perspective, vulnerability means being susceptible to certain diseases or to environmental risk. However, vulnerability can also be understood as a product of the interaction between available resources (personal, family, community, cultural, economic, institutional), the sociocultural context of the patient, structural elements, and exposure to risk [12,17–20]. Therefore, vulnerability is a result of health inequity.

To document inequity in health, the syndemic model has proven useful to analyze the interaction of disease with social determinants that condition inequality in health, and how these lead to increased physical and environmental vulnerability [17,18,21,22]. Syndemics aggregate the interaction of two or more concurrent diseases, as well as the sociocultural and healthcare contexts which can exacerbate the negative effects of this interaction on the health of individuals, communities, and societies [21]. The syndemic framework evaluates the interaction of any type of disease in conditions of health inequality caused by poverty, stigmatization, stress or structural violence [21–23]. Thus, syndemics encompass social determinants, vulnerabilities, and inequities and inequalities in health as well.

Previous studies have shown that syndemics are a good comprehensive model to document inequity and inequality in health. In a study of RMD in Indigenous populations in Latin America, as well as a study of patients with low back pain, disease is associated with being a woman, belonging to an indigenous population, and having low educational attainment. It is also exacerbated by the presence of comorbidities, especially those within the mental health domain [8,24].

Given the intricacy of a syndemic approach, conventional statistical methodologies are insufficient. Instead, using strategies from graph theory (network analysis) and machine learning (cluster analysis) is necessary to perform complex analyses that document health inequities comprehensively. The syndemic approach is useful to identify health inequities and vulnerabilities in different population groups.

We hypothesize that there is a syndemic in Latin American populations suffering from rheumatic diseases, associated with comorbidities such as diabetes and hypertension, and living in a fragmented health care context. We also hypothesize that this phenomenon is more significant in vulnerable populations such as Indigenous peoples. Therefore, we proposed the following study to measure syndemics comparatively between Indigenous and non-Indigenous populations with RMD in Latin America.

MATERIALS AND METHODS

Design

This is a secondary analysis, based on multilevel network analysis using a syndemic framework, of a previously published large-scale cross-sectional study on the prevalence of RMD in five Latin American countries.

Data sources

We used a database compiled by GEEMA (Grupo de Estudios Epidemiológicos de Enfermedades Músculo Articulares), COPCORD-LATAM (Community Oriented Program for Control of Rheumatic Diseases-Latin America) and GLADERPO (Grupo Latino Americano de Estudios de Enfermedades Reumáticas en Pueblos Originarios).

GLADERPO recorded information on the Qom and Wichí Indigenous populations of Argentina [10,25], Saraguro of Ecuador [26], Yucatec-Maya and Mixtec of Mexico [8,9] and the Chaimas, Kariñas and Warao of Venezuela [27].

COPCORD-LATAM was developed with the results of epidemiological studies conducted on the non-Indigenous populations of Colombia [28], Ecuador [29], Mexico [30] and Venezuela [31], using COPCORD (Community Oriented Program for Control of Rheumatic Diseases) methodology, culturally and linguistically adapted to the different communities studied, and subsequently validated in each country.

The COPCORD methodology consists of trained health personnel administering a questionnaire house to house, which identifies patients with pain of non-traumatic origin, historical and in the last seven days. The participation of certified rheumatologists allowed for the diagnosis of RMDs [29–33].

The same measurements were collected in all the studies: sociodemographic variables, joint biomechanical stress, comorbidities, physical disability and accessibility to local health care.

Sociodemographic variables such as age, gender, self-defined ethnicity according to the laws of each country (Indigenous and non-Indigenous), formal schooling (numbers of years studied in the official education system) and place of residence (urban/rural).

Level of joint biomechanical stress was classified according to self-reported occupation. Individuals were asked for a visual recreation of their activity, according to the degree of effort and the body regions involved. Following a survey on the level of physical load repetitiveness, each occupation was classified into three levels of joint biomechanical stress in the workplace: high (e.g. farmers, homemakers, machine operators), medium (e.g. artisans, drivers, technicians) and low (e.g. merchants, professionals, students, teachers, retirees).

Comorbidities were self-reported [32,33], while physical disability was measured with the **Health Assessment Questionnaire-Disability Index** (HAQ-DI), validated for each country and with an established cut-off point of greater than 0.8 [34].

Accessibility to the local healthcare system was classified by conducting an exercise of comparisons and equivalences among the researchers from the five participating countries. Considering all characteristics of the healthcare systems, the three subgroups used to classify accessibility were: *partial coverage*, involving a public system that covers physician appointments, laboratory tests and basic but not high specialty medications; *full coverage*, involving a social security system that covers all health expenses; and *private coverage*, where patients pay fully for their care.

Analysis

A multi-phase analysis was performed.

Phase 1. We applied inferential statistics (i.e., bivariate analysis) to explore associations between ethnicity (Indigenous or non-Indigenous) and country of origin, and sociodemographic characteristics (i.e., age, gender, formal schooling, urban/rural residence),

rheumatic diagnoses, comorbidities, disability (HAQ-DI) and levels of accessibility (partial, total and private coverage).

Phase 2. We performed simple logistic regression models to identify factors (i.e., sociodemographic, comorbidities, disability, accessibility, and joint biomechanical stress) associated with RMD diagnosis (i.e., present or absent) as a dependent variable by ethnicity (Indigenous vs. non-Indigenous). We estimated odds ratios (OR), along with 95% confidence intervals (CI 95%) and significance (p).

Phase 3. We used a network analysis approach [35] to generate groups with similar characteristics (e.g., sociodemographic, country, comorbidities, diagnoses, etc.) called clusters. These clusters helped to determine the negative characteristics associated with disease and disability using the syndemic framework. The network analysis method requires the definition of a characteristic that allows creation of connections between subjects; a measure of similarity was defined to create these. The similarity measure determined the relationships between the different subjects within the database. The measure of similarity evaluated the number of similarities between two subjects regarding the results of their evaluations. To construct the first part of the similarity measure, a vector was defined with the following variables: a) accessibility level, b) level of joint biomechanical stress, and c) urban/rural residence. Using the cosine similarity method, this vector was used to calculate a similarity index for each individual concerning the rest of the population [36]. The final similarity index was obtained by applying a weighted difference by years of education between each individual.

