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Prevalence of rheumatoid arthritis in South America: a systematic review and meta-analysis

Prevalência da artrite reumatoide na América do Sul: revisão sistemática e meta-análise

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Abstract *Rheumatoid arthritis (RA) is among the most prevalent chronic autoimmune and inflammatory diseases worldwide. The aim of this study was to establish a pooled estimate of the RA prevalence in South America by means of a meta-analysis of the available epidemiologic studies. Systematic searches in PubMed, Lilacs, SciELO, Scopus, and Web of Science databases (updated May 2019) were done followed by a systematic grey literature search to identify original research articles and reports, published after 2000, providing data of RA prevalence in any South American country. Proportion meta-analysis of weighted pooled was performed, with between-trial heterogeneity assessed by the inconsistency relative index. Sensitivity analyses and sub-group analyses were also done. A total of 25 articles, representing 27 population-based studies were included. Pooled prevalence of RA resulted in 0.48% with 591,981 cases in a population of 114,537,812 individuals (I2=99%). Brazil and Colombia presented the lowest rates of RA prevalence 0.22%, and 0.24%, respectively. RA prevalence in indigenous population was higher 1.45%, and studies using COPCORD method reported also the highest rates 1.07%.*

Key words *Arthritis Rheumatoid, Prevalence, Latin America, Health Services Accessibility, Meta-Analysis as Topic*

Resumo *A artrite reumatóide (AR) está entre as doenças autoimunes e inflamatórias crônicas mais prevalentes no mundo. O objetivo deste estudo foi estabelecer uma estimativa conjunta da prevalência da AR na América do Sul por meio de uma meta-análise dos estudos epidemiológicos disponíveis. Buscas sistemáticas nas bases de dados PubMed, Lilacs, SciELO, Scopus e Web of Science (atualizado em maio de 2019) foram seguidas por uma busca sistemática na literatura cinzenta para identificar artigos e relatórios de pesquisa originais, publicados após 2000, fornecendo dados de prevalência de AR em qualquer país da América do Sul. Foi realizada uma meta-análise da proporção de dados agrupados ponderados, com heterogeneidade entre experimentos avaliada pelo índice relativo de inconsistência. Análises de sensibilidade e de subgrupos também foram realizadas. Foram incluídos um total de 25 artigos, representando 27 estudos de base populacional. A prevalência agrupada de AR resultou em 0,48% com 591.981 casos em uma população de 114.537.812 indivíduos (I2=99%). Brasil e Colômbia apresentaram as menores taxas de prevalência de AR 0,22% e 0,24%, respectivamente. A prevalência da AR na população indígena foi maior 1,45%, e estudos pelo método COPCORD relataram também as maiores taxas 1,07%.*

Palavras-chave *Artrite Reumatoide, Prevalência, América Latina, Acesso aos Serviços de Saúde, Metanálise como Assunto*

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Introduction

Rheumatoid arthritis (RA) is among the most prevalent chronic autoimmune and inflammatory diseases worldwide[1]. When analyzing the 2010 Global Burden of Disease (GBD) initiative, overall estimated prevalence of RA was 0.24%[2]. RA affects the population mainly during their working age, limiting their functional capacity and generating a heavy economic burden for the individual and the community. A meta-analysis published by Dadoun et al.[3] showed that mortality from RA has decreased over the last five decades, increasing the life expectancy of RA patients, but also the complications of the disease. In recent decades, knowledge about the pathophysiology and laboratory and imaging tests for RA have positively evolved, resulting in improvements in RA treatment, outpatient care, and earlier diagnosis[4].

RA is spread worldwide, although regional variations in reported prevalence are significant, with the majority of estimates much higher that the GBD calculations. Although some African studies show a null disease prevalence rate[5], such as the Democratic Republic of Congo, global reported estimates varying from 0.6% to 0.9%[6]. A systematic review published in 2006[7] found a RA prevalence of 0.33% for Southern Europe, 0.50% for Northern European countries, and 0.35% for developing countries outside Africa. In China, these rates are around 0.42%. Although estimates of the global RA prevalence are about 1%, this overall rate may be influenced by the higher prevalence found in US and UK studies[8]. It seems that RA occurrence varies among countries and regions of the world, with higher prevalence in Latin American countries with 1.25%[9], and lower prevalence in Southern European countries[8] and the French Antilles (Martinique)[10]. No studies evaluating the prevalence of RA in South America were found.

