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Incidence and Prevalence of Multiple Sclerosis in the Americas: A Systematic Review

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Key Words
Incidence · Prevalence · Multiple sclerosis · Systematic review

Abstract
Background: The incidence and prevalence of multiple sclerosis (MS) varies considerably around the world. No previous study has performed a comprehensive review examining the incidence and prevalence of MS across the Americas. The purpose of this study was to systematically review and assess the quality of studies estimating the incidence and/or prevalence of MS in North, Central and South American regions. ***Methods:*** A comprehensive literature search was performed using MEDLINE and EMBASE from January 1985 to January 2011. Search terms included 'multiple sclerosis', 'incidence', 'prevalence' and 'epidemiology'. Only full-text articles published in English or French were included. Study quality was assessed using an assessment tool based on recognized guidelines and designed specifically for this study. ***Results:*** A total of 3,925 studies were initially identified, with 31 meeting the inclusion criteria. The majority of studies examined North American regions (n = 25). Heterogeneity was high among all studies, even when stratified by country. Only half of the studies reported standardized rates, making comparisons difficult. Quality scores ranged from 3/8 to 8/8. ***Conclusion:*** This review highlights the gaps that still exist in the epidemiological knowledge of MS in the Americas, and the inconsistencies in methodologies and quality among the published studies. There is a need for future studies of MS prevalence and incidence to include uniform case definitions, employ comparable methods of ascertainment, report standardized results, and be performed on a national level. Other factors such as sex distribution, ethnic make-up and population lifestyle habits should also be considered.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, and is the most common cause of nontraumatic disability in young adults [1, 2]. MS is a highly variable and unpredictable disease that places a considerable burden on patients and their families, health care systems and societies [3].

Although the cause of MS remains unknown, it is believed to be associated with genetic factors and environmental exposures [4]. Studies examining the epidemiology of MS have been conducted over many decades, and it is well recognized that there is considerable variability in MS incidence and prevalence worldwide. Unfortunately, the methodology and quality of these studies is varied, and estimates of the frequency of MS are often difficult to evaluate and compare. Obtaining accurate estimates of incidence and prevalence is critical as they represent the most fundamental epidemiological measures of disease, and provide an essential starting point for continued investigation of the etiology of MS. Although variations between studies can make it challenging to conduct a systematic review, these reviews are necessary to identify gaps in knowledge, ascertain the true burden of disease, make regional and temporal comparisons, and direct further research [4].

The purpose of this systematic review was to examine the incidence and prevalence of MS within North, Central and South America, and to systematically and objectively evaluate the quality of all included studies.

Materials and Methods

Selection of Studies

A comprehensive literature search was performed using a search strategy developed by three authors with expertise in neurology, clinical epidemiology and systematic review methodology (N.J., R.A.M., and C.W.) and in consultation with a research librarian experienced in systematic reviews. Both MEDLINE and EMBASE were searched for the terms 'multiple sclerosis', 'incidence', 'prevalence' and 'epidemiology' on February 4, 2011 (see online suppl. appendix I for detailed search strategies; see www.karger.com/doi/10.1159/000342779 for all online suppl. material). Review articles and bibliographies of original studies were also hand searched for potentially relevant studies.

Inclusion and Exclusion Criteria

This review was part of a larger study on the worldwide incidence and prevalence of MS that included all original studies published in English or French between January 1, 1985 and January 31, 2011, and which reported the incidence or prevalence of MS for any region after January 1, 1985. To allow for a manageable examination and discussion, we then further grouped those studies, reporting incidence or prevalence for North, Central and South America. The time limit was chosen because the introduction of magnetic resonance imaging in or around 1985 substantially influenced the diagnosis of MS and is likely to have influenced the reliability of case definitions included in the studies. Only full-text articles reporting original data were included. Papers that presented updates of previously published results were treated as a single study; unique and updated data were abstracted from each of the related papers, but only a single quality assessment was performed. Studies reporting data collected exclusively prior to January 1, 1985 were excluded.

Review Methods

All duplicate records were removed and the remaining abstracts were screened by two reviewers (R.A.M., S.K. or C.W.) independently to assess their eligibility. When eligibility could not be confirmed through abstract review, two of the reviewers screened the full text of the article. Complete copies of the potentially eligible studies were obtained and each study was reviewed independently by two trained reviewers (R.A.M., S.K. or C.E.). Data, which were extracted by one reviewer using a standardized form, included study location, dates of data collection, prevalence day or period, sources for case ascertainment, diagnostic criteria and how cases were assessed, and age of the study population. Crude and standardized (if available) prevalence and incidence values were recorded for all reported regions, subgroups and time periods. Extracted data were verified by a second reviewer.

The two reviewers then independently completed a quality review for each study. Quality was evaluated using an assessment tool designed specifically for this study based on a scoring system suggested by Boyle [5]. Quality scores were determined by answers to 8 key questions (each affirmative answer yielded 1 point): (1) Was the target population clearly described? (2) Were cases ascertained either by survey of the entire population or by probability sampling? (3) Was the response rate >70%? (4) Were the nonresponders clearly described? (5) Was the sample representative of the population? (6) Were data collection methods standardized? (7) Were validated diagnostic criteria for MS used to assess the presence/absence of disease? (8) Were the estimates of prevalence or incidence given with confidence intervals? For studies based solely on health administrative data, the reviewers were asked to mark 'yes' for questions 3, 4, 5 and 6; for studies that used multiple sources of ascertainment, the reviewers were asked to mark 'not applicable' for question 4, and quality was thus scored out of 7. The quality assessment tool also contained 12 subquestions to help the reviewers decide on the main questions; all questions on the form had to be completed for the form to be submitted (see online suppl. appendix II). A score of 8/8 or 7/7 indicated high quality while a score of 1/8 or 1/7 indicated low quality. Conflicts were resolved by consensus, and any unresolved conflicts were decided by a third reviewer. All data abstraction and quality reviews were performed using the web-based DistillerSR program (Evidence Partners, Ottawa, Ont., Canada). Using 'R' software, we examined the I^2 statistic, a statistic describing the proportion of variation in point estimates due to heterogeneity between studies rather than to sampling error; a χ^2 test of homogeneity was performed to determine strength of evidence that heterogeneity was genuine. Given the disparity of the studies (I^2 = 99.9%, Q = 47,922.1, d.f. = 30, $p < 0.0001$), a meta-analysis was not performed.