The similarity index was used to determine an individual's degree of similarity to the rest of the population and to build the relations between individuals. In the network definition, each individual is a node; an axis of relations is generated when the similarity index between two

individuals is greater than the average of the similarity indices plus the standard deviation of the whole population [37]. The network obtained is simulated in Gephi [38] and the final position of the nodes or individuals is used to define the new groups using the DBSCAN method [39].

Due to the complexity of the representation of the clusters, we conducted a consensus process among all researchers to select the most relevant clusters regarding socio-economic and clinical impact, which included healthcare access, disability, educational level, and type of RMD. Selected clusters were further analyzed in network analysis, including the following factors in a hierarchical order of importance: 1) prevalence of RMD, 2) prevalence of rheumatoid arthritis (RA), and 3) the number of individuals comprising the cluster. All researchers assigned every cluster a weighted score for each of the three selected variables. Finally, six clusters were selected per group (i.e., Indigenous and non-Indigenous) according to their amount of representation of health inequity factors.

Phase 4. We conducted a sensitivity analysis to confirm no biases using a randomly selected weighted sample of Indigenous/non-Indigenous populations from the three countries that studied both at the same time (Ecuador, Mexico, and Venezuela), and two countries that only had samples of Indigenous (Argentina) or non-Indigenous (Colombia) populations. The clusters obtained through this analysis were defined by factors such as living in a rural setting, lower health coverage, and greater disability, which went beyond our initial Indigenous/non-Indigenous classification and impacted the management of rheumatic diseases. These emerging differences can be used to document inequity insofar as they highlight the variables which negatively affect the health of people with RMD.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design or conduct, or reporting, or dissemination plans of our research. The members of the public were involved at original stages of each study including as cultural liaisons. We disseminated the main results to all participants and health authorities to improve health conditions.

RESULTS

A total of 44,560 individuals from five Latin American countries (Argentina, Colombia, Ecuador, Mexico and Venezuela) were studied. Of these, 29.78% (13,269) self-identified as Indigenous and 27,145 (60.92%) were female, with an average age of 43.25 (SD = 18.02) years and a mean of 8.06 (SD = 5.02) years of schooling. RMD was diagnosed in 13,528 (30.36%) individuals. Rheumatic regional pain syndromes (RRPS) was the rheumatic diagnosis with the highest prevalence (6100, 13.69%) followed by osteoarthritis (3690, 8.28%), while RA was reported in (877, 1.97%) individuals (Table 1).

Table 1. Comparison of sociodemographic characteristics, country, health coverage, rheumatic diagnosis, pain, disability and comorbidities between Indigenous and non-Indigenous groups.

	Indigenous n = 13269 (29.78)	**Non-Indigenous n = 31291 (70.22)**	**Total n = 44560 (100.00)**	**p**
Gender (female)	8010 (60.37)	19135 (61.15)	27145 (60.92)	0.123
Age (years), mean (SD)	42.23 (18.17)	43.69 (17.94)	43.25 (18.02)	<0.001
Urban setting	3877 (29.22)	24331 (77.76)	28208 (63.30)	<0.001
Educational level, mean number of years (SD)	7.13 (5.07)	8.46 (4.95)	8.06 (5.02)	<0.001
Countries				
Argentina	2295 (17.30)	0 (0.00)	2295 (5.15)	<0.001
Colombia	234 (1.76)	6454 (20.63)	6688 (15.01)	<0.001
Ecuador	2682 (20.21)	4858 (15.53)	7540 (16.92)	<0.001
Mexico	6525 (49.17)	16085 (51.40)	22610 (50.74)	<0.001
Venezuela	1533 (11.55)	3894 (12.44)	5427 (12.18)	<0.01
Health coverage *				
Full	3481 (26.23)	4493 (14.36)	7974 (17.89)	<0.001
Partial	7441 (56.08)	18314 (58.53)	25755 (57.80)	<0.001

Private	795 (5.99)	1741 (5.56)	2536 (5.69)	0.079
Other**	330 (2.49)	221 (0.71)	551 (1.24)	<0.001
Joint biomechanical stress ***				
High	5000 (37.68)	10199 (32.59)	15199 (34.11)	<0.001
Medium	1538 (11.59)	4720 (15.08)	6258 (14.04)	<0.001
Low	4014 (30.25)	9213 (29.44)	13227 (29.68)	0.090
Unspecified	1815 (13.68)	2784 (8.90)	4599 (10.32)	<0.001
Rheumatic disease				
Totals	4012 (30.24)	9516 (30.41)	13528 (30.36)	0.721
Osteoarthritis	1433 (10.80)	2257 (7.21)	3690 (8.28)	<0.001
Rheumatoid arthritis	278 (2.10)	599 (1.91)	877 (1.97)	0.223
Back pain	1548 (11.67)	1281 (4.09)	2829 (6.35)	<0.001
RRPS	505 (3.81)	5595 (17.88)	6100 (13.69)	<0.001
Musculoskeletal disorders	521 (3.93)	664 (2.12)	1185 (2.66)	<0.001
Fibromyalgia	181 (1.36)	212 (0.68)	393 (0.88)	<0.001
Other ****	45 (0.34)	118 (0.38)	163 (0.37)	0.602
Pain				
Historical pain	5408 (40.76)	11780 (37.65)	17188 (38.57)	<0.001
Non-traumatic pain (7 days)	2258 (17.02)	8024 (25.64)	10282 (23.07)	<0.001
Physical disability (Health Assessment Questionnaire-Disability Index (HAQ-DI)				
HAQ-DI ≥ 0.8	761 (5.74)	2558 (8.17)	3319 (7.45)	<0.001
Comorbidities				
Diabetes mellitus	814 (6.13)	2279 (7.28)	3093 (6.94)	<0.001
High blood pressure	1649 (12.43)	5613 (17.94)	7262 (16.30)	<0.001
Cardiovascular disease	415 (3.13)	1106 (3.53)	1521 (3.41)	0.033
Smoking	1138 (8.58)	4996 (15.97)	6134 (13.77)	<0.001
Alcoholism	1751 (13.20)	1068 (3.41)	2819 (6.33)	<0.001
Anxiety/depression	2304 (17.36)	3727 (11.91)	6031 (13.53)	<0.001
No comorbidities	6391 (48.16)	14450 (46.18)	20841 (46.77)	<0.001

* Missing data: 1222 (9.21%) Indigenous and 6522 (20.84%) non-Indigenous, total 7744 (17.38%)

** Other: Traditional healthcare

*** Missing data: 902 (7.01%) indigenous and 4375 (13.80%) not indigenous.

**** Others: *Indigenous*: 29 ankylosing spondylitis, 9 gout, 4 scleroderma and 3 psoriasis. *Non-Indigenous*: 39 ankylosing spondylitis, 74 gout, 1 scleroderma and 4 psoriasis.