Epidemiological data demonstrating regional variations contribute to understanding of how genetic and environmental factors may affect the development of RA in patients. However, the wide variation of the prevalence observed in different studies may also be associated with methodological differences between these studies. It is also important to take into consideration that genetic susceptibility to RA or to disease severity (e.g. presence of extra-articular manifestations, degree of radiographic joint destruction, production of rheumatoid factor) are associated with the histocompatibility antigens of the HLA-DR groups. However, this may vary with race. Caucasians are the most affected by HLA mutations, while Hispanic and African American patients present slightly or no associations with these genes[11]. Additionally, is important to compare data from studies using similar methods based on the same disease identification criteria, to subsequently generate a valid global scenario for RA epidemiology[8].

Further investigations on the epidemiological features of RA are paramount to developing optimal therapeutic guidelines. Thus, considering that RA prevalence may vary among regions worldwide and according to different sources of information, the aim of this study was to establish a pooled estimate of the RA prevalence in South America by means of a meta-analysis of the available epidemiologic studies.

Methods

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane Collaboration recommendations[12,13] so that all steps of screening of titles and abstracts, full-text appraisal, data extraction, and studies' quality assessment were performed by two reviewers independently, with a third author to resolve discrepancies.

Search and study selection

PubMed, Lilacs, SciELO, Scopus, and Web of Science databases were systematically searched (updated May 2019), without restrictions for time-frame or language. A manual search in the reference lists of the included studies was also performed. Additionally, grey literature was searched through a systematic search in google.com.

Studies with original research design were included if they reported the prevalence of RA in any country or region of South America. The following exclusion criteria were applied: 1) studies not considering the prevalence of RA as main outcome; 2) articles published before 2000. In studies published in more than one article assessing prevalence on the same population, only the one with larger population was included.

During the screening phase (title and abstract reading), articles were excluded if considered irrelevant to the study goals. The full-text eligibility phase excluded articles that did not present enough data for the estimation of prevalence, or articles published in non-Roman characters.

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Data extraction and quality assessment

The data extracted from each study included the following: type of study and year of publication; city/country of origin; population (number and ethnicity); definition of RA; data source (Community Oriented Program for the Control of the Rheumatic Diseases (COPCORD) methodology, clinical registries, or capture-recapture method); prevalence and year of estimation.

Although several tools have been developed to assess quality and risk of bias of primary studies, most of them are intended for interventional studies, being those relevant to observational studies generally unspecific or unsatisfactory and not widely used[14,15]. Considering that the validity of prevalence studies is a function of sampling, measurement, and analysis[15] and given the heterogeneity among studies design assessing RA prevalence, we assessed the quality of the included studies using a checklist adapted from Hoy et al.[16] constituted by nine items. Briefly, these nine items refer to: study's target population, sampling frame, random selection of the sample, non-response bias, data collection, case definition, instrument of measurement, mode of data collection, adequate numerator and denominator for the parameter of interest.

Statistical analyses

Proportion meta-analysis of weighted pooled (prevalence of RA) were performed considering both fixed and random-effect methods. Results were reported with a 95% confidence interval (CI). In addition, subgroup analyses considering population (ethnicity), year of publication, country of origin, and data source (clinical registries, COPCORD methodology or capture-recapture method) were performed by using Comprehensive Meta-Analysis (CMA) (Version 2.0, Biostat, Englewood, NJ).

Between-trial heterogeneity was assessed with the inconsistency relative index I2. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (i.e. chance). Values of I2>50% and p-values<0.05 indicates high and significant heterogeneity, that should be further investigated[12]. We also conducted sensitivity analyses to test the robustness of the results and to evaluate the effect of individual studies on heterogeneity. The sensitivity analysis consisted of the hypothetical and sequential removal of one study from the meta-analysis. No study was permanently removed after the sensitivity analysis. Cumulative meta-analyses (sequence of meta-analyses performed adding one study at a time in chronological order) and meta-regression analyses considering time of publication as independent variable were also performed. The logit of the event rates as dependent variable were also performed. All graphs were built in Comprehensive Meta-Analysis (CMA) (Version 2.0, Biostat, Englewood, NJ).

Results

A total of 400 records were retrieved from the databases after duplicates removal. During the screening phase, 37 records were considered for full-text analysis, of which 25 articles, representing 27 population-based studies were included. Twelve articles were excluded after full-text appraisal because: n=4 published before 2000; n=3 not reported data on RA prevalence; n=3 were not an original research (e.g. review, comment); n=1 did not include patients from South America; n=1 included duplicated patients (Figure 1)[11,17-40].

