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M Macias-Islas⁹ and J Correale¹⁰**

Abstract

The incidence and prevalence of multiple sclerosis (MS) varies geographically as shown through extensive epidemiological studies performed mainly in developed countries. Nonetheless, scant data is available in Latin America and the Caribbean (LAC). The objective of this review is to assess epidemiological data of MS in LAC. We conducted a systematic review of published articles and gray literature from January 1995 to May 2011. Twenty-two studies met the inclusion criteria after full-text review. Incidence data were found in only three studies and ranged from 0.3 to 1.9 annual cases per 100,000 person-years. Prevalence was reported in 10 studies and ranged from 0.83 to 21.5 cases per 100,000 inhabitants. The most prevalent subtype of MS was the relapsing–remitting form (48% to 91% of the series). No data about mortality were found. This study showed low frequency for MS in LAC compared with North American and European countries. The role of environmental and genetic factors should be well studied, providing new insights about its etiology.

Keywords

Multiple sclerosis, Latin America, epidemiology, incidence, prevalence

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Introduction

Incidence and prevalence of multiple sclerosis (MS) varies geographically as has been shown in several epidemiological reports mainly from developed countries.^{1–4} In Europe, Canada and the United States, prevalence rates range between 60 and more than 100 cases per 100,000 inhabitants.^{3,4} Data from African and Asian countries suggest prevalence lower than 40/100,000 for those regions.³

Scant data have been published from Latin America and the Caribbean (LAC).^{2,5–9} As epidemiological and clinical characteristics of MS may vary according to environmental and genetic factors, it appears crucial to delineate the characteristics of MS in LAC in order to elucidate the disease pattern in this population of diverse ethnic composition.^{3–10}

The objective of the present study was to perform a systematic review of the epidemiology in the region, including incidence, prevalence, disease subtypes and mortality.

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Material and methods

Search strategy and selection criteria

We conducted a systematic non-language-restricted literature search of LAC MS reports from January 1995 to May 2011, using electronic databases included in Cochrane CENTRAL, MEDLINE, EMBASE and LILACS (Annex 1). In addition, regional databases, the Internet and databases containing regional proceedings of congresses, annals and doctoral theses were searched. We also consulted web sites from main regional medical societies, experts and associations related to the topic. An annotated search strategy for gray literature was included to retrieve information from relevant sources such as regional Ministries of Health, the Pan American Health Organization (PAHO) and reports from hospitals following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic review reporting and meta-analyses (Annex 2)^{11,12} We included cohort, case-control, cross-sectional studies and case-series in which prevalence, incidence, subtype of MS, death and other relevant information about the disease was provided. Only abstracts with full-length articles were included whenever they met all the inclusion criteria in order to assess the research methodology applied. Authors from selected articles were contacted to obtain missing or additional information when needed or in cases of duplicate data. If data were duplicated or data subsets appeared in more than one publication, the study with the largest sample size was used. For disease subtype, we included only those studies published after 1995, when the definition of clinical forms was unified, and with at least 50 cases in order to avoid bias.¹³ Regarding the selected number of 50 cases, we agreed that it was a figure that might avoid the possibility of bias in the selection and reporting of MS disease subtype because it included approximately all the patients of a center or was at least representative of the entire number of patients in a center.

For studies that included other demyelinating diseases (neuromyelitis optica), only MS patients were taken into account. MS was considered only when validated criteria were fulfilled (i.e. definite MS by Poser or McDonald 2001, 2005 or 2010).^{14–17} Outcome measures were: incidence, prevalence, subtype of MS and mortality attributable to MS.

Screening and data abstraction

Two reviewers (MR and JIR) independently pre-screened titles and abstracts of all identified citations, selected potentially eligible studies, assessed full-text and checked inclusion criteria. Any discrepancies were resolved by consensus in both phases. Data were abstracted using a previously piloted electronic chart.

Assessment of risk of bias

Methodological quality used in the reviewed studies and risk of bias was assessed by two reviewers using a modified checklist available in Strengthening the Reporting of Observational studies in Epidemiology¹⁸ (STROBE) and in Fowkes and Fulton.¹⁹ We estimated a bias risk summary considering six criteria: methods for selecting study participants, methods for measuring exposure and outcome variables, methods to control confounding, design-specific sources of bias, comparability among groups and statistical methods and declaration of conflicts of interest (Annex 3). Publication bias was investigated through a funnel-plot in an attempt to investigate the likelihood of overt publication bias.²⁰

Statistical analyses

Proportions meta-analyses were performed with included studies. We applied an arc-sine transformation to stabilize the variance of proportions (Freeman-Tukey variant of the arc-sine square-root of transformed proportions method).^{21,22}

Measure of the overall variation was calculated with the estimate I^2 . In case of moderate or high heterogeneity (I^2 greater than 50%), the source was investigated (subgroup analysis considering country, latitude, quality, population age and study date); results are presented separately. Stats-direct, Comprehensive Meta-Analysis and Stata 9.1 were used for the analysis.

Results

Nine hundred and thirty-nine citations were identified. After reviewing titles and abstracts, 108 studies were considered eligible (Figure 1). After full-text review, 22 met inclusion criteria (18 from MEDLINE and four from a regional database) and were selected for data abstraction, analysis of incidence-prevalence, subtype of MS and mortality (Table 1).^{8,23–43} Information was obtained from nine countries. Three countries contributed more than one study: Brazil (nine studies), Argentina (three studies) and Colombia (three studies) (Table 1). Twenty studies used Poser's criteria,¹⁵ and two used McDonald's diagnostic criteria.^{14,16}

We could not perform a meta-analysis regarding incidence and prevalence as well as subtype of MS reported because of the high heterogeneity found between studies (Annex 4). Analysis of the mortality by MS was not performed because of the lack of enough available information.