A lower urban origin (18.71%) and less years of formal schooling (6.74, SD = 5.71) were observed in the Indigenous population, while the non-Indigenous population had a predominance of private coverage (10.89%). High joint biomechanical stress (47.01%) and historical pain (39.99%) were more frequent in Indigenous populations. The prevalence of RMD was similar between populations studied; RA was more prevalent in Indigenous people (2.26% vs 1.74%), but not significantly. Non-Indigenous people had greater disability (8.15% with HAQ ≥0.8) and higher prevalence of diabetes mellitus, high blood pressure and

smoking (7.09%, 18.59% and 15.16%). Among Indigenous people, alcohol consumption and anxiety/depression were more prevalent (13.98% and 19.55%) (see supplementary table).

In terms of the sub-analysis by country, Argentina had the youngest individuals (35.98, SD:=14.25); Ecuador and Colombia recorded a higher level of schooling (9.31, SD= 5.49) and a higher prevalence of RMD (47.69% and 40.76%); Argentina and Mexico had the highest prevalence of RA (3.01% and 2.22%); Colombia had a higher prevalence of historical and non-traumatic pain (73.95% and 43.94%); and Ecuador had the highest number of disabled people (8.70% with HAQ ≥0.8) (Table 2).

Table 2. Comparison of sociodemographic characteristics, health coverage, rheumatic diagnosis, pain, disability, and comorbidities between populations of five Latin American countries.

	Argentina n (%) n = 2295 (5.15)	**Colombia n (%) n = 6688 (15.01)**	**Ecuador n (%) n = 7540 (16.92)**	**Mexico n (%) n = 22610 (50.74)**	**Venezuela n (%) n = 5427 (12.18)**	**Totals* n (%) n = 44560 (100.00)**	**p**
Ethnicity (Indigenous)	2295 (100.00)	234 (3.50)	2682 (35.57)	6525 (28.86)	1533 (28.25)	13269 (29.78)	<0.001
Gender (female)	1393 (60.70)	4280 (64.00)	4590 (60.88)	13634 (60.30)	3248 (59.85)	27145 (60.92)	<0.001
Age (years), mean (SD)	35.98 (14.25)	46.41 (18.35)	43.39 (18.60)	43.08 (17.93)	42.98 (17.63)	43.25 (18.02)	<0.001
Urban setting	0 (0.00)	6688 (100.00)	3384 (44.88)	14242 (62.99)	3894 (71.75)	28208 (63.30)	<0.001
Educational level, mean number of years (SD)	5.43 (3.60)	9.19 (4.00)	9.31 (5.49)	7.41 (4.98)	8.77 (5.27)	8.06 (5.02)	<0.001
Health coverage *							
Total	2295 (100.00)	6527 (97.60)	5453 (72.32)	17114 (75.70)	5427 (100.00)	36816 (82.62)	
Full	29 (1.26)	1920 (28.71)	3148 (41.75)	2877 (12.72)	0 (0.00)	7974 (17.89)	<0.001
Partial	2053 (89.46)	4465 (66.76)	405 (5.37)	13674 (60.48)	5158 (95.04)	25755 (57.80)	<0.001
Private	183 (7.97)	39 (0.58)	1482 (19.66)	563 (2.49)	269 (4.96)	2536 (5.69)	<0.001
Other**	30 (1.31)	103 (1.54)	418 (5.54)	0 (0.00)	0 (0.00)	551 (1.24)	<0.001
Joint biomechanical stress ***							
Totals	1698 (74.00)	6686 (99.97)	7440 (98.67)	20253 (89.58)	3206 (59.08)	39283 (88.16)	
High	420 (18.30)	3511 (52.50)	3382 (44.85)	6667 (29.49)	1219 (22.46)	15199 (34.11)	<0.001
Medium	159 (6.93)	1569 (23.46)	516 (6.84)	3438 (15.21)	576 (10.61)	6258 (14.04)	<0.001
Low	120 (5.23)	1604 (23.98)	3510 (46.55)	6684 (29.56)	1309 (24.12)	13227 (29.68)	<0.001
Unspecified	999 (43.53)	2 (0.03)	32 (0.42)	3464 (15.32)	102 (1.88)	4599 (10.32)	<0.001
Rheumatic disease							
Totals	705 (30.72)	2726 (40.76)	3596 (47.69)	5092 (22.52)	1409 (25.96)	13528 (30.36)	<0.001
Osteoarthritis	88 (3.83)	521 (7.79)	470 (6.23)	1797 (7.95)	814 (15.00)	3690 (8.28)	<0.001
Rheumatoid arthritis	69 (3.01)	84 (1.26)	120 (1.59)	501 (2.22)	103 (1.90)	877 (1.97)	<0.001
Back pain	460 (20.04)	237 (3.54)	474 (6.29)	1357 (6.00)	301 (5.55)	2829 (6.35)	<0.001
RRPS	41 (1.79)	2726 (40.76)	2671 (35.42)	461 (2.04)	201 (3.70)	6100 (13.69)	<0.001
Musculoskeletal disorders	50 (2.18)	0 (0.00)	62 (0.82)	1013 (4.48)	60 (1.11)	1185 (2.66)	<0.001
Fibromyalgia	3 (0.13)	27 (0.40)	214 (2.84)	126 (0.56)	23 (0.42)	393 (0.88)	<0.001
Other ****	2 (0.09)	26 (0.39)	32 (0.42)	80 (0.35)	23 (0.42)	163 (0.37)	0.179
Pain							
Historical pain	938 (40.87)	4946 (73.95)	3420 (45.36)	6141 (27.16)	1743 (32.12)	17188 (38.57)	<0.001
Non-traumatic pain (7 days)	402 (17.52)	2939 (43.94)	1525 (20.23)	4204 (18.59)	1212 (22.33)	10282 (23.07)	<0.001