These studies were published between 2001 and 2019 and conducted in Argentina (n=6 studies), Brazil (n=2), Chile (n=1), Colombia (n=7), Ecuador (n=2), Paraguay (n=1), Peru (n=4), and Venezuela (n=4). Seven records (25.0%) evaluated RA in specific ethnicities (e.g. African Colombians, Amerindians, Indigenous). The ACR 1987 revised criteria was used for patient's diagnosis in 12 studies (37.5%), while seven (29.2%) mentioned the ICD-10 for disease classification. Clinical registries were the main data source (54.2% of studies), followed by COPCORD methodology (41.7%) and capture-recapture method (8.3%). The main characteristics of the included studies are presented in Chart 1. The quality assessment showed and overall moderate risk of bias for around 60% of studies. Most of studies (74%) did not present a sampling frame truly or closely representative of the target population. Census or random selection sampling were undertaken in 40% of studies. The numerator and denominator for the calculation of prevalence were properly described in only one third of studies. No significant problems were observed for the domains of parameter of interest measurement and subjects' data collection.

Overall, prevalence of RA was estimated in 0.48% [95%CI 0.38%-0.62%] (with high between-trial heterogeneity: I^2=99%) with 591,981 cases in a population of 114,537,812 individuals (denominator population) (Figure 2). Sensitivity

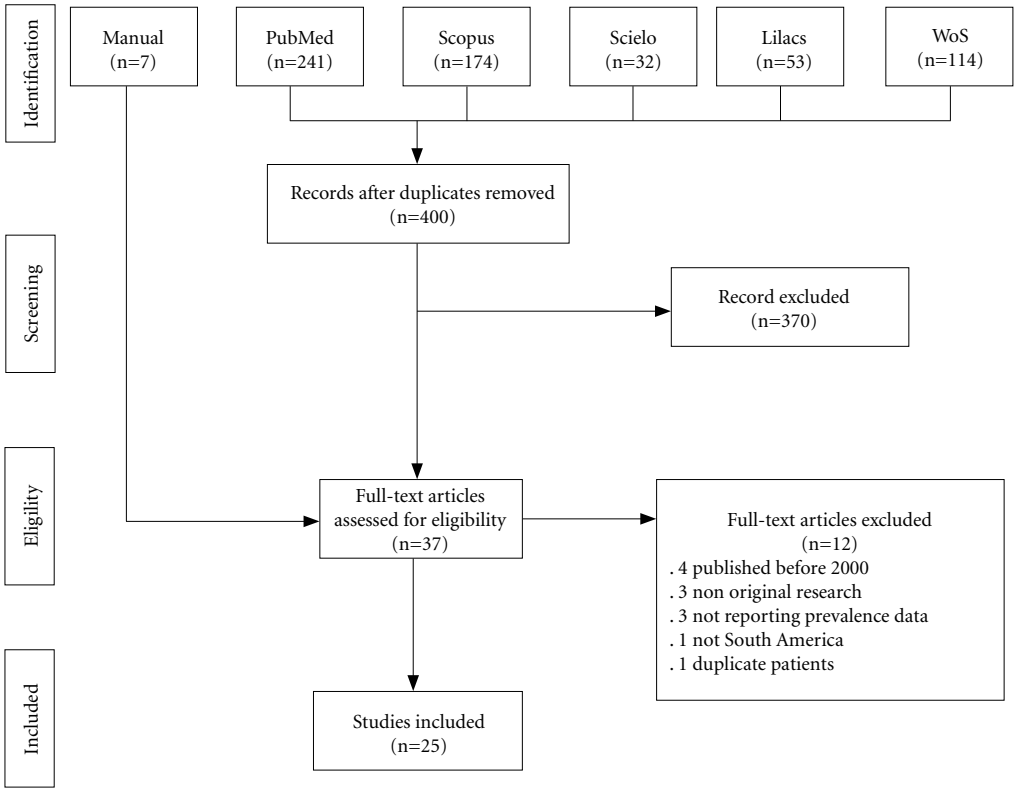

Figure 1. PRISMA flowchart of the systematic review.