Incidence

Only three studies, (French West Indies, Argentina and Panama) evaluated incidence.^{6,24,27} Values ranged from 0.15 to 1.9 annual cases per 100,000 person-year (Table 2).

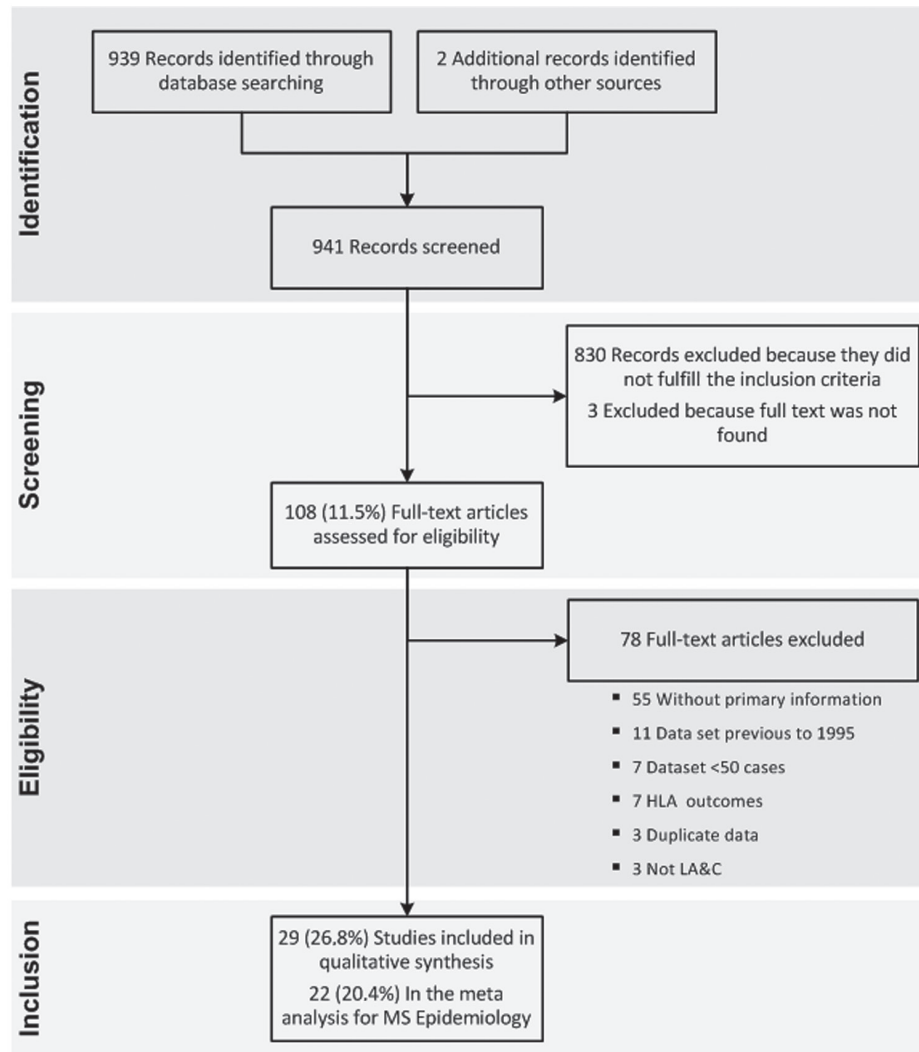


Figure 1. Flow of studies through the systematic review.

Prevalence

Ten studies assessed prevalence in the region (Table 3). Reported prevalence ranged from 0.75 to 21.5 cases per 100,000 inhabitants. A detailed analysis of prevalence data provided by each study is displayed in Figure 2 and Table 3. The reported prevalence was lower in Ecuador, Colombia and Panama (range = 0.75 to 6.5 cases per 100,000 inhabitants) while Brazil and Argentina reported 12 to 21.5 cases per 100,000 inhabitants. A high dispersion was observed in West French Indies populations (eight and 21 cases per 100,000 inhabitants in Guadelupe and Martinique, respectively (Table 3)).

MS subtypes

Fifteen studies described MS subtypes in LAC. The most prevalent subtype was the relapsing–remitting form, ranging from 48% to 91%. (Table 4).

No publication bias was detected in the analysis of outcomes.

Discussion

During the last decade there has been a surge of interest in the epidemiology of MS in LAC, and several investigations began to provide a reasonable estimate of the disease in the region. We found the annual incidence rate reported in three studies (Table 2) ranged from 0.15 to 1.9 cases per 100,000 person-years. Prevalence rates ranged from 0.75 to 21.5 cases per 100,000 inhabitants in 10 studies analyzed (Table 3). Fifteen studies described the subtype of MS in the population evaluated (Table 4). When heterogeneity was investigated by subgroup analysis, latitude as well as countries in which studies were performed explained much of the heterogeneity found.

This study represents the first systematic review of MS burden in LAC, synthesizing data reports from nine

Table 1. Main characteristics of included studies for epidemiological analysis of multiple sclerosis (MS) in Latin America and the Caribbean.