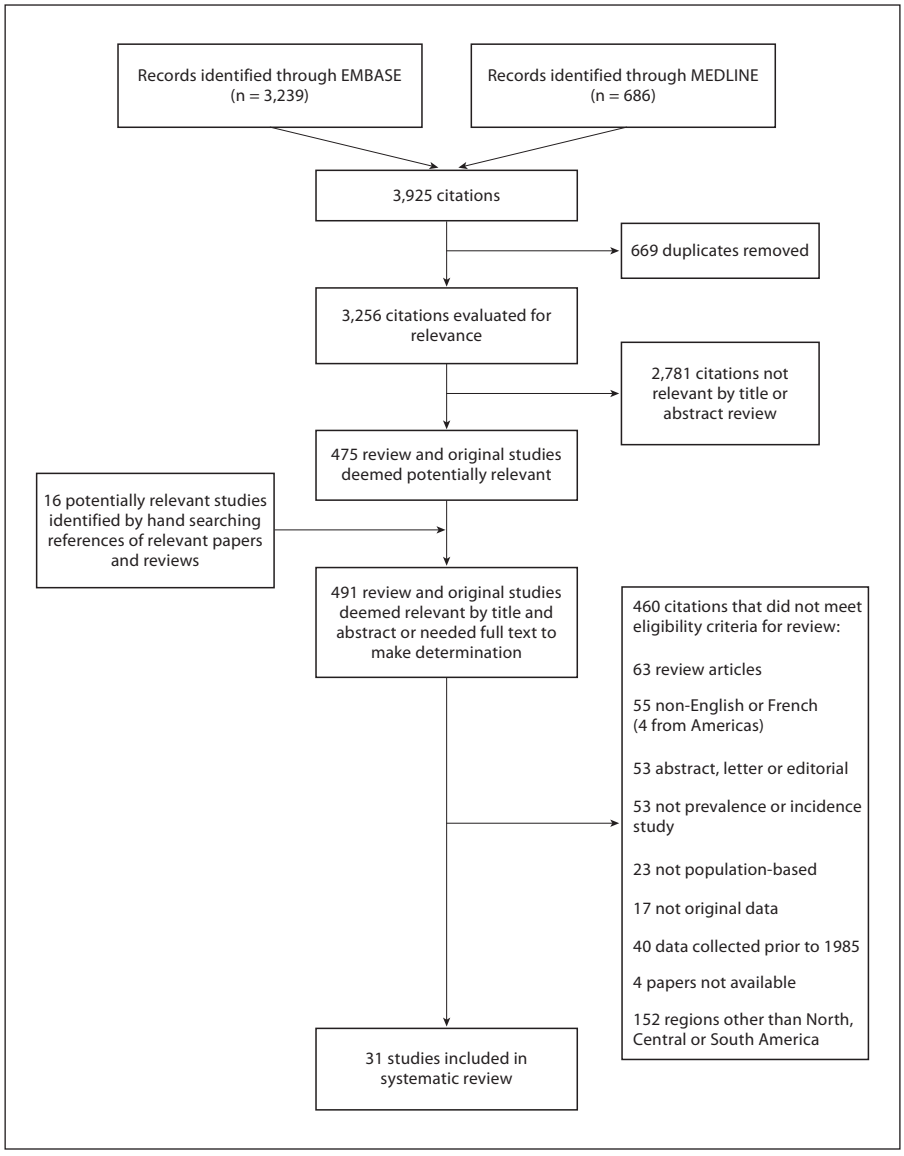

Fig. 1. Flow diagram of study selection.

Results

The initial search resulted in 3,925 citations, with 31 studies from the Americas meeting the inclusion criteria (fig. 1). The studies were published between 1986 and 2010, with the majority published after 2000 (tables 1, 2). Most of these studies (n = 25) examined regions in North America (fig. 2). Prevalence was reported most often, either alone (n = 19), or together with incidence estimates (n = 10). Only 2 studies reported incidence alone. Approximately half of the studies (n = 16) reported standardized rates and almost all (n = 15) were from studies on North American regions. Even when stratified by country, heterogeneity estimates among studies were high ($I^2 > 89.9\%$, $p < 0.0001$) for all regions except for Argentina ($I^2 = 0\%$, $Q = 0.1$, d.f. = 1, $p = 0.7687$) (fig. 3, 4).