Physical disability (Health Assessment Questionnaire-Disability Index (HAQ-DI)							
HAQ ≥ 0.8	95 (4.14)	400 (5.98)	656 (8.70)	1741 (7.70)	427 (7.87)	3319 (7.45)	<0.001
Comorbidities							
Diabetes mellitus	125 (5.45)	428 (6.40)	382 (5.07)	1898 (8.39)	260 (4.79)	3093 (6.94)	<0.001
High blood pressure	379 (16.51)	1591 (23.79)	1046 (13.87)	3078 (13.61)	1168 (21.52)	7262 (16.30)	<0.001
Cardiovascular disease	144 (6.27)	435 (6.50)	250 (3.32)	471 (2.08)	221 (4.07)	1521 (3.41)	<0.001
Smoking	497 (21.66)	2409 (36.02)	1587 (21.05)	1080 (4.78)	561 (10.34)	6134 (13.77)	<0.001
Alcoholism	379 (16.51)	0 (0.00)	470 (6.23)	1523 (6.74)	447 (8.24)	2819 (6.33)	<0.001
Anxiety/depression	123 (5.36)	1463 (21.88)	1843 (24.44)	2185 (9.66)	417 (7.68)	6031 (13.53)	<0.001
No comorbidities	882 (38.43)	2483 (37.13)	2460 (32.63)	12471 (55.16)	2545 (46.90)	20841 (46.77)	<0.001

* Missing data: 7744 (17.38)

**Other: Traditional healthcare

*** Missing data: 5277 (11.84)

**** Others: Ankylosing spondylitis, gout, scleroderma, psoriasis.

A logistic regression analysis was performed by ethnicity. In the Indigenous population, the variables significantly associated with RMD diagnosis were living in a rural setting, younger age, relying on the public health system for treatment, high levels of joint biomechanical stress, greater pain and greater disability. In turn, the variables associated with RMD diagnosis in the non-Indigenous population were being a woman, living in an urban setting, older age, relying on the private sector for treatment, more frequent joint biomechanical stress regardless of the level, greater pain, greater disability and less association with having diabetes mellitus (Table 3).

Table 3. Logistic regression. Dependent variable: a rheumatic disease. Independent variables: gender, place of residence, age, schooling, health coverage, biomechanical stress, pain, functional capacity, and comorbidities.

	Indigenous		**Non-Indigenous**	
	OR (95% CI two-sided)	**p**	**OR (95% CI two-sided)**	**P**
Intercept	0.02 (0.01 - 0.03)	< 0.01	0.10 (0.08 - 0.12)	< 0.01
Gender (female)	1.10 (0.96 - 1.25)	0.164	1.19 (1.11 - 1.27)	< 0.01

Age (years)	0.49 (0.41 - 0.59)	< 0.01	1.49 (1.37 - 1.62)	< 0.01
Urban setting	1.02 (1.02 - 1.02)	< 0.01	1.00 (1.00 - 1.01)	< 0.01
Educational level	0.99 (0.97 - 1.00)	0.051	1.01 (1.00 - 1.01)	0.081
Health coverage				
Full	1.46 (1.11 - 1.91)	< 0.01	0.82 (0.74 - 0.91)	< 0.01
Partial	1.15 (0.88 - 1.50)	0.322	0.59 (0.55 - 0.64)	< 0.01
Private	1.55 (1.10 - 2.19)	0.013	1.43 (1.25 - 1.64)	< 0.01
Other	1.36 (0.87 - 2.13)	0.172	0.98 (0.70 - 1.36)	0.900
Level of joint biomechanical stress				
High	1.18 (1.00 - 1.40)	0.054	1.55 (1.41 - 1.69)	< 0.01
Medium	1.22 (0.96 - 1.56)	0.110	1.31 (1.17 - 1.46)	< 0.01
Low	1.17 (0.97 - 1.42)	0.101	1.52 (1.38 - 1.66)	< 0.01
Pain				
Historical pain	27.77 (24.09 - 32.01)	< 0.01	3.84 (3.59 - 4.11)	< 0.01
Non-traumatic pain (7 days)	2.51 (2.18 - 2.89)	< 0.01	2.26 (2.11 - 2.43)	< 0.01
Physical disability (Health Assessment Questionnaire-Disability Index (HAQ-DI)				
HAQ ≥ 0.8	1.25 (1.00 - 1.56)	0.045	1.37 (1.23 - 1.52)	< 0.01
Comorbidities				
Diabetes mellitus	0.95 (0.75 - 1.20)	0.653	0.82 (0.73 - 0.93)	< 0.01
High blood pressure	0.98 (0.82 - 1.18)	0.842	0.95 (0.87 - 1.03)	0.226
Cardiovascular disease	0.83 (0.62 - 1.12)	0.219	1.06 (0.91 - 1.24)	0.433
Smoking	0.93 (0.74 - 1.16)	0.504	1.06 (0.97 - 1.16)	0.217
Alcoholism	0.78 (0.64 - 0.94)	< 0.01	1.15 (0.97 - 1.37)	0.107
Anxiety/depression	0.99 (0.84 - 1.17)	0.926	1.05 (0.96 - 1.16)	0.266
No comorbidities	0.87 (0.74 - 1.03)	0.111	0.73 (0.67 - 0.80)	< 0.01

Twenty clusters were identified in the Indigenous population and seventeen in the non-Indigenous population. In order to best represent the results, six clusters were selected for each group, using consensus and weighing as described in the methodology.

The six clusters selected from the Indigenous population were: Cluster 1 was represented by individuals with partial coverage, younger, with lower educational attainment, higher prevalence of RA and low back pain, and higher pain and smoking. Cluster 11 included

individuals with full coverage, greater functional limitation, and higher prevalence of RA and anxiety/depression. Cluster 13 was represented by individuals with less schooling and a high percentage of smoking and alcoholism. Cluster 14 was represented by individuals with full coverage, high prevalence of RMD, and higher percentage of anxiety/depression and pain. Cluster 15 was the largest, with partial coverage, high level of joint biomechanical stress, and higher prevalence of RMD and associated pain. Lastly, Cluster 16 was the smallest and included individuals with private coverage, high level of joint biomechanical stress, older age, anxiety/depression and alcoholism, and the highest prevalence of RMD and associated pain out of all the clusters (Figure 1).