Studies	Design	Country	City	Latitude	Outcomes	Risk of bias
Cabrera-Gomez JA, 1998	Design: case series Setting: ambulatory reference center	Cuba	Santiago de Cuba	23° 17' N	Demographic data (subtypes MS)	High
Cabrera-Gomez JA, 1999	Design: case series Setting: ambulatory reference center	Cuba	Santiago de Cuba	23° 17' N	Demographic data (subtypes MS)	High
Moreira, 2000	Design: cohort study Setting: ambulatory reference center	Brazil	San Pablo	23° 34' S	Demographic data (subtypes MS)	High
Sanchez, 2000	Design: population based cross sectional Setting: ambulatory reference center	Colombia	Risaralda Santander Caldas Antioquia	12° 30' S	Prevalence	Low
Arruda, 2001	Design: case series Setting: ambulatory reference center	Brazil	Curitiba	25° 25' 40" S	Demographic data (subtypes MS)	High
Callegaro, 2001	Design: population based cross sectional Setting: ambulatory reference center	Brazil	San Paulo	23° 24' S	Prevalence	Low
Sanchez, 2001	Design: case series Setting: ambulatory reference center	Colombia	Antioquia	06° 13" N	Demographic data (subtypes MS)	High
Velazquez-Quintana, 2003	Design: case series Setting: ambulatory reference center	Mexico	Mexico DF	19, 26 N	Demographic data (subtypes MS)	High
Ferreira, 2004	Design: cohort study Setting: ambulatory reference center	Brazil	Pernambuco	08° 0' S	Demographic data (subtypes MS)	Medium
Cabre, 2005	Design: population based cross sectional Setting: ambulatory Reference Center	West French Indies	Martinique Guadalupe	14° 30' N	Prevalence-Incidence	Low
Cardoso, 2006	Design: case series Setting: ambulatory reference center	Brazil	Bahia	13°00' S	Demographic data (subtypes MS)	High
Córdova, 2007	Design: case series Setting: ambulatory reference center	Mexico	Mexico DF	19, 26 N	Demographic data (subtypes MS)	High
Fragoso, 2007	Design: population based cross sectional Setting: ambulatory reference center	Brazil	Santos	23° 57' S	Prevalence	Low

Table 1. (Continued)

Studies	Design	Country	City	Latitude	Outcomes	Risk of bias
Toro, 2007	Design: population based cross sectional Setting: ambulatory reference center	Colombia	Bogotá	4° 35' N	Prevalence Demographic data (subtypes MS)	Low
Melcon, 2008	Design: population based cross sectional Setting: ambulatory reference center	Argentina	Patagonia	36° and 55° S	Prevalence	low
Alves-Leon, 2008	Design: cohort study Setting: ambulatory reference center	Brazil	Rio de Janeiro	22° 54' S	Demographic data (subtypes MS)	Medium
Cristiano, 2009	Design: population based cross sectional Setting: ambulatory reference center	Argentina	Buenos Aires	34° S	Prevalence	Low
Finkelsztejn, 2009	Design: cohort study Setting: ambulatory reference center	Brazil	Porto Alegre	20°50' S	Demographic data (subtypes MS)	High
Gracia, 2009	Design: population based cross sectional Setting: ambulatory reference center	Panama	Panama city	7° 12'07"N	Prevalence –Inci- dence	Low
Vizcarra Escobar, 2009	Design: population based cross sectional Setting: ambulatory reference center	Perú	Lima	12° 03' S	Prevalence	Low
Abad, 2010	Design: population based cross sectional Setting: ambulatory reference center	Ecuador	Quito Cuenca Guayaquil	0° 15' S 2° 53'57" S 2° 13' S	Prevalence	Low
Cristiano, 2010	Design: population based cohort study Setting: ambulatory reference center	Argentina	Buenos Aires	34° S	Incidence	Low

countries. Considering the highly sensitive systematic search, including gray literature, it is unlikely that relevant studies were omitted.

Reported prevalence and incidence of MS in the region was substantially lower than previously found in developed countries.^{1,3,4,10} Reasons for these differences are unknown; however, some evidence strongly suggests that certain environmental and genetic factors and their interactions may play a role.^{44,45}

Regarding environmental factors, increased solar exposure and subsequent vitamin D levels have been associated

with a decreased risk of developing MS.^{46,47} This may account for the increased risk observed in areas located at a greater distance from the Equator. It has been proposed that improved hygiene, which partially explains the reduced rate of infections in Western countries, might be a starting point to clarify the increased incidence of allergic and autoimmune diseases in the same population.⁴⁸ Several factors could contribute to the so-called hygiene hypothesis. A striking association was initially described between hay fever and family size and being the first child born to the family or not.⁴⁹ Thus, incidence of atopic diseases or

Table 2. Reported multiple sclerosis (MS) incidence of studies in Latin America and the Caribbean.

Author, year	City, country latitude	Number of persons with MS (numerator)	Population of origin (denominator)	Incidence reported per 100,000 persons year (95% CI)
Cabre, 2005	West French Indies 14° 30' N	47	683,000	1.4 (1–1.8)
Cabre, 2005	Martinique, West French Indies 14° 30' N	35	343,000	1.9 (1.2–2.6)
Cabre, 2005	Guadalupe, West French Indies 14° 30' N	12	340,000	0.6 (0.3–0.9)
Gracia, 2009 (Period 1990–99)	Panama City, Panama 7° 12' 07"	65	3,228,186	0.3 (0.15–0.4)
Gracia, 2009 (Period 2000–2005)	Panama City, Panama 7° 12' 07"	79	3,228,186	0.51 (0.28–0.61)
Cristiano, 2010	Buenos Aires, Argentina 34° S	18	145,000	1.76 (1.1–2.8)

Crohn's disease is higher in first-born children who are not exposed in their infancy to the infections of siblings. This social effect is observed in many areas of LAC and could be a factor involved in the low prevalence of autoimmune diseases observed in the region. In addition, individual and collective hygiene, such as the quality of drinking water and food, as well as vaccinations might also help explain differences in prevalence between LAC and Western Europe and North American countries.