Case ascertainment varied across studies, and most identified MS cases from multiple sources. The most common sources were clinics or hospitals (n = 19), neurologists (n = 16), other physicians (n = 14), patient associations (n = 15) and administrative databases (n = 13). Confirmation of MS cases was primarily based on widely accepted diagnostic criteria (n = 26), with the most common being the Poser criteria [6] (n = 18). The remaining studies identified MS cases using definitions based on

Table 1. Prevalence studies of MS, the Americas, January 1985 to January 2011

Study (year)	Region/ subgroup	Prevalence day/ period	Case ascertainment	Diagnostic criteria (established by)	Crude overall prevalence (95% CI) /100,000	Age-standardized overall prevalence (95% CI) /100,000	Crude prevalence (95% CI) /100,000		Standardized prevalence (95% CI) /100,000		Quality score
							males	females	males	females	
North America											
Pryse-Phillips (1986) [10]	CANADA *Newfoundland*	03-31-1985	Hospital/clinic Neurologists Other physicians Patient associations	Modified Schumacher (clinical assessment; chart review)	56.4 (50–63)	–	–	–	–	–	6/7
Warren (1992) [47]	CANADA *Alberta* Barrhead County	01-01-1990	Hospital/clinic Other physicians Nursing home/LTC Patient associations	Poser (clinical assessment; chart review)	196 (118–305)	–	184 (84–349)	207 (99–381)	–	–	5/7
Warren (1993) [48]	CANADA *Alberta* Westlock County	01-01-1991	Hospital/clinic Other physicians Nursing home/LTC Patient associations	Poser (clinical assessment)	200 (127–300)	–	169 (81–311)	232 (123–397)	–	–	6/7
Klein (1994) [49]	CANADA *Alberta* Crowsnest Pass and Cardston	06-21-1989	Hospital/clinic Neurologists Other physicians	Modified Schumacher (clinical assessment, chart review)	217 (121.5–358)	–	–	–	–	–	7/7
Svenson (1994) [34]	CANADA *Alberta*	04-01-1984 to 03-31-1989	Administrative databases	Not specified (administrative data codes)	216.7 (NR)	–	173.1 (NR)	260.3 (NR)	145.3 (NR)	289.9 (NR)	6/8
Mirsattari (2001) [27]	CANADA *Manitoba* Aboriginals	01-01-1970 to 12-31-1996	Hospital/clinic	Poser (clinical assessment; other; imaging tests; CSF; evoked potentials)	40 (NR)	–	–	–	–	–	4/8
Beck (2005) [9]	CANADA (overall)	NR	Canadian Community Health Survey	Not specified (self-report)	240 (210–280)	–	–	–	–	–	5/8
	Quebec				180 (90–260)						
	Atlantic Canada				350 (230–470)						
	Ontario				230 (130–250)						
	Prairies				340 (240–440)						
	British Columbia				240 (160–320)						
Sloka (2005) [50]	CANADA *Newfoundland and Labrador*	12-31-2001	Neurologists Administrative databases	Poser (chart review)	94.4 (90.2–98.7)	–	–	–	–	–	6/7
Svenson (2007) [26]	CANADA *Alberta*	1994–2002	Administrative databases	Not specified (data codes for ≥1 hospitalizations or ≥2 physician visits over previous 10 years)	–	335 (328.5–341.5)	–	–	187.5 (180.6–194.5)	481.5 (470.6–492.4)	7/8
	First Nations					99.9 (78.4–121.4)	–	–	38 (19.5–56.5)	158 (119.7–196.3)	

Table 1 (continued)

Study (year)	Region/ subgroup	Prevalence day/ period	Case ascertainment	Diagnostic criteria (established by)	Crude overall prevalence (95% CI) /100,000	Age-standardized overall prevalence (95% CI) /100,000	Crude prevalence (95% CI) /100,000		Standardized prevalence (95% CI) /100,000		Quality score
							males	females	males	females	
Hader (2007) [11]	CANADA *Saskatchewan* Saskatoon	01-01-2005	Neurologists Other physicians Administrative databases Nursing homes/LTC Patient associations Registry	Poser Allison and Millar Schumacher (chart review)	298 (274.7–323.6)	329 (NR)	–	–	180.7 (NR)	407.1 (NR)	7/7
Warren (2008) [13]	CANADA *Alberta*	1990–2004	Administrative databases	Not specified (administrative data codes for ≥1 hospitalizations or ≥2 physician visits for MS or received diagnosis from a neurologist)	–	357.6 (351.0–364.2)	–	–	–	–	7/8
Marrie (2010) [38]	CANADA *Manitoba*	NR	Administrative databases	International Criteria (2005) (chart review; administrative data codes, questionnaire)	260.9 (NR)	262.4 (253.1–271.7)	–	–	136.6 (126.9–146.3)	386.1 (370.4–401.8)	8/8
Helmick (1989) [51]	USA *Florida* Key West	09-01-1985	Hospital/clinic Neurologists Other physicians Patient associations	Poser (self-report of diagnosis made by health professional)	70.1 (48–99)	63.3 (NR)	–	–	–	–	6/7
Wynn (1990) [35]	USA *Minnesota* Olmstead County	01-01-1985	Centralized diagnostic index at Mayo Clinic and Rochester Epidemiology Program Project	Poser (chart review)	159.8 (113–207)	170.8 (143–198)	79.8 (NR)	231.9 (NR)	–	–	8/8
Hopkins (1991) [52]	USA *Ohio* Gallion, Polk County	NR	Other physicians Patient associations Media campaign	Poser (clinical assessment; chart review)	112 (64–174)	–	–	–	–	–	6/7
Mayr (2003) [14]	USA *Minnesota* Olmstead County	12-01-2000	Centralized diagnostic index at Mayo Clinic and Rochester Epidemiology Program Project	Poser (chart review)	176.6	191.2 (165.6–216.8)	111.2 (NR)	239.1 (NR)	–	–	7/8
Neuberg (2004) [53][b]	USA *Missouri* Sugar Creek and Independence	01-01-1998 to 12-31-2001	Hospital/clinic Neurologists Administrative databases Nursing homes/LTC Death certificate	Poser (chart review)	115 (94–139)	113 (93–136)	48 (35–64)	177 (151–206)	–	–	4/7
Cowen (2007) [37]	USA *Illinois* Savanna, Depue, Morrison, Paw Paw, Lewiston	1998–2002	Nursing homes/LTC Patient associations Media campaign Outreach coordinators Local public health departments Town meetings	Poser (chart review; self-report)	166.9 (NR)	–	30.7 (NR)	299.6 (NR)	–	–	4/7