Source: Elaborated by the authors.

analyses with the hypothetical removal of trials showed few reductions in the heterogeneity (I^2 values ranging from 86% to 99%) with similar effect sizes. Possible reasons for this heterogeneity may include population characteristics (e.g. race, age), disease features (e.g. duration of RA, diagnostic and classification criteria), sampling, case index definition, study design, and methodology.

The results for subgroup analyses are demonstrated in Table 1. Analyses showed that Brazil and Colombia presented the lowest rates of RA prevalence (0.22% [0.05%-0.91%], I^2=95% and 0.24% [0.15%-0.39%], I^2=99% respectively), while Ecuador followed by Venezuela had the higher rates (0.89% [0.69%-1.16%], I^2=0% and 0.86% [0.41%-1.77%], I^2=83%, respectively). Higher rates of RA prevalence were also obtained for the subgroup of indigenous population (1.45% [0.88%-2.37%]; I^2=85%) when compared to the overall population (0.44% [0.33%-0.58%]; I^2=99%) ($p<0.001$). I^2 values remained high (>80%) even when conducting sensitivity analyses.

Lower rates of RA prevalence were found in studies using clinical registries as data source (0.26% [0.18%-0.37%], I^2=99%) compared to studies using a population-based design like the COPCORD methodology (1.07% [0.74%-1.55%], I^2=90%) ($p<0.001$). Further analyses considering data sources by country (Table 2) confirm these findings. Argentina had an event rate of 0.21% [0.18%-0.25%] (I^2=75%) when using clinical registries as source, compared to an estimate of 2.76% [2.22%-3.34%] (I^2=20%) given by COPCORD. Similarly, the prevalence rates for Peru were of 0.32% [0.31%-0.33%] (I^2=0%) and 0.82% [0.33%-2.01%] (I^2=80%), respectively.

Cumulative analyses and meta-regression of events rates showed an increase in the prevalence of RA over the past years (slope of 0.082;

Chart 1. Baseline characteristics of included studies.

Study	Type of document	Country	Ethnicity	Study period	RA definition	Data source
Caturegli and Caturegli, 2016[30]	Journal article	Peru	Amerindian	2015	-	Clinical registries
Di et al., 2016[27]	Journal article	Argentina	All	2015	2010 ACR/ EULAR criteria	Capture-recapture
Díaz-Rojas et al., 2016[31]	Journal article	Colombia	All	2005	ICD-10	Clinical registries
Fernández-Ávila et al., 2019[40]	Journal article	Colombia	All	2012-2016	ICD-10	Clinical registries
Franco et al., 2016[32]	Journal article	Paraguay	All	2015	ICD-10	Clinical registries
Gamboa et al., 2009[23]	Journal article	Peru	All	2004	ACR 1987 revised criteria	COPCORD*
Granados et al., 2015[25]	Journal article	Venezuela	All	2011	ACR 1987 revised criteria	COPCORD*
Granados et al., 2016[29]	Journal article	Venezuela	Indigenous	-	ACR 1987 revised criteria	COPCORD*
Guevara-Pacheco et al., 2016[28]	Journal article	Ecuador	All	2014	ACR 1987 revised criteria	COPCORD*
Anaya et al., 2001[11]	Journal article	Colombia	African Colombian	1996	ACR 1987 revised criteria	Clinical registries
Londoño et al., 2018[38]	Journal article	Colombia	All	2014	ACR criteria	COPCORD*
Machado-Alba et al., 2015[26]	Journal article	Colombia	All	2009-2013	ICD-10	Clinical registries
Mestanza-Peralta et al., 2006[22]	Conference abstract	Ecuador	All	-	-	COPCORD*
Medina et al., 2006[21]	Conference abstract	Peru	Mestizo	2004	-	Clinical registries
Fabiani Muñoz,2006[20]	Thesis	Chile	All	2004	ICD-10	Clinical registries
Palmezano-Díaz et al., 2018[39]	Journal article	Colombia	All	2012-2016	ICD-10	Clinical registries
Peláez-Ballestas et al., 2018[35]	Journal article	Argentina	Qom	2011-2015	ACR 1987 revised criteria	COPCORD*
		Venezuela	Warao			
			Chaima			
Quintana et al., 2018[36]	Journal article	Argentina	Indigenous	-	ACR 1987 revised criteria	COPCORD*
FCEAC, 2017[33]	Book	Colombia	All	2015-2016	ICD-10	Clinical registries
Scublinsky et al, 2010[24]	Journal article	Argentina	All	2008	ACR 1987 revised criteria	Capture-recapture
Senna et al., 2004[19]	Journal article	Brazil	All	-	ACR 1987 revised criteria	COPCORD*
Soriano et al., 2003[18]	Conference abstract	Argentina	All	2002	ACR 1987 revised criteria	Clinical registries
Spindler et al., 2002[17]	Journal article	Argentina	All	1998-1999	ACR 1987 revised criteria	Clinical registries
Tolentino, 2017[34]	Thesis	Brazil	All	2016	-	Clinical registries
Vega-Hinojosa et al., 2017[37]	Journal article	Peru	All	2010	ACR 1987 revised criteria	COPCORD*

*Population based studies.
Source: Elaborated by the authors.