Regarding genetic factors, LAC populations are very heterogeneous, and while Argentina and Uruguay have the largest Caucasian influence, numerous LAC inhabitants are racially constituted by mestizos, a complex admixture of Caucasian and Amerindian peoples.⁵⁰ In this group certain genes appear to emerge as protective factors against MS. Likewise, protection or resistance has also been observed in similar ethnic groups, such as Canadian aboriginals and Japanese cohorts.^{51,52}

Finally, subdiagnosis may contribute to underestimating the MS prevalence found in LAC. This situation occurs in several regions of the world and may be a factor in LAC as well.^{2,53}

It is also worth mentioning and discussing the difference in the frequency of MS found between studies from different latitudes and countries in the LAC region, and even in studies performed in the same country. The number of prevalent cases was not greater than five cases per 100,000 inhabitants around the 0° of latitude (Ecuador, Colombia and Panama). A progressive increase of prevalence was observed in countries far from 0° of latitude (seven cases per 100,000 in Peru, 15 per 100,000 in Brazil, 17 per 100,000 in Argentina and 14.8 in the French West Indies). We also found differences in the annual incidence of MS. The lowest reported was 0.3 annual

cases per 100,000 person-years in Panama and increased away from the Equator (1.4 in the French West Indies and 1.7 annual cases per 100,000 person-years in Buenos Aires).

These findings are in line with a recent study that found a latitudinal prevalence gradient in Latin American countries between Panama and Argentina.⁵⁴ This variation is smaller than that observed for Europe and North America, where a gradient of 1.29 per 100,000 inhabitants per degree latitude was observed,⁵⁵ while in South America, a gradient of 0.33 per 100,000 inhabitants per degree latitude was found.⁵⁴ The observed difference reflects a wider range in prevalence between hemispheres: At higher latitudes, prevalence can exceed 200 per 100,000 in the northern hemisphere⁴ whereas at similar latitudes 20 per 100,000 is barely reached in Latin America.⁵⁴ When interpreting the latitudinal differences in LAC, both genetic and environmental factors once again should be considered. The distribution of population genetics in LAC could account for the observed differences.^{5,54} In Argentina, the population is predominantly Caucasian, whereas in Colombia and Ecuador it is predominately mestizo; and probably this can partially explain the higher risk of MS in the southern part of the continent compared with the central region.^{54,56} Based on the positive correlation described between increasing latitude and increasing MS prevalence,⁵⁷ it is possible to hypothesize a south-north gradient in the southern hemisphere. Epidemiological studies in different Chilean regions (latitudes 56° S to 17° S)⁵⁸ and the Argentinean Patagonia (latitudes 55° S to 36° S)²⁸ failed to demonstrate such a gradient, suggesting that other human factors such as ethnicity play an important role in determining the geographic distribution of MS regardless of the impact of latitude.⁵⁹

Table 3. Main results of studies reporting multiple sclerosis (MS) prevalence in Latin America.

Author, year	City, country latitude	Number of persons with MS (numerator)	Population of origin (denominator)	Prevalence reported per 100,000 inhabitants (95% CI)
Sanchez, 2000 ^a	Risaralda, Colombia 12° 30' N	45	903,924	4.98 (3.52–6.43)
	Santander, Colombia 12° 30' N	48	1,900,121	2.53 (1.81–3.24)
	Caldas, Colombia 12° 30' N	17	1,074,856	1.58 (0.83–2.33)
	Antioquia N, Colombia 12° 30'	75	5,182,839	1.48 (1.12–1.78)
Callegaro, 2001	São Paulo, Brazil 23° 24' S	1483	10,114,632	15(13.9–15.4) ^b
Cabre, 2005	West French Indies 14° 30' N	101	683,000	14.8 (11.9–17.7)
	Martinique, West French Indies 14° 30' N	72	343,000	21 (16.1–25.9)
	Guadalupe, West French Indies 14° 30' N	29	340,000	8.5 (5.4–11.6)
Fragoso, 2007	Santos, Brazil 23° 57' S	65	418,316	15.54(12–19.8) ^b
Toro, 2007	Bogotá, Colombia 4° 35' N	296	6,712,247	4.41 (3.9–4.9)
Melcon, 2008	Patagonia, Argentina 36° and 55° S	72	417,666	17.2 (13.7–21.7) ^b
Cristiano, 2009 ^a	Buenos Aires, Argentina 34° S	1833	12,594,974	17.8 (14–19.8)
Gracia, 2009	Panama City, Panama 7° 12'07" N	193	3,228,186	5.24 (4.49–6.07)
Vizcarra Escobar, 2009	Lima, Perú 12° 03' S	616	8,005,778	7.69 (7.03–8.3)
Abad, 2010	Quito, Ecuador 0° 15' S	103	2,036,260	5.05 (4.03–6.03)
	Cuenca, Ecuador 2° 53' 57" S	50	2,206,213	2.26 (1.62–2.91)
	Guayaquil, Ecuador 2° 13' S	5	666,085	0.75 (0.024–0.175)

CI: confidence interval; ^aStudies used capture-recapture method to estimate global prevalence. Cases included were adjusted cases; ^b95% CI: not reported in the original publication.