Table 1 (continued)

Study (year)	Region/ subgroup	Prevalence day/ period	Case ascertainment	Diagnostic criteria (established by)	Crude overall prevalence (95% CI) /100,000	Age-standardized overall prevalence (95% CI) /100,000	Crude prevalence (95% CI) /100,000		Standardized prevalence (95% CI) /100,000		Quality score
							males	females	males	females	
Williamson (2007) [25][a]	USA *Texas* 19 counties surrounding Lubbock	01-01-1998 to 12-31-2000	Hospital/clinic Neurologists Other physicians Nursing homes/LTC Patient associations Death certificates Self-report	Poser (chart review)	42.8 (36.8–49.5)	–	16.6 (11.6–23.1)	68.6 (58.0–80.6)	–	–	6/7
	Hispanic				11.2 (6.4–18.2)						
	Non-Hispanic Black				22.1 (8.1–48.1)						
	Non-Hispanic White				56.0 (47.1–66.1)						
	Lubbock County				54.4 (45.5–64.5)						
	18 rural counties				27.4 (20.4–36.4)						
Turabelidze (2008) [54]	USA *Missouri* Jefferson County	01-01-1998 to 12-31-2002	Hospital/clinic Neurologists Other physicians Nursing homes/LTC Patient associations Media campaign Death certificates Self-report	Poser (chart review; administrative data codes)	105 (91–121)	107 (95–119)	41 (29–56)	169 (145–197)	–	–	7/7
Noonan (2010) [15][a, b]	USA *Missouri* Sugar Creek and Independence	01-01-1998 to 12-31-2000	Hospital/clinic Neurologists Nursing homes/LTC Patient associations Death certificates Self-report	Poser (chart review)	87.7 (71.6–106.4)	70.6 (56.9–84.3)	34.5 (21.3–53.2)	136.8 (109.3–169.2)	–	–	6/7
	Ohio Lorain County				112.4 (99.8–125)	86.5 (76.8–96.2)	59.4 (46.4–72.4)	163.4 (142.2184.6)			
Cabre (2001) [55]	MARTINIQUE	12-31-1998	Hospital/clinic Neurologists Other physicians Rehabilitation units	Poser (clinical assessment)	17.4 (13.1–21.7)	10.3 (NR)	24.8 (NR)	–	–	–	6/7
Cabre (2005) [16]	MARTINIQUE	12-31-1999	Hospital/clinic Neurologists Other physicians Administrative databases Physiotherapists	McDonald (2001) (clinical assessment)	21 (16.1–25.9)	19.6 (14.9–24.3)	–	–	–	–	7/7
	GUADELOUPE				8.5 (5.4–11.6)	8.8 (5.7–11.9)					

Table 1 (continued)

Study (year)	Region/ subgroup	Prevalence day/ period	Case ascertainment	Diagnostic criteria (established by)	Crude overall prevalence (95% CI) /100,000	Age-standardized overall prevalence (95% CI) /100,000	Crude prevalence (95% CI) /100,000		Standardized prevalence (95% CI) /100,000		Quality score
							males	females	males	females	
Central and South America											
Callegaro (1992) [56]	BRAZIL São Paulo	07-01-1990	Hospital/clinic Neurologists Patient associations Registry	Poser (chart review)	4.27 (NR)	–	2.89 (NR)	5.59 (NR)	–	–	5/7
Callegaro (2001) [57]	BRAZIL São Paulo	07-01-1997	Hospital/clinic Neurologists Patient associations MRI services	Poser (clinical assessment; chart review)	15.0 (NR)	–	8.5 (NR)	20.1 (NR)	–	–	5/7
Toro (2007) [8]	COLOMBIA Bogota	12-31-2002	Hospital/clinic	McDonald (2001) (chart review)	4.41 (3.9–4.9)	–	2.71 (2.2–3.3)	5.98 (5.2–6.8)	–	–	5/7
Melcon (2008) [17]	ARGENTINA *Argentine Patagonia*	03-01-2002	Hospital/clinic Neurologists Other physicians Patient associations Media campaign Chronic care facilities Lay/family referral	Poser (clinical assessment; chart review)	17.2 (NR)	17.2 (NR)	12.2 (NR)	22.1 (NR)	12.7 (NR)	21.4 (NR)	5/7
Cristiano (2009) [58]	ARGENTINA	07-1996	Hospital/clinic Patient associations	Poser (clinical assessment)	14–19.8 (NR)	–	–	–	–	–	3/7
Gracia (2009) [7]	PANAMA	2000–2005	Hospital/clinic Neurologists Other physicians Administrative databases	McDonald (2001) Poser (clinical assessment; chart review; CSF, imaging tests; evoked potential)	5.24 (4.49–6.07)	–	1.6 (1.07–2.21)	8.94 (7.56–10.5)	–	–	5/7

LTC = Long-term care; NR = not reported; CSF = cerebrospinal fluid.

[a] Results for Texas reported by both Williamson et al. [25] and Noonan et al. [15]. Results only presented under Williamson in the table.

[b] Results for Missouri similarly reported by both Neuberger et al. [53] and Noonan et al. [15] except for a 1-year difference in prevalence period.