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Anaya, 2001	0,0002	0,0001	0,0003	-36,9830	0,0000
Spindler, 2002	0,0020	0,0018	0,0021	-163,9665	0,0000
Soriano, 2003	0,0024	0,0020	0,0028	-75,9263	0,0000
Senna, 2004	0,0046	0,0027	0,0078	-20,0661	0,0000
Fabiani Muñoz, 2006	0,0056	0,0029	0,0108	-15,4810	0,0000
Medina, 2006	0,0032	0,0031	0,0033	-300,2985	0,0000
Mestanza-Peralta, 2006	0,0093	0,0055	0,0157	-17,3724	0,0000
Gamboa, 2009	0,0051	0,0027	0,0094	-16,6403	0,0000
Scublinsky, 2010	0,0038	0,0033	0,0044	-79,1264	0,0000
Granados, 2015	0,0043	0,0027	0,0069	-22,4219	0,0000
Machado-Alba, 2015	0,0016	0,0015	0,0017	-237,7529	0,0000
Caturegli, 2016	0,0047	0,0019	0,0111	-11,9708	0,0000
Di, 2016	0,0033	0,0030	0,0036	-120,4942	0,0000
Díaz-Rojas, 2016	0,0090	0,0090	0,0091	-2418,5804	0,0000
Granados, 2016	0,0111	0,0069	0,0177	-18,4234	0,0000
Guevara Pacheco, 2016	0,0088	0,0065	0,0119	-30,8289	0,0000
Franco, 2016	0,0239	0,0222	0,0258	-93,7927	0,0000
Tolentino, 2017	0,0011	0,0008	0,0014	-54,7631	0,0000
FCEAC, 2007	0,0020	0,0020	0,0020	-1621,3653	0,0000
Londoño, 2018	0,0149	0,0123	0,0181	-41,5718	0,0000
Palmezano-Díaz, 2018	0,0010	0,0009	0,0012	-137,8559	0,0000
Peláez-Ballestas, 2018 (a)	0,0242	0,0178	0,0328	-23,1092	0,0000
Peláez-Ballestas, 2018 (b)	0,0051	0,0017	0,0158	-9,0947	0,0000
Peláez-Ballestas, 2018 (c)	0,0188	0,0109	0,0321	-14,1278	0,0000
Quintana, 2018	0,0301	0,0237	0,0382	-27,5631	0,0000
Vega-Hinojosa, 2017	0,0128	0,0076	0,0215	-16,1591	0,0000
Fernández-Ávila, 2019	0,0052	0,0052	0,0052	-2614,8309	0,0000
	0,0048	0,0038	0,0062	-41,8867	0,0000

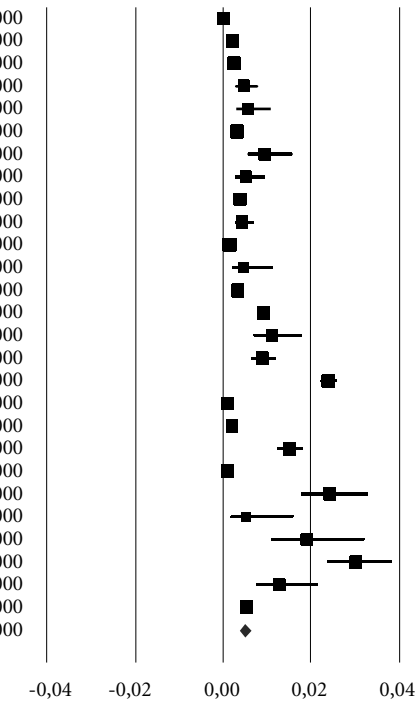

Figure 2. Overall estimates of prevalence of RA in South America.

Note: Event rate with 95% confidence interval (lower and upper limits), random effects model.