In the non-Indigenous population, the six selected clusters were: Cluster 4 was the largest, represented by individuals with partial coverage, high level of joint biomechanical stress, higher percentage of pain, and higher prevalence of RMD, high blood pressure and anxiety/depression. Cluster 7 was the smallest, with a low percentage of pain and RMD, but greater physical disability. Cluster 8 included individuals with less years of formal schooling, partial health coverage, higher prevalence of RMD and anxiety/depression, medium level of joint biomechanical stress, and high physical disability.

Cluster 9 included individuals with higher educational attainment, full coverage, higher prevalence of RRPS, greater pain, greater level of smoking and less disability. Cluster 10 was represented by individuals with partial coverage, and lower prevalence of RMD and associated pain, but with greater limitation. Cluster 17 included only Mexican individuals with partial coverage, high level of joint biomechanical stress, lower educational attainment, and higher prevalence of RA, diabetes mellitus and high blood pressure (Figure 2).

DISCUSSION

The syndemic approach analyzes the synergistic interrelationship between different biological and non-biological factors that lead to disease. The application of this approach to the area of health is relatively recent. Multiple studies describe how epidemiological and socioeconomic factors are related to disability and inequity in patients with RMD [40]. However, there are few publications that evaluate inflammatory joint diseases and other chronic musculoskeletal conditions from a broader social and biocultural context, taking into consideration how the socioeconomic characteristics of the environment interact with the disease.

In the present study, a syndemic approach was used to identify factors associated with health inequity [41]. The results obtained through a complex analysis of networks showed a greater clustering of patients with rheumatic diseases who shared common social determinants, such as rural setting and lower schooling. This coincides with the results published by Norton et al, who have described that the greater the comorbidities, the greater the risk of a negative impact on the evolution of RMD [42] and, consequently, the greater the difficulty to adequately control the disease [43].

This study identified factors associated with inequity in individuals with RMD in five Latin American countries with a syndemic approach. The clusters obtained through our analysis show differential negative impacts in the groups that were formed. The relevant emerging factors are living in rural communities, having lower educational attainment, and depending on the public healthcare system, described as fragmented in all participating countries. Comorbidities such as smoking, alcoholism and those related to mental health (anxiety/depression) are most prevalent overall, and greater in the Indigenous population. The differences detected through the clusters can be considered health inequities, since they

constitute avoidable differences such as low schooling and a health care system without full coverage. Furthermore, the clusters that have greater impact are those which include Indigenous people. All of the above attests to the inequity in RMD in low- and middle-income countries in general, and even more so in historically vulnerable populations, such as Indigenous groups.

Multiple reports describe disparity and inequity among patients with RMD. Though they contemplate the interaction of disease with epidemiological, biological and socioeconomic factors, most of the research of this phenomenon does not include a conjunct and comprehensive analysis of all factors as is achieved by syndemics [40].

Another important finding of the study is the clusters with higher prevalence of comorbidities, particularly high blood pressure, tobacco, and alcohol consumption, and those related to mental health (anxiety/depression). As previously reported, the greater the comorbidity, the greater the risk of negative impact on the evolution of RMD [42]. The coexistence of two or more conditions prevents the proper control of disease activity, hindering the achievement of therapeutic goals like those proposed by the treat to target recommendations [43].

The coexistence of several chronic conditions involving systemic inflammatory processes and deterioration in functional capacities, leads to a greater impact on the quality of life and greater demand of health services, to which many populations in Latin America have no universal access. Indeed, the results of this analysis identified several clusters with partial or no access to medical care coinciding with greater comorbidity (cluster 1, 10,11). The association between RMD severity and comorbidities as biological interactions is clear, but it is important to correlate these at a social level, since not having access to timely diagnoses

or specialized care increases the possibility of greater comorbidity and complications. Additionally, it is important to address the interaction of certain prevalent comorbidities (smoking, alcoholism, and mental health struggles) which contribute to the syndemic as both social and biological factors. While there is sufficient evidence to suggest the possibility of common pathophysiological mechanisms with inflammatory joint diseases, it has also been shown that states of anxiety and depression can be triggered by non-biological factors such as social isolation, poverty, mental health worldview or cultural stigmatization, and/or lack of access to healthcare [44].

When comparing inequity between population groups, the poverty rate in Indigenous and rural communities is higher, as reported in this study: 29.78% of the population self-identified as Indigenous, with a higher level of individuals from rural areas and fewer years of schooling. The prevalence of RA specifically was more pronounced in the Indigenous population, with the highest rates in Argentina and Mexico (3.01% and 2.22%) [8,10]. Previous research has similarly found that RMD are more frequent in the Indigenous populations than in the non-Indigenous populations of Canada, Australia, New Zealand and the United States [17].

The Indigenous population had a lower prevalence of disability despite presenting greater high level of joint biomechanical stress, historical pain and RA, which may be related to a worldview favoring normalization or underestimation of symptoms. In addition, the interpretation of these symptoms may be one of the causes of delay in seeking specialized care [11]. The relationship between ethnicity and health outcomes seems to be influenced by acculturation; that is, when one ethnic group is forced to adopt the beliefs and practices of another, the members develop negative health behaviors as coping mechanisms [45].

Health systems in Latin America are diverse and complex. Individuals in this study are distributed among the spectrum of public (partial or full) and private systems. Most Indigenous communities have public health coverage, though this does not guarantee access or continuity of care and treatment. Limited access is not merely due to economic barriers, but also related to ethnic, cultural and geographical factors, among others [8,24,40,46]. Indigenous communities are among the most vulnerable groups and, due to the conditions described above, their inclusion into the healthcare system is complex [11,46,47].

The inaccessibility of the healthcare system, socioeconomic conditions, presence of comorbidities involving mental health, and RMD disease activity, are all factors that exist in interacting layers to create specific conditions of vulnerability for different patient populations. A model of vulnerability in layers, called a palimpsest design [12], analyzes how the determinants of health at different levels—genetic, biological, psychological, social and political—interact over time, creating barriers that lead to health inequity. The syndemic approach, in taking into consideration all factors and their interactions conjunctly, corresponds with a palimpsest model, providing evidence for the vulnerability of RMD patients associated with social factors such as rurality, low educational attainment, and greater reliance on the public health system (Figure 3).