Table 2. Incidence studies of MS, the Americas, January 1985 to January 2011

Study (year)	Region/ subgroup	Study interval (type of incidence)	Case ascertainment	Diagnostic criteria (established by)	Crude overall incidence (95% CI) /100,000	Age-standardized overall incidence (95% CI) /100,000	Crude incidence (95% CI) /100,000		Standardized incidence (95% CI) /100,000		Quality score
							males	females	males	females	
North America											
Warren (1992) [47]	CANADA *Alberta* Barrhead County	1980–1989 (mean annual)	Hospital/clinic Other physicians Nursing homes/LTC Patient associations	Poser (clinical assessment; chart review)	4.22 (1.15–10.8)	–	–	–	–	–	5/7
Warren (1993) [48]	CANADA *Alberta* Westlock County	1980–1989 (10-year)	Hospital/clinic Other physicians Nursing homes/LTC Patient associations	Poser (clinical assessment)	7.26 (3.13–14.3)	–	–	–	–	–	6/7
Sloka (2005) [50]	CANADA *Newfoundland and Labrador*	1994–2001 (mean annual)	Neurologists Administrative databases	Poser (chart review)	5.6 (NR)	–	–	–	–	–	6/7
Warren (2007) [12]	CANADA *Alberta* General population	2002 (annual)	Administrative databases	Not specified (administrative data codes)	–	20.6 (18.9–22.2)	–	–	12.7 (10.9–14.6)	32.2 (29.2–35.0)	7/8
	First Nations					7.6 (2.6–12.7)			7.6 (1.2–14.0)	12.7 (4.9–20.4)	
Warren (2008) [13]	CANADA *Alberta*	2004 (annual)	Administrative databases	Not specified (administrative data codes for ≥1 hospitalization or ≥2 physician visits for MS or received MS diagnosis from neurologist)	–	23.9 (22.2–25.6)	–	–	–	–	7/8
Hader (2007) [11]	CANADA *Saskatchewan* Saskatoon	2000–2004 (5-year)	Neurologists Other physicians Administrative databases Nursing homes/LTC Patient associations Registry	Poser Allison and Millar Schumacher (chart review)	8.1	7.9 (7.27–8.59)	4.7 (NR)	11.2 (NR)	–	–	7/7
Marrie (2010) [38]	CANADA *Manitoba*	1998–2006 (annual)	Administrative databases	International Criteria (2005) (chart review; administrative data codes; questionnaire)	–	13.4 (12.7–14.1)	–	–	6.7 (6.03–7.45)	19.8 (18.6–21.1)	8/8
Mayr (2003) [14]	USA *Minnesota* Olmstead County	1985–2000 (annual)	Centralized diagnostic index at Mayo Clinic and Rochester Epidemiology Program Project	Poser (chart review)	7.5 (NR)	7.3 (6.0–8.6)	4.5 (NR)	10.4 (NR)	–	–	7/8
Cabre (2005) [16]	MARTINIQUE	07-01-1999 to 06-01-2002 (mean annual)	Hospital/clinic Neurologists Other physicians Administrative databases Physiotherapists	McDonald (2001) (clinical assessment)	2.0 (1.4–2.6)	1.9 (1.2–2.6)	–	–	–	–	7/7
	GUADELOUPE				0.7 (0.3–1.0)	0.6 (0.3–0.9)					

Table 2 (continued)

Study (year)	Region/ subgroup	Study interval (type of incidence)	Case ascertainment	Diagnostic criteria (established by)	Crude overall incidence (95% CI) /100,000	Age-standardized overall incidence (95% CI) /100,000	Crude incidence (95% CI) /100,000		Standardized incidence (95% CI) /100,000		Quality score
							males	females	males	females	
Cabre (2009) [59]	MARTINIQUE and GUADELOUPE	07-01-1992 to 06-30-2007 (mean annual)	Hospital/clinic Neurologists Other physicians Administrative databases Patient associations Registry	McDonald (2005) (not reported)	1.27 (1.16–1.38)	1.18 (1.01–1.35)	0.51 (0.41–0.61)	1.98 (1.79–2.17)	–	–	5/7
Central and South America											
Melcon (2008) [17]	ARGENTINA *Argentine* Patagonia	NR	Hospital/clinic Neurologists Other physicians Patient associations Media campaigns Chronic care facilities Lay/family referral	Poser (clinical assessment; chart review)	1.4 (NR) (estimate on the basis of prevalence and disease duration)	–	–	–	–	–	5/7
Gracia (2009) [7]	PANAMA	1990–2005 (annual)	Hospital/clinic Neurologists Other physicians Administrative databases	McDonald (2001) Poser (clinical assessment; chart review; CSF; imaging tests; evoked potential)	0.15–0.61 (NR)	–	–	–	–	–	5/7

LTC = Long-term care; NR = not reported; CSF = cerebrospinal fluid.

administrative data codes (n = 4) and self-report (n = 1), only 1 of which verified cases using medical records. For the most part (n = 24), a diagnosis of MS was established either through a clinical assessment performed by a health professional, or a review of medical charts (tables 1, 2).

Quality scores ranged from 3/7 to 8/8; studies examining regions in North America typically scored higher (median score 6, interquartile range: 6, 7) than those studying areas in South or Central America (median score 5, interquartile range: 4.5, 5; table 3). Although quality scores improved over time among the Canadian studies, the same trend in improvement was not seen for the other regions. All included studies clearly described the target population, and except for 2 studies [7, 8], all ascertained MS cases from the entire population or used probability sampling. Samples were generally representative of the population being studied, and standardized data collection was evident in most studies. Lower quality scores were typically the result of incomplete or unclear reporting, especially with respect to response rates.