Source: Elaborated by the authors.

Table 1. Subgroup analysis of prevalence rates of rheumatoid arthritis in South America.

	Studies (N)	Event rate	95%CI	I2	P-value*
Subgroup by country					
Argentina	6	0.59%	0.32%-1.10%	99%	<0.001
Brazil	2	0.22%	0.05%-0.91%	95%	
Chile**	1	0.56%	0.29%-1.08%	-	
Colombia	7	0.24%	0.15%-0.39%	99%	
Ecuador	2	0.89%	0.69%-1.16%	0%	
Paraguay**	1	2.40%	2.22%-2.58%	-	
Peru	4	0.55%	0.27%-1.11%	89%	
Venezuela	4	0.86%	0.41%-1.77%	83%	
Subgroup by ethnicity					
All population	19	0.44%	0.33%-0.58%	99%	<0.001
African**	1	0.20%	0.10%-0.30%	-	
Indigenous	6	1.45%	0.88%-2.37%	85%	
Mestizo**	1	0.32%	0.31%-0.33%	-	
Subgroup by data source					
Clinical registries	13	0.26%	0.18%-0.37%	99%	<0.001
COPCORD***	12	1.07%	0.74%-1.55%	90%	
Capture-recapture	2	0.35%	0.30%-0.41%	68%	

*Mixed effect analysis; **Potentially misleading association due to the high heterogeneity produced by one study; ***Population-based studies.

Source: Elaborated by the authors.

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Table 2. Subgroup analyses of prevalence rates according to data source by country.

Country	Clinical registries			COPCORD		
	Studies (N)	Event rate [95%CI]	I2	Studies (N)	Event rate [95%CI]	I2
Argentina	2	0.21% [0.18%-0.25%]	75%	2	2.76% [2.22%-3.34%]	20%
Brazil	1*	0.11% [0.08%-0.14%]	-	2	0.46% [0.27%-0.78%]	0%
Chile	1*	0.56% [0.29%-1.08%]	-	-	-	-
Colombia	6	0.18% [0.11%-0.30%]	99%	1*	0.15% [0.12%-0.18%]	-
Ecuador	-	-	-	2	0.89% [0.69%-0.12%]	0%
Paraguay	1*	2.40% [2.22%-2.58%]	-	-	-	-
Peru	2	0.32% [0.31%-0.33%]	0%	2	0.82% [0.33%-2.01%]	80%
Venezuela	-	-	-	4	0.86% [0.41%-1.76%]	83%

*Potentially misleading association due to the high heterogeneity produced by one study.

Source: Elaborated by the authors.

$p<0.001$) as demonstrated in Figure 3. Prevalence varied from around 0.02% to 0.10% between 2001 and 2003, reaching around 0.20% in 2006, to more than 0.30% after 2015.

Discussion

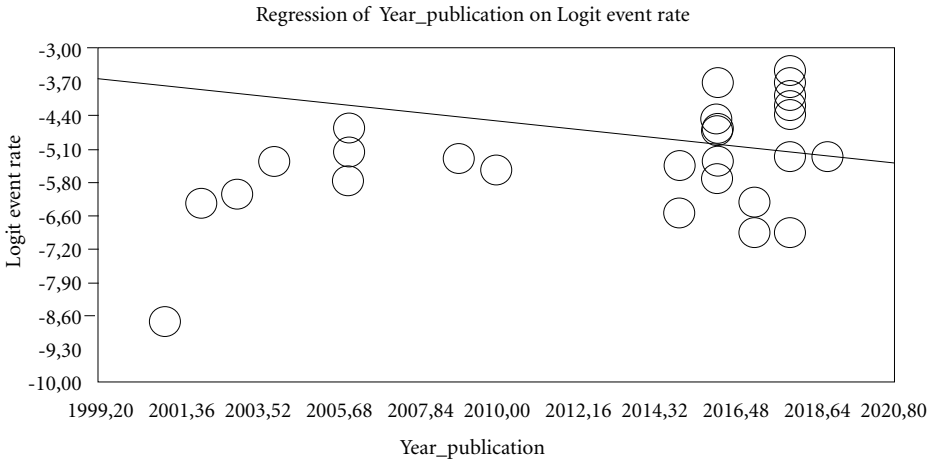
We found a polled RA prevalence in South America of about 0.5%, with country variations ranging from 0.2% to 2.4%. We also found higher prevalence estimates when used a consistent population-based methodology like COPCORD, compared to non-population-based prevalence estimates obtained from registry analyses or capture-recapture method. These estimates are in accordance with the range of estimates in other studies worldwide.