Previous studies have shown that the female-to-male sex ratio of MS increases over time when serial cross-sectional comparisons were made.⁶⁰ Unfortunately, data collected in this study do not allow us to analyze this parameter.

In summary, there is still much to be learned about MS epidemiology in LAC. This study provides information on

epidemiological features of MS in the region, including incidence, prevalence and subtype of MS. Future research including other outcomes like economic and social variables related to MS burden, genetic research and also data from patient-reported outcomes will expand the knowledge and contribute to a better management of the disease in the region.

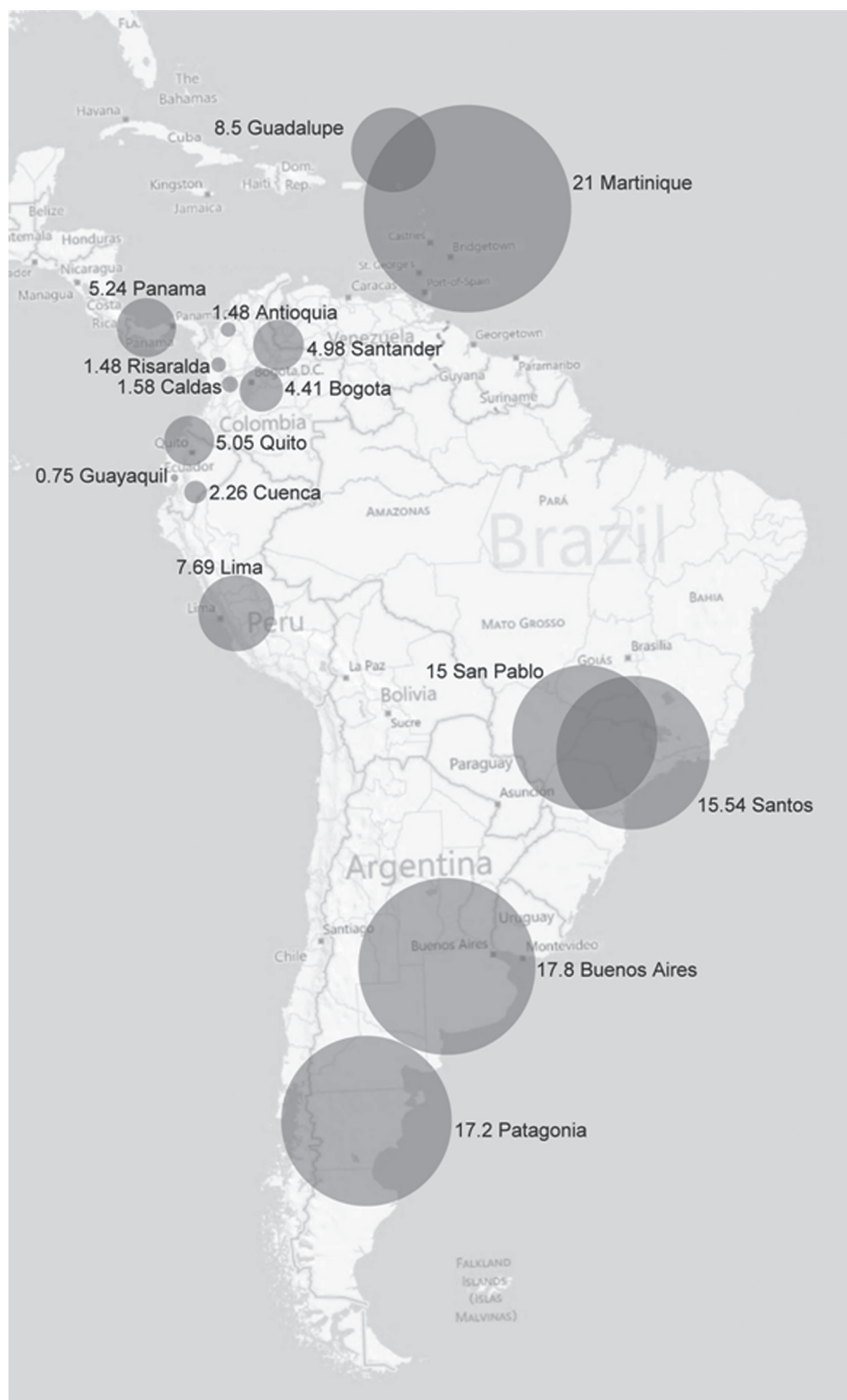


Figure 2. City-region multiple-sclerosis (MS) prevalence reported by 100,000 inhabitants in the studies included in the review.

Table 4. Subtypes of multiple sclerosis (MS) cases in Latin America and the Caribbean.