North America

Canada

Canada was the most studied region for both prevalence and incidence. Prevalence studies have been conducted regularly since the mid-1980s, although most have focused on the western part of the country. Only 1 study was nationwide, and it used self-reported information from a national population health survey conducted in 2000–2001 using a stratified random sample to estimate the crude prevalence of MS to be 240/100,000 (95% confidence interval, CI: 210–280) [9]. However, the small number of respondents who self-reported MS (n = 332) and resultant wide CIs indicate the imprecision of the results. Crude prevalence in individual regions throughout the country ranged from 56.4/100,000 (95% CI: 50–63) in Newfoundland in 1985 [10] to 298/100,000 (95% CI: 274.7–323.6) in Saskatoon, Sask. in 2005 [11]. The highest reported incidence was in Alberta, with an age-standardized incidence of 20.6/100,000 (95% CI: 18.9–22.2) in 2002 [12], and 23.9/100,000 (95% CI: 22.2–25.6) for 2004 [13]. However, this result was based on an administrative (health claims) case definition which was not validated.

United States of America

We identified 9 studies from the USA that estimated MS prevalence; most reported prevalence for eastern regions, leaving much of the country unstudied (fig. 2).

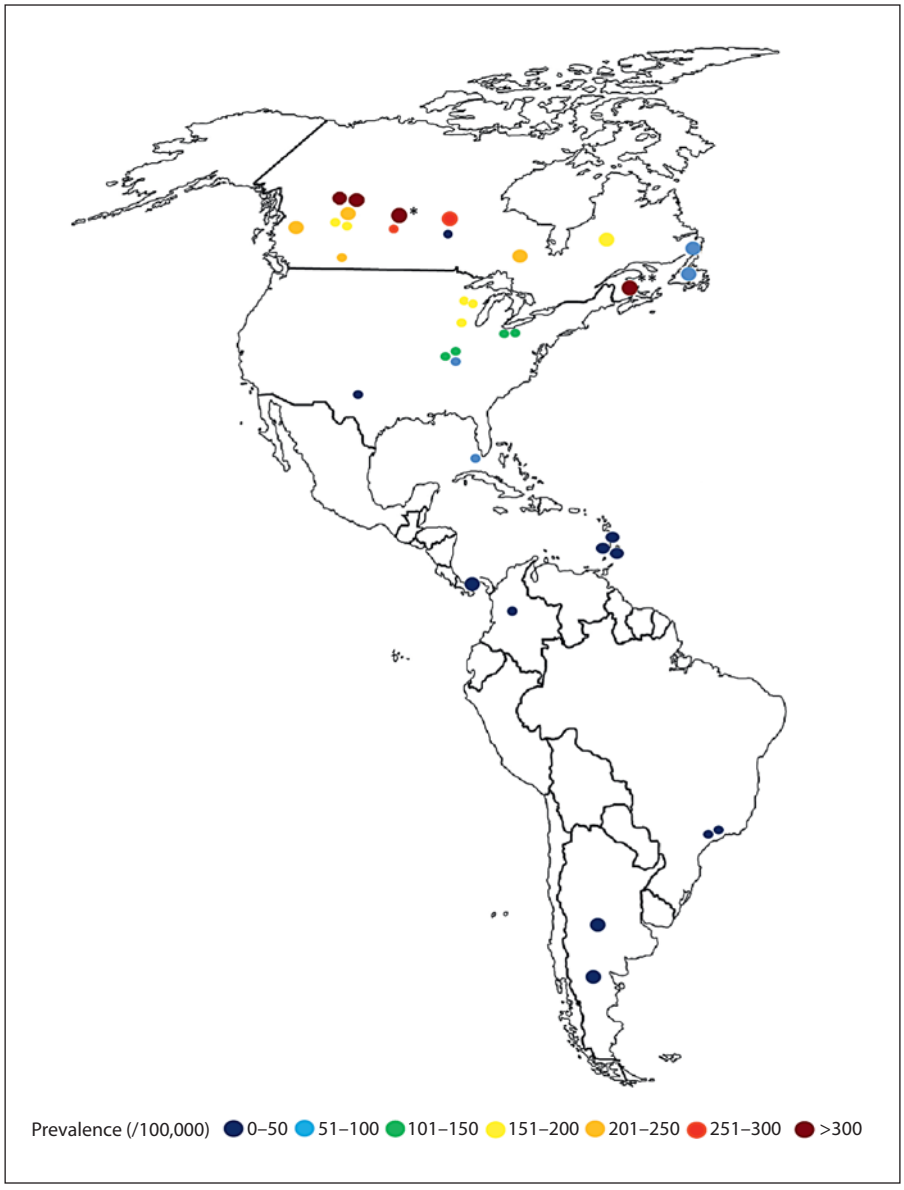

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Fig. 2. Prevalence of MS in the Americas as reported in studies published between 1985 and 2011. Larger circles represent national or provincial/state studies; smaller circles represent county or city studies. * Prairie region; ** Atlantic Canada.

Prevalence was highest in Olmstead County, Minn. (age-standardized 191.2/100,000; 95% CI: 165.6–216.8) [14] and lowest in Lubbock, Tex. and the 19 surrounding counties (age-standardized 39.9/100,000; 95% CI: 34.0–45.7) [15]. Incidence was reported in only 1 American study (Olmstead County, Minn.), with an annual age-standardized rate of 7.3/100,000 (95% CI: 6.0–8.6) from 1985 to 2000 [14].