Limitations

The cross-sectional nature of our study is a limitation to establish causality. However, the network and cluster analysis allowed the grouping of individuals by variables to document inequity, the principal objective of this study.

Another limitation is the documentation of comorbidities through self-reporting, which can condition a measurement error. However, an attempt was made to verify these reports through the medications that individuals informed having taken.

In conclusion, the complex analysis from a syndemic approach allowed us to identify the greatest inequity in the clusters that group younger individuals, residents of rural areas, those who self-identify as Indigenous, have lower educational attainment, higher prevalence of RMD and RA specifically, greater comorbidities especially related to mental health and high blood pressure, and partial coverage in the public healthcare system. Given the above we can assume that these social vulnerabilities and comorbidities lead to health inequities for populations living in countries in which RMD are not considered a priority, resulting in lack of coverage for prevention, diagnosis and management.

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Data sharing. The data are available but must be requested from the researcher IPB through a specific application request for the use of data, which will be evaluated by all Group.

Transparency declaration. The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Ethics approval

As the present investigation involves data collected as a part of prior studies, no specific study protocol approval was needed, as all Institutional and Ethics Committees of each participating institution (Argentina:1619/2010 and 0127/2011; Ecuador: 2016-129IN, and Mexico: DI/11/4044B/3/123) had already approved pertinent studies and authorities from participating indigenous communities (18).

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Figure Legend

Figure 1. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the Indigenous population. (Title)

RRPS: Rheumatic regional pain syndromes. Health Assessment Questionnaire-Disability Index (HAQ-DI) cut-off point of greater than 0.8.
* Age and formal schooling show mean value (standard deviation)
**Circle size represents the number of individuals per cluster for visual comparison. The cluster positions are the result of the network simulation; the position of each cluster is obtained during the simulation depending on the similarity of the individuals.

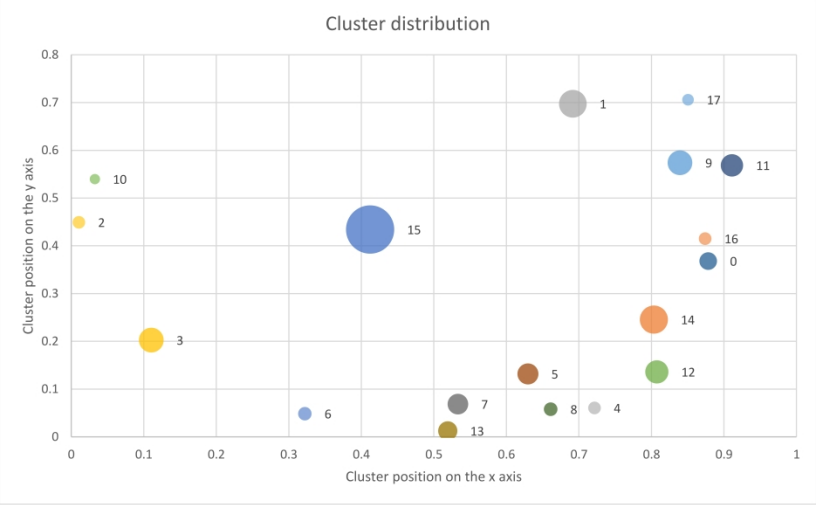
Figure 2. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the non-Indigenous population. (Title).

RRPS: Rheumatic regional pain syndromes. Health Assessment Questionnaire-Disability Index (HAQ-DI) cut-off point of greater than 0.8.
* Age and formal schooling show mean value (standard deviation)
**Circle size represents the number of individuals per cluster for visual comparison. The cluster positions are the result of the network simulation; the position of each cluster is obtained during the simulation depending on the similarity of the individuals.

Figure 3. Inequities and vulnerabilities in RMDs: a palimpsest model (Title)

A model of vulnerability in lavers analyzes how the determinants of health at different levels -genetic, biological, psychological, social and political- interact over time, creating barriers that lead to health inequity. (Figure caption)

Figure 1. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the indigenous population.



Cluster	1	11	13	14	15	16
Total	1062	694	514	1097	3234	224
Health coverage	Partial	Full	Partial	Full	Partial	Private
Joint biomechanical stress	Unspecified	High	Medium	High	High	High
Gender	60.36	63.83	57.39	64.18	65.31	57.14
Age*	37.32 (15.00)	41.10 (21.68)	39.26 (15.52)	45.58 (18.60)	44.68 (17.61)	50.40 (17.39)
Formal schooling*	5.10 (3.56)	9.32 (5.52)	4.83 (4.39)	6.11 (4.55)	4.92 (3.74)	5.88 (4.63)
Argentina	82.86	0.00	28.40	0.00	11.87	8.04
Colombia	0.00	0.00	0.00	0.00	0.00	0.00
Ecuador	0.00	84.15	3.11	93.16	5.04	75.45
Mexico	7.72	15.85	19.07	6.84	60.36	16.52
Venezuela	9.42	0.00	49.42	0.00	22.73	0.00
Rheumatic disease (any)	31.83	32.28	29.57	41.66	40.45	47.32
Osteoarthritis	6.21	14.12	7.39	18.87	12.83	23.21
Rheumatoid arthritis	3.01	3.17	2.72	1.73	2.94	2.68
Backpain	19.02	10.66	14.98	18.60	15.34	15.18
RRPS	1.98	4.18	2.53	7.29	2.29	5.36
Musculoskeletal disorders	2.17	4.90	2.72	3.65	8.94	5.36
Fibromyalgia	0.09	3.46	0.58	4.92	1.67	5.80
Others	0.09	0.29	0.78	0.18	0.43	0.45
Historical pain	44.82	40.63	36.19	49.95	52.26	54.91
Non-traumatic pain (7 days)	20.72	7.49	17.32	10.12	27.40	13.84
Physical disability (HAQ-DI)	3.48	12.82	4.28	11.39	3.96	7.14
Diabetes mellitus	5.18	5.04	3.89	5.10	6.77	7.14
High blood pressure	15.35	10.23	7.78	12.94	13.42	17.41
Cardiovascular disease	5.74	1.30	2.72	3.01	3.34	4.02
Smoking	18.74	3.46	16.15	4.19	9.86	7.14
Alcoholism	14.69	10.95	19.84	14.77	23.13	23.66
Anxiety/depression	4.14	39.77	4.09	49.59	22.70	43.75
No comorbidities	42.09	34.44	53.89	27.53	35.44	23.21

RRPS: Rheumatic regional pain syndromes. Health Assessment Questionnaire-Disability Index (HAQ-DI) cut-off point of greater than 0.8.
* Age and formal schooling show mean value (standard deviation)
**Circle size represent amount of individual per cluster for visual comparison. The cluster positions are the result of the network simulation, the position of each cluster is obtained during the simulation depending on the similarity of the individuals.