Studies	City, country	Number of cases reported	Number of RRMS cases	Number of SPMS cases	Number of PPMS cases	Number of PRMS cases
Cabrera-Gomez JA, 1998	Santiago de Cuba, Cuba	55	31 (62%)	7 (13%)	17 (31%)	3 (5%)
Cabrera-Gomez JA, 1999	Santiago de Cuba, Cuba	50	32 (64%)	3 (6%)	8 (16%)	2 (4%)
Moreira, 2000	São Paulo, Brazil	302	217 (72%)	41 (14%)	41 (14%)	—
Sanchez, 2001	Antioquia, Colombia	65	45 (69.5%)	1 (1.5%)	19 (29%)	—
Arruda, 2001	Curitiba, Brazil	200	182 (91%)	2 (1%)	16 (8%)	0
Velazquez-Quintana, 2003	Mexico DF, Mexico	303	145 (48%)	39 (13%)	51 (17%)	48 (16%)
Ferreira, 2004	Pernambuco, Brazil	118	83 (70%)	28 (24%)	7 (6%)	—
Cardoso, 2006	Bahia, Brazil	121	110 (91%)	3 (2%)	7 (6%)	—
Córdova, 2007	Mexico DF, Mexico	312	197 (63%)	87 (27%)	28 (10%)	—
Toro, 2007	Bogotá, Colombia	296	224 (76%)	19 (16%)	9 (3%)	4 (1%)
Alves-Leon, 2008	Rio de Janeiro, Brazil	122	106 (86.8%)	21 (17.2%)	16 (13.1)	0
Finkelsztejn, 2009	Porto Alegre, Brazil	67	55 (82%)	7 (10%)	5 (8%)	—
Abad, 2010	Quito, Ecuador	94	62 (66%)	20 (21%)	7 (8%)	5 (5%)
Abad, 2010	Guayaquil, Ecuador	45	38 (84%)	5 (11%)	—	2 (5%)
Abad, 2010	Cuenca, Ecuador	4	2 (50%)	2 (50%)	—	—

RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary–progressive MS; PPMS: primary–progressive MS; PRMS: progressive–relapsing MS.

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Conflicts of interest

EC has received honoraria, and travel expenses for speaking, consultancy and board activities from Bayer, Biogen Idec, Merck and Novartis.

JIR has received honoraria in concept of scientific advisor from Novartis Argentina, and grants to assist to international congress from Novartis Argentina and Merck Serono Argentina.

MR has received honoraria in concept of scientific work from Novartis Latinoamérica & Canada.

NF is working at Novartis Regional Office as a Medical Director for Neuroscience for Latinoamérica & Canada.

GM is working at Novartis as Director for Health Economics and Outcomes Research, Latinoamérica & Canada.

DC The Author declares that there is no conflict of interest.

TC The Author declares that there is no conflict of interest.

JF The Author declares that there is no conflict of interest.

FG The Author declares that there is no conflict of interest.

MMI The Author declares that there is no conflict of interest.

DHG has received honoraria in concept of scientific work from Novartis Latinoamérica & Canada.

JC is a board member of Merck-Serono Argentina, Novartis Argentina, Biogen-Idec LATAm, and Merck Serono LATAM. Dr

Correale has received reimbursement for developing educational presentations for Merck-Serono Argentina y LATAM, Biogen–Idec Argentina, and TEVA-Tuteur Argentina as well as professional travel accommodations stipends.

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Annex 1: Search strategy and inclusion/exclusion criteria

Search Strategy for Medline

- **MEDLINE**
- **(Multiple sclerosis [Mesh] OR Multiple*[tiab]) AND (sclerosis [Mesh]) AND**
(Americas[MeSH Terms:noexp] OR America*[all] OR Latin America[Mesh] OR
Latin America*[all] OR Latinamerica*[all] OR Latinoamerica*[all] OR Latin*[all]
OR Hispanic Americans[Mesh] OR Hispanic America*[all] OR
Hispanoamerica*[all] OR Hispano*[all] OR Hispanic*[all] OR Iberoamerica*[all]
OR Ibero Americ*[all] OR Panamerican*[all] OR Central America[Mesh] OR
Central America*[all] OR Centroamerica*[all] OR Mesoamerica*[all] OR Meso
America*[all] OR Middle America*[all] OR South America[Mesh] OR South
America*[all] OR Southamerica*[all] OR Sudamerica*[all] OR America del
sur[all] OR Caribbean Region[Mesh] OR Caribbean[all] OR Caribe*[all] OR
West Indies[Mesh] OR West Indi*[all] OR Antill*[all] OR American Native
Continental Ancestry Group[Mesh] OR Amerindian*[all] OR Indians[all] OR
American Indian*[all] OR Native America*[all] OR Patagoni*[all] OR Andes[all]
OR Andean*[all] OR Amazon*[all] OR Argentina[Mesh] OR Argentin*[ad] OR
Argentin*[all] OR Argentina[pl] OR Bolivia[Mesh] OR Bolivia*[ad] OR
Bolivia*[all] OR Bolivia[pl] OR Brazil[Mesh] OR Brazil*[ad] OR Brasil*[ad] OR
Brazil*[all] OR Brasil*[all] OR Brazil[pl] OR Colombia[Mesh] OR Colombia*[ad]
OR Colombia*[all] OR Colombia[pl] OR Chile[Mesh] OR Chile*[ad] OR
Chile*[all] OR Chile[pl] OR Ecuador[Mesh] OR Ecuador*[ad] OR Ecuador*[ad]
OR Ecuador*[all] OR Ecuador[pl] OR French Guiana[Mesh] OR Guiana*[ad]
OR Guiana*[all] OR French Guiana[pl] OR Guyana[Mesh] OR Guyan*[ad] OR
Guyan*[all] OR Guyana[pl] OR Paraguay[Mesh] OR Paraguay*[ad] OR
Paraguay*[all] OR Paraguay[pl] OR Peru[Mesh] OR Peru*[ad] OR Peru*[all]
OR Peru[pl] OR Suriname[Mesh] OR Surinam*[ad] OR Surinam*[all] OR
Suriname[pl] OR Uruguay[Mesh] OR Uruguay*[ad] OR Uruguay*[all] OR
Uruguay[pl] OR Venezuela[Mesh] OR Venez*[ad] OR Venez*[all] OR
Venezuela[pl] OR Belize[Mesh] OR Belize*[ad] OR Belize*[all] OR Belize[pl]
OR Costa Rica[Mesh] OR Costa Ric*[ad] OR Costarric*[ad] OR Costaric*[ad]
OR Costa Ric*[all] OR Costarric*[all] OR Costaric*[all] Costa Rica[pl] OR El
Salvador[Mesh] OR Salvador*[ad] OR Salvador*[all] OR El Salvador[pl] OR