Geographic variations are widely observed in the prevalence rate of RA, possibly due to the combination of behavioral, climatic, environmental, genetic and clinical presentation of the disease. Even, within ethnic groups, the prevalence of RA varies according to geographic area of residence. Prevalence reported for southern European countries range from 0.31% to 0.38%[41]. Additionally, patients in southern Europe, especially in the Mediterranean region, have fewer extra-articular and radiological manifestations, which may be associated with the Mediterranean diet and climatic factors that have protective effects on the development of the disease[42].

The influence of genetic factors on the appearance of RA is evident at individual level, but also at population level. To date, more than 100 genetic loci have been associated with RA, however, the relationship of all these loci to the disease remains to be elucidated[43]. It is known that class II major antigens HLA-DR have been implicated in the pathogenesis of RA and that reidentification of PADI4 was associated with significant risk to RA in Europeans. HLA-DRB1 alleles have been reported in Native Americans, Mexican American ancestry, Colombian population, Chilean population, Peruvian population, Brazilian population and Mexican Mestizo population with a larger proportion of European ancestry[43-45]. Duran et al.[46] observed a national RA prevalence of 0.6% in the Chilean population, which was similar the Spanish prevalence of 0.5% reported by Carmona et al.[47]. Duran et al.[46] supported theses coincident rates on the predominant Spanish ancestry in Chile.

The prevalence of RA does not behave homogeneously in South America, as observed in our meta-analysis ($I^2>90\%$), perhaps because of the heterogeneous ethnic origins of the populations constituting this region (i.e. degree of admixture according to the major ancestry population component). In several countries, indigenous populations have higher RA prevalence, with estimates ranging from 2 to 6 times higher than non-indigenous populations. Indigenous populations from Canada, United States, Australia, and New Zealand presented RA prevalence ranging from 0.7 to 6.8%[48]. The adjusted RA prevalence in the Central Canadian indigenous population is more than double that of the general population[49]. A meta-analysis conducted in Mexico found RA prevalence from 0.28% to 0.7% in the indigenous population[50]. Previous researches show that important phenotypic differences may exist between indigenous and non-indigenous populations with rheumatic diseases. For example, an aboriginal cohort with RA followed at a tertiary

(A)



(B)

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Anaya, 2001	0,0002	0,0001	0,0003	-36,9830	0,0000
Spindler, 2002	0,0006	0,0001	0,0066	-5,9882	0,0000
Soriano, 2003	0,0010	0,0005	0,0020	-18,5471	0,0000
Senna, 2004	0,0014	0,0007	0,0027	-20,0177	0,0000
Fabiani Muñoz, 2006	0,0018	0,0010	0,0032	-20,9878	0,0000
Medina, 2006	0,0020	0,0013	0,0029	-31,5853	0,0000
Mestanza-Peralta, 2006	0,0024	0,0017	0,0035	-32,0255	0,0000
Gamboa, 2009	0,0026	0,0018	0,0037	-33,4208	0,0000
Scublinsky, 2010	0,0027	0,0020	0,0037	-37,7420	0,0000
Granados, 2015	0,0028	0,0021	0,0038	-39,4992	0,0000
Machado-Alba, 2015	0,0027	0,0020	0,0036	-39,8396	0,0000
Caturegli, 2016	0,0028	0,0021	0,0036	-40,7208	0,0000
Di, 2016	0,0028	0,0022	0,0036	-44,6775	0,0000
Díaz-Rojas, 2016	0,0031	0,0019	0,0052	-22,4569	0,0000
Granados, 2016	0,0034	0,0021	0,0055	-22,9306	0,0000
Guevara Pacheco, 2016	0,0036	0,0023	0,0058	-23,5315	0,0000
Franco, 2016	0,0041	0,0026	0,0064	-24,2432	0,0000
Tolentino, 2017	0,0038	0,0025	0,0058	-25,1099	0,0000
FCEAC, 2007	0,0037	0,0023	0,0059	-22,8258	0,0000
Londoño, 2018	0,0039	0,0025	0,0063	-23,1398	0,0000
Palmezano-Díaz, 2018	0,0037	0,0023	0,0058	-23,9531	0,0000
Peláez-Ballestas, 2018 (a)	0,0040	0,0026	0,0063	-24,1405	0,0000
Peláez-Ballestas, 2018 (b)	0,0041	0,0026	0,0063	-24,5338	0,0000
Peláez-Ballestas, 2018 (c)	0,0043	0,0028	0,0066	-24,7622	0,0000
Quintana, 2018	0,0047	0,0031	0,0071	-24,9078	0,0000
Vega-Hinojosa, 2017	0,0049	0,0032	0,0073	-25,2113	0,0000
Fernández-Ávila, 2019	0,0048	0,0038	0,0062	-41,8867	0,0000
	0,0048	0,0038	0,0062	-41,8867	0,0000