Martinique and Guadeloupe

Located in the eastern Caribbean Sea, the islands of Martinique and Guadeloupe are part of the French West Indies. Three studies were conducted in this region, with results reported separately for each island. The age-standardized prevalence of MS in Martinique at the end of 1999 was 19.6/100,000 (95% CI: 14.9–24.3) compared to 8.8/100,000 (95% CI: 5.7–11.9) for Guadeloupe [16]. The mean annual incidence from July 1, 1999 to June 1, 2002, was 1.9/100,000 (95% CI: 1.2–2.6) and 0.6/100,000 (95% CI: 0.3–0.9) for Martinique and Guadeloupe, respectively [16].

Central and South America

A total of 6 studies from 4 countries examined MS prevalence and incidence in Central and South America

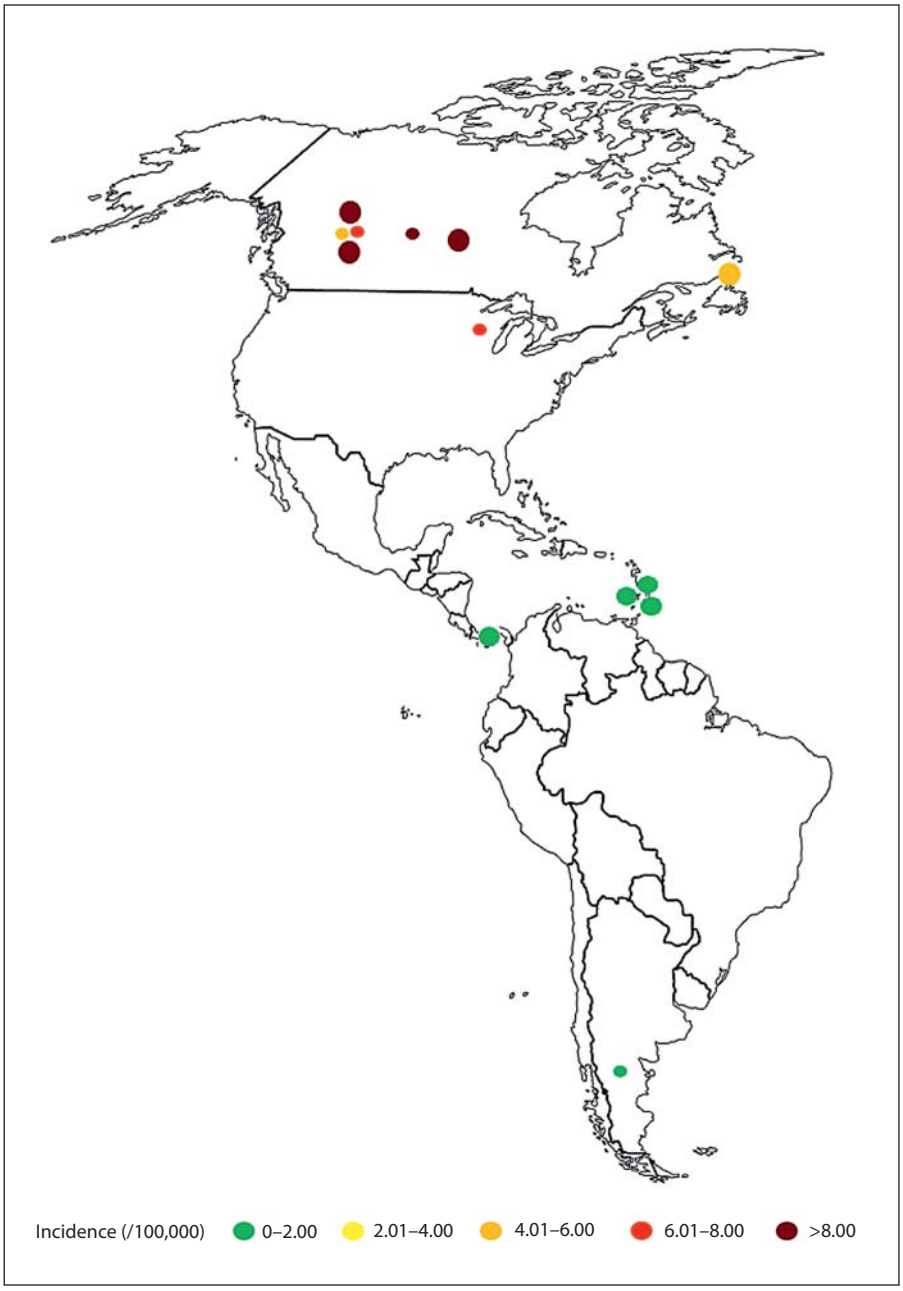

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Fig. 3. Incidence of MS in the Americas as reported in studies published between 1985 and 2011. Larger circles represent national or provincial/state studies; smaller circles represent county or city studies.

(fig. 2). Only 1 study produced estimates for the entire country; the crude prevalence for Panama during 2000–2005 was 5.24/100,000 (95% CI: 4.49–6.07), and the reported annual incidence from 1990 to 2005 was 0.15–0.61/100,000 [7]. Both prevalence and incidence were highest in the Argentine Patagonia region: in 2002 the crude prevalence was 17.2/100,000, with an annual incidence of 1.4/100,000 [17].