Figure 1. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the indigenous population. (Title)
RRPS: Rheumatic regional pain syndromes. Health Assessment Questionnaire-Disability Index (HAQ-DI) cut-off point of greater than 0.8.
* Age and formal schooling show mean value (standard deviation)
**Circle size represents the number of individuals per cluster for visual comparison. The cluster positions are the result of the network simulation; the position of each cluster is obtained during the simulation depending on the similarity of the individuals.

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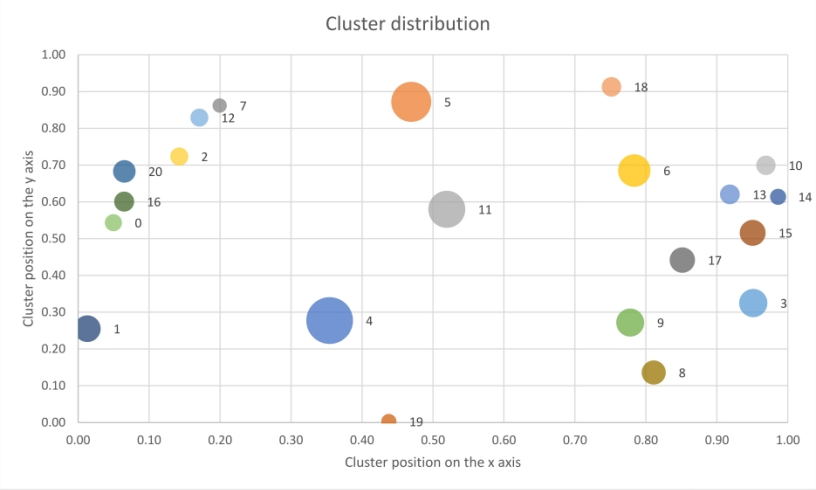
Figure 2. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the non-indigenous population



Cluster	4	7	8	9	10	17
Total	4586	429	1223	1647	789	1353
Health coverage	Partial	Public Full	Partial coverage	Full coverage	Partial coverage	Private
Joint biomechanical stress	Unspecified	High	Medium	High	High	High
Gender	78.28	59.67	78.00	50.27	61.22	87.66
Age*	46.99 (17.78)	40.82 (16.70)	44.45 (17.07)	44.11 (18.83)	41.36 (17.53)	47.33 (17.15)
Formal schooling*	7.78 (4.08)	7.85 (4.29)	7.92 (4.53)	11.38 (5.14)	8.69 (4.65)	7.50 (5.09)
Argentina	0.00	0.00	0.00	0.00	0.00	0.00
Colombia	50.81	0.00	4.17	34.30	0.13	0.00
Ecuador	0.00	0.70	36.96	42.74	0.00	0.00
Mexico	39.77	99.30	58.87	22.95	99.62	100.00
Venezuela	9.42	0.00	0.00	0.00	0.25	0.00
Rheumatic disease (any)	40.49	29.84	42.44	41.89	20.41	13.90
Osteoarthritis	11.32	9.09	7.44	5.59	7.48	4.95
Rheumatoid arthritis	2.46	2.80	1.88	1.82	3.55	4.07
Backpain	6.56	9.09	4.74	3.10	4.94	1.85
RRPS	23.92	2.80	26.17	34.00	1.14	0.89
Musculoskeletal disorders	4.49	5.36	2.04	2.43	2.92	2.00
Fibromyalgia	0.41	1.17	1.88	0.67	0.76	0.07
Others	0.37	0.23	0.25	0.79	0.13	0.30
Historical pain	57.78	20.51	35.32	47.54	23.32	17.44
Non-traumatic pain (7 days)	38.60	28.67	33.69	27.26	23.19	15.08
Physical disability (HAQ-DI)	7.76	15.15	14.23	6.44	13.05	12.34
Diabetes mellitus	8.26	7.93	8.91	6.86	9.38	10.20
High blood pressure	22.68	13.75	19.46	18.40	17.87	20.40
Cardiovascular disease	4.93	3.26	3.92	4.80	3.68	2.14
Smoking	17.84	10.26	16.11	32.54	7.48	0.81
Alcoholism	4.91	6.76	3.19	2.37	4.31	0.59
Anxiety/depression	3.92	7.46	12.43	6.07	9.76	8.50
No comorbidities	38.03	43.36	34.10	38.13	46.01	58.39

RRPS: Rheumatic regional pain syndromes. Health Assessment Questionnaire-Disability Index (HAQ-DI) cut-off point of greater than 0.8.
* Age and formal schooling show mean value (standard deviation)
**Circle size represent amount of individual per cluster for visual comparison. The cluster positions are the result of the network simulation, the position of each cluster is obtained during the simulation depending on the similarity of the individuals.

Figure 2. Network and cluster analysis to describe groups with shared variables according to the syndemic framework in the non-indigenous population. (Title)RRPS: Rheumatic regional pain syndromes. Health Assessment Questionnaire-Disability Index (HAQ-DI) cut-off point of greater than 0.8.* Age and formal schooling show mean value (standard deviation)**Circle size represents the number of individuals per cluster for visual comparison. The cluster positions are the result of the network simulation; the position of each cluster is obtained during the simulation depending on the similarity of the individuals.