Figure 3. Meta-regression (A) and cumulative meta-analysis (B) of prevalence of rheumatoid arthritis by study's year of publication.

Note: Each line represents the pooled effect size of a meta-analysis containing all the previous studies.

Source: Elaborated by the authors.

care center in Canada was more frequently seropositive and had worse HAQ (Health assessment questionnaire) scores than Caucasian patients. American Indian and Alaska Native populations with RA also present more extra-articular manifestations, erosive disease and more severe radiographic findings, which are associated with a high frequency of HLA-B27 gene and subtype HLA-DRB1*1402. Additionally, indigenous population share similarities in difficulties in access to healthcare coverage, which may influence clinical outcomes[35,51,52].

Conversely, several studies showed that the frequencies of genetic alleles that increase RA susceptibility are more prevalent in Caucasians than in Africans. Other studies demonstrated that several polymorphisms associated with RA were almost undetectable in West and Central Africa[53,54]. RA is poorly reported in black Africans in West and Central Africa and its prevalence is still unknown or based in very old studies. One study in South Africa[55] that investigated rural population showed a prevalence of RA of 0.0026%. Another study in a rural population of Nigeria[5] found a zero prevalence of the disease. After the redefinition of diagnostic criteria of RA that identify patients with RA at an early stage of the disease, these old studies may not be useful any more[56].

When reliable, prevalence estimates are a good way to describe the burden of RA in a specific population[57]. In our meta-analysis we found different methods to obtain data for calculating prevalence of RA. Registries, such as clinical records and health insurance databases, are data sources that contain a large amount of real-world data collected for a population over a period of time. Apart from the potential inaccuracies originated by poor recording practices, registries may produce biased information due to sub-diagnose or insufficient coverage of care plans. But reliability of registries is especially affected by their dependence on the stability of the definition of RA cases through the time[56].

Capture-recapture is usually presented as a quick and inexpensive method that allows correct prevalence estimates, even if data come from incomplete sources. However, this method should be carefully used, especially in populations with very low prevalence rates[58]. Reliability of capture-recapture depends also of counting with diversified health data sources that allow covering different segments of the population[59].

The International League of Associations for Rheumatology together with the World Health Organization launched the Community Oriented Program for Control of Rheumatic Diseases (COPCORD) initiative with the aim of gathering data on pain and disability associated to rheumatic diseases by using low-cost means (http://copcord.org/). In our meta-analysis, the COPCORD studies found higher prevalence than the rest of the epidemiological studies. This is probably because COPCORD method, as any population-based study, overcomes the limitations of registry studies associated to under-estimation due to sub-optimal medical care[60]. In fact, assuming that the actual RA prevalence in South America coincides with the prevalence of RA diagnosed individuals may be completely wrong due to the effect of ignoring potential RA disease under-diagnose. To evaluate the quality of the RA care, further studies should identify the prevalence-diagnose-treatment gap.

Conclusions

Our meta-analysis identifies a pooled prevalence of RA in South America of 0.48%, ranging from 0.22% in Brazil to 2.40% in Paraguay. Indigenous populations presented higher prevalence than any other ethnic group. COPCORD studies (population-based design) obtained a higher and more reliable prevalence estimates than registry data.

Collaborations

J Reis-Pardal, FS Tonin, R Pontarolo, AC Melchiors and F Fernandez-Llimos participated in conceptualization. JL Germano and J Reis-Pardal participated in data curation. JL Germano, J Reis-Pardal and FS Tonin participated in formal analysis and investigation. R Pontarolo was responsible for funding acquisition. J Reis-Pardal, FS Tonin and F Fernandez-Llimos designed the methodology. AC Melchiors and F Fernandez-Llimos participated in project administration and supervision. FS Tonin and F Fernandez-Llimos participated in validation. All the authors participated in writing, review and editing.

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