Guatemala[Mesh] OR Guatemal*[ad] OR Guatemal*[all] OR Guatemala[pl] OR Honduras[Mesh] OR Hondur*[ad] OR Hondur*[all] OR Honduras[pl] OR Nicaragua[Mesh] OR Nicaragu*[ad] OR Nicaragu*[all] OR Nicaragua[pl] OR Panama[Mesh] OR Panam*[ad] OR Panam*[all] OR Panama[pl] OR Mexico[Mesh] OR Mexic*[ad] OR Mexic*[all] OR Mejjc*[all] OR Mexico[pl] OR Cuba[Mesh] OR Cuba*[ad] OR Cuba*[all] OR Cuba[pl] OR Dominican Republic[Mesh] OR Dominic*[ad] OR Dominic*[all] OR Dominican Republic[pl] OR Haiti[Mesh] OR Haiti*[ad] OR Haiti*[all] OR Haiti[pl] OR Jamaica[Mesh] OR Jamaic*[ad] OR Jamaic*[all] OR Jamaica[pl] OR Puerto Rico[Mesh] OR Puerto Ric*[all] OR Puertorric*[all] OR Puertoric*[all])

Inclusion criteria

- Cohort studies, case-control studies, cross-sectional studies, and case-series in which data addressing prevalence, incidence, subtype of MS, death and other relevant information about this disease in Latin America is provided.
- Randomized controlled trials and quasi randomized controlled trials if they provide epidemiological data for Latin American patients.
- Studies in which MS was defined by validated criteria for MS(definite MS by Poser or McDonald 2001, 2005 or 2010).
- For prevalence, incidence and mortality, only studies performed after 1995 were included.
- For disease subtypes, only studies performed after 1995 and with at least 50 cases were included.

Exclusion criteria

- Studies performed in countries outside Latin America
- Studies that did not provide information regarding the epidemiological outcomes defined.

- Studies in which MS was defined by unclear criteria or by different criteria than those stated in the inclusion criteria.
- Studies performed before 1995.
- Studies with less than 50 cases for MS subtype.
- Studies without a full manuscript so as to evaluate methodological quality.

Annex 2. Checklist PRISMA

Section/Topic		Checklist Item	Reported on Page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate if a review	Protocol is not

		protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	registered, because is not an interventional systematic review.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5 Annex 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5 Annex 1
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining	Page 6

		and confirming data from investigators.	
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Annex 2. Page 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 8 9 Table 2 and 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	Page 8.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 1 annex 2.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 7-8

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1 flow chart.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	Table 1. Table 4.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2. Table 3. Table 4.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	We were not able to perform meta-analysis
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies	We were not able to perform meta-analysis
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression)	We were not able to perform meta-analysis
DISCUSSION			
Summary of evidence	24	Summarize the main	Table 2, 3,4. Pages

		findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	8,9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	Page 9,10,11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 9,10,11 -12 ,13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 18

Annex 3. Checklist used for Quality Assessment of Observational Studies.

Domain	Tool item must address	Met domain criteria?#				
		No	Partially	Yes	?	NA
	MAJOR CRITERIA					
*Methods for selecting study participants	The selection procedures (inclusion and exclusion criteria, sources and selection methods) are appropriate to represent the universe of interest? Ideally sampling should be probabilistic (all participants have a known probability of being selected). Did the study use an appropriate sampling method to avoid selection bias. The risk of bias is high in convenience samples or if the technique of sampling or selection of controls is not clear.					
	Is the sample a representative spectrum of the population of interest? Take into account how the study sample is representative of the population of interest (general population, admitted patients, outpatients in a health center, age group, schooled). The risk of bias increases in studies conducted in special populations. In case-control studies, cases should represent all the cases and controls represent the community from which they are drawn. Notice if the specific groups within the sample (level of instruction, employment, origin, etc) are proportionally represented. Assess if the cases and the controls come for the same population and if they come of a consecutive series or if there is any kind of selection involved.					
	Was the sample size estimated? Assess if the estimation has been made for employment, place of residence, level of instruction					
	The subjects who agreed to participate and the ones who actually participate affect the extrapolation of results to the population of interest? Analyze differences and similarities between the population of interest and the studied one taking into account the spatial and temporal context (e.g. prevalence of exposition), inclusion criteria, definition and measurement of the exposition and the outcome, confidence on the estimations, etc.					
	<i>Summarizing, an adequate sample, similar to the population of interest minimizes the selection bias</i>					