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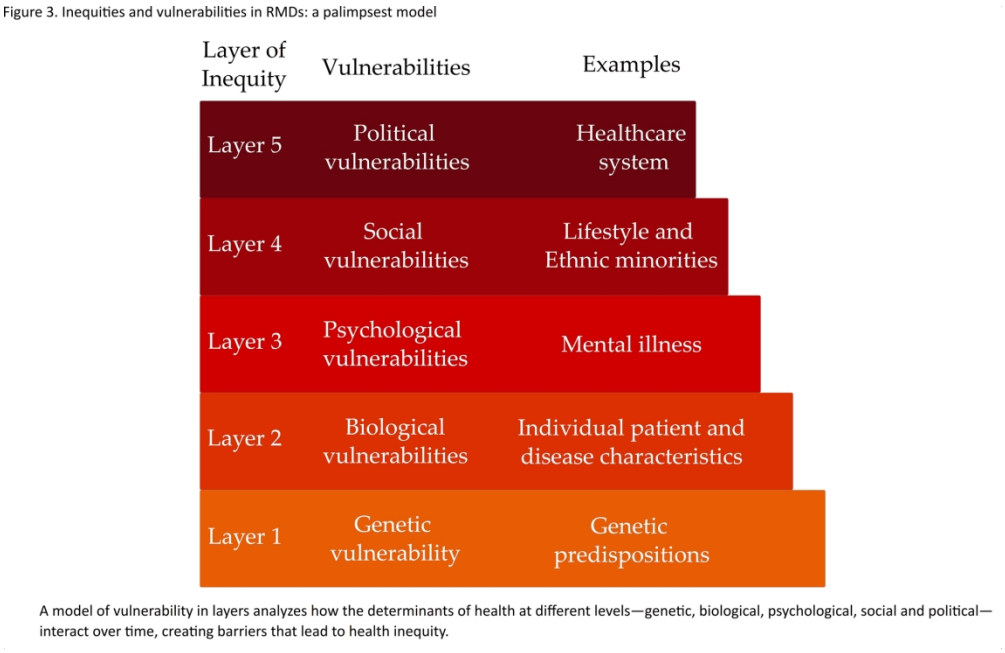

Figure 3. Inequities and vulnerabilities in MDs: a palimpsest model.(Title)
A model of vulnerability in layers analyzes how the determinants of health at different levels- genetic, biological, psychological, social and political-interact over time, creating barriers that lead to health inequity.

177x114mm (300 x 300 DPI)

Supplementary Table. Comparison of sociodemographic characteristics, health coverage, rheumatic diagnosis, pain, disability and comorbidities between indigenous and non-indigenous groups from Ecuador, Mexico and Argentina

	Indigenous n (%) 4599 (50.00)	**Non-indigenous n (%)** 4599 (50.00)	**Totals n (%)** 9198 (100.00)	**p**
Gender (female)	2788 (60.62)	2729 (59.34)	5517 (59.98)	0.217
Age (years), mean (SD)	42.90 (18.71)	42.98 (17.58)	42.94 (18.16)	0.163
Urban setting	832 (18.09)	3624 (78.80)	4456 (48.45)	<0.001
Educational level, mean number of years (SD)	6.74 (5.17)	9.17 (5.15)	7.95 (5.30)	<0.001
Health coverage *				
Full	1351 (29.38)	551 (11.98)	1902 (20.68)	<0.001
Partial	2536 (55.14)	2401 (52.21)	4937 (53.67)	<0.01
Private	245 (5.33)	501 (10.89)	746 (8.11)	<0.001
Other**	171 (3.72)	34 (0.74)	205 (2.23)	<0.001
Joint biomechanical stress ***				
High	2162 (47.01)	1176 (25.57)	3338 (36.29)	<0.001
Medium	534 (11.61)	503 (10.94)	1037 (11.27)	0.323
Low	1472 (32.01)	1574 (34.22)	3046 (33.12)	0.025
Unspecified	254 (5.52)	267 (5.81)	521 (5.66)	0.588
Rheumatic disease				
Totals	1428 (31.05)	1521 (33.07)	2949 (32.06)	0.040
Osteoarthritis	616 (13.39)	334 (7.26)	950 (10.33)	<0.001
Rheumatoid arthritis	104 (2.26)	80 (1.74)	184 (2.00)	0.087
Back pain	521 (11.33)	138 (3.00)	659 (7.16)	<0.001
RRPS	142 (3.09)	895 (19.46)	1037 (11.27)	<0.001
Musculoeskeletical disorders	170 (3.70)	83 (1.80)	253 (2.75)	<0.001
Fibromyalgia	89 (1.94)	50 (1.09)	139 (1.51)	<0.01
Other ****	26 (0.57)	21 (0.46)	47 (0.51)	0.559
Pain				
Historical pain	1839 (39.99)	1487 (32.33)	3326 (36.16)	<0.001
Non-traumatic pain (7 days)	819 (17.81)	1012 (22.00)	1831 (19.91)	<0.001
Physical disability (Health Assessment Questionnaire-Disability Index (HAQ-DI)				
HAQ ≥ 0.8	308 (6.70)	375 (8.15)	683 (7.43)	<0.01
Comorbidities				
Diabetes mellitus	236 (5.13)	326 (7.09)	562 (6.11)	<0.001
High blood pressure	528 (11.48)	855 (18.59)	1383 (15.04)	<0.001
Cardiovascular disease	142 (3.09)	150 (3.26)	292 (3.17)	0.677
Smoking	332 (7.22)	697 (15.16)	1029 (11.19)	<0.001
Alcoholism	643 (13.98)	198 (4.31)	841 (9.14)	<0.001
Anxiety/depression	913 (19.85)	501 (10.89)	1414 (15.37)	<0.001
No comorbidities	2261 (49.16)	1991 (43.29)	4252 (46.23)	<0.001

* Missing data: 296 (6.44%) indigenous and 1112 (24.18%) non-indigenous (total 1408 (15.31%))

** Other: Traditional healthcare

*** Missing data:177 (3.85%) indigenous and 1079 (23.46%) non-indigenous (total 1256 (13.65%))

**** Others: *Indigenous*: 18 ankylosing spondilytis, 4 gout, 1 sclerodermia and 2 psoriasis. *Non-indigenous*: 2 ankylosing spondilytis, 14 gout, and 1 psoriasis.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	6,7
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8,10
Objectives	3	State specific objectives, including any prespecified hypotheses	10
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10,11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not Applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11,12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*12*
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12,13,14
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	Not Applicable
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Not Applicable

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	13

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	Not Applicable
		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	17
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not Applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not Applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	*15-16*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17,18,19
		(*b*) Report category boundaries when continuous variables were categorized	Not Applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	19
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	20,21
Discussion			
Key results	18	Summarise key results with reference to study objectives	21,22,23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	23
Generalisability	21	Discuss the generalisability (external validity) of the study results	24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.