*Methods for measuring exposure and outcome variables: intervention /exposition, outcome, confounding o modifier variable	The main variables have adequate conceptual (theoretical) and operational (measurement scale classification system, diagnostic criteria, etc.) definitions?					
(In comparative studies the methods for measuring must be the same for both groups)	Clear definition of the cases and the controls. The state of illness of the patients in the cases group has been determined and validated in a reliable way.					
	The instruments used to measure the principal variables have validity and reliability which are known and adequate? Assess if studies which evaluated these instruments are correctly cited. For questionnaires originally designed for a determined culture or language, assess if they have been adapted to where they are going to be used. Evaluate if data was obtained from direct measurements, survey of medical records or self report events. Take into account if inter- and intra- observer variability have been addressed					
	The techniques used to measure the main variables are adequately described? Are appropriate? In case of comparative studies, are the same for both groups? Take into consideration the possibility of recall bias (the cases remember better the expositions than the controls) or interviewer bias. If the interviewer training was necessary, noted if it has been done.					
	Are there co-interventions or co-exposures likely to have biased the results?					
	The results were evaluated blindly or through objective criteria?					
	The follow up was long enough to allow observe the outcomes?					
	Was there quality control of the primary data?					
	Summarizing, the measurement and survey of the principal variables have been made in an appropriate way. The risk of information bias has been minimized					
*Methods for confounders control	Have been taken into account the potential main confounders in the design and analysis of the study? In the design, variables associated with the studied problem should be taken into account; and in the analysis, estimation of the primary outcome should be stratified or adjusted by these variables (multivariate analysis).					

	Notice if raw and adjusted measures have been reported, if the variables by which the results were adjusted are indicated, and if justification of which included (or not) in the analysis. Consider whether there were deviations in the protocol and the reasons of why. Summarizing, all known confounding variables have been gathered and the analysis has been adjusted by them.					
*Comparability among groups. (If there is no comparison between groups, the answer must be “not applicable” in each statement in this category)	Are the source populations of the individuals in each group and the periods of recruitment similar? (sociodemographic variables, prognostic factors or other variables who might alter the results). According to the selection process, both populations have similar characteristics, are comparable throughout except for the study factors (cases and controls definition)?. In cohort studies should assess whether patients were recruited at a similar point in the evolution of the disease.					
	Were the same strategies and measurement techniques used in both groups? Were the same variables measured?					
	The participant losses (missing data, dropouts, emigration, etc) affect the groups in different ways? The differences between groups concerning the losses must be less than 20%. Non-response rate and the reasons of non response are similar. A high non-response rate could be accepted if there is evidence that the groups remain similar. In case-control studies assess if there overmatching has been existed.					
	Summarizing, the groups are comparable; the possibility of selection bias has been minimized.					
MINOR CRITERIA						
Statistical Methods (excluding control of confounding)	The statistical analysis was determined at the onset of the study? (not post-hoc).					
	The statistical tests are appropriate? The allocation unit (community, institution, group, cluster, individuals) and the unit of analysis match? In case of mismatch an adjustment has been made? Are the methods appropriate to any anomalous data distributions (eg skewed, multimodal?) Was there adequate adjustment for any differences in length of follow-up (prospective studies) or time between the intervention and outcome (case-controls)?					

	In the analysis, losses of participants, missing data or other design defects (e.g. different probabilities of selection) were adequately treated? In certain cases the exclusion of cases to allow perform sensitivity analysis would be appropriate. An intention to treat analysis would be suitable for prospective comparative studies. Losses of more than 20% in short follow-up (less than a year) and more than 30% in larger periods should be considered high. In any case losses shouldn't affect the minimum sample size required to perform the statistical analysis.					
	Does reporting address parameter estimate uncertainty (ie with SEs or CIs)?					
	Was there a dose-response relationship between the intervention/exposition and the outcome shown?					
	Summarizing, the analysis is appropriate.					
Conflict of interest	Summarizing, the conflict of interest does not condition the results or the conclusions of the study.					

DOMAIN VALUATION (must consider only the applicable items)

N (No)

P (Partially)

Y (Yes),

U (Unclear accomplishment of domain criteria because there is no enough information to assess) should be considered N for major criteria and P for minor criteria.

NA (Not Applicable because of the design)

OVERALL RISK OF BIAS ASSESSMENT		
Quality		
Very Low	Very High	Selection Bias (first major criteria)= N and Information Bias (second major criteria)= N/P/U OR Selection Bias = N/P/U and Information Bias= N
Low	High	3 major criteria= N and one major=Y 2 major criteria= U 1 major criteria = P + 1 major criteria =U
Moderate	Moderate	Both 2 major criteria =Y + at least 1 minor criteria=N 1 major criteria =Yes + 1 major criteria =U/P 1 major criteria =Yes + 2 minor criteria =U/P At least 2 major criteria P 2 major criteria =Y + 2 minor criteria= U/P
High	Low	All the major criteria= Y + ≤1 minor criteria= P o U + No minor criteria=N

In case there were items qualified as **NA (Not Applicable)** because of the design) and the criteria for any risk of bias were not met, the summary risk of bias will be decided on the basis of the available criteria.

1 criteria P between two Applicable majors = **M (Moderate risk of bias)**

E.g. 3 criteria applicable P, Y, P = **M (Moderate risk of bias)**

E.g. 3 criteria applicable Y, P, Y = **M (Moderate risk of bias)**

If the selection is P, Y, Y = **M (Moderate risk of bias)**

E.g. 2 criteria applicable P, Y = **M (Moderate risk of bias)**

If none major criteria are applicable the study has a risk of bias Not Applicable.