Discussion

This systematic review identified 31 studies published between January 1985 and January 2011 that estimated the prevalence and/or incidence of MS in North, Central and South American regions. Only 2 studies estimated prevalence across an entire country (Canada [9] and Panama [7]). All other studies reported results for specific regions, and several reexamined the same geographic ar-

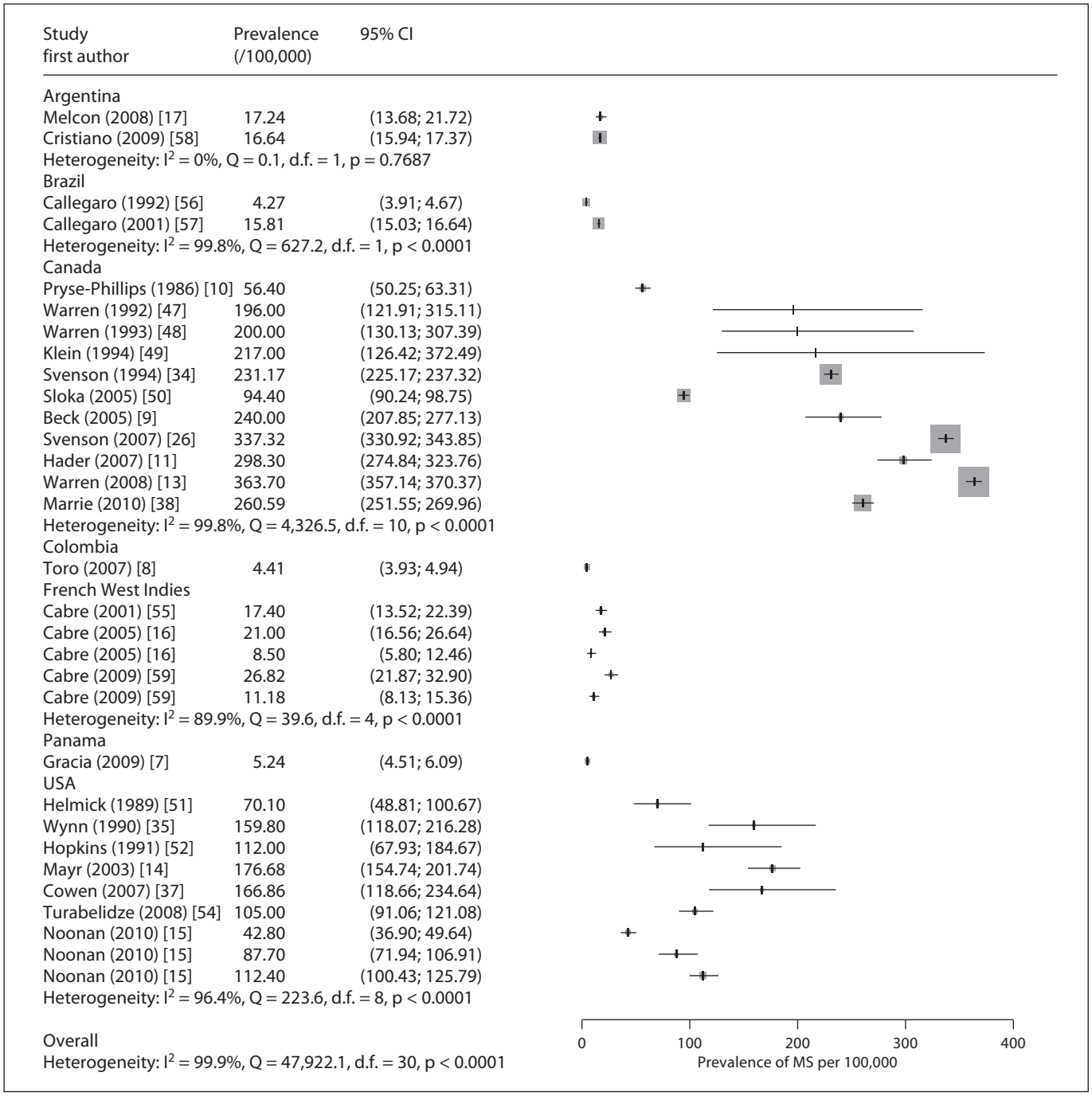

Fig. 4. Heterogeneity of included studies, stratified by country.

eas at different time points. As such, our knowledge of the epidemiology of MS in many regions throughout the Americas remains extremely limited.

One well-studied aspect of MS epidemiology is geoepidemiology. First recognized in the early 1920s by Charles Davenport [18], it is now widely accepted that there is geographical variation in the incidence and prevalence of MS. While many studies have demonstrated an increased incidence and prevalence in regions at higher latitudes [19–21], other studies have found no such asso-

Table 3. Quality assessment scores of multiple sclerosis incidence and prevalence studies

Study (year)	Q1: Target population described?	Q2: Cases from entire population or probability sampling?	Q3: Response rate >70%?	Q4: Non-responders clearly described?	Q5: Sample representative of population?	Q6: Data collection methods standardized?	Q7: Validated criteria to assess disease?	Q8: Were estimates given with confidence intervals?	Total Score
North America									
Pryse-Phillips (1986) [10]	Yes	Yes	NR	NA	Yes	Yes	Yes	Yes	6/7
Warren (1992) [47]	Yes	Yes	NR	NA	Yes	NR	Yes	Yes	5/7
Warren (1993) [48]	Yes	Yes	NR	NA	Yes	Yes	Yes	Yes	6/7
Klein (1994) [49]	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	7/7
Svenson (1994) [34]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	6/8
Mirsattari (2001) [27]	Yes	Yes	NR	No	Yes	NC	Yes	No	4/8
Beck (2005) [9]	Yes	Yes	Yes	No	NR	Yes	No	Yes	5/8
Sloka (2005) [50]	Yes	Yes	NR	NA	Yes	Yes	Yes	Yes	6/7
Svenson (2007) [26]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7/8
Hader (2007) [11]	Yes	Yes	Yes	NA	Yes	NC	Yes	Yes	7/7
Warren (2007) [12]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7/8
Warren (2008) [13]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7/8
Marrie (2010) [38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
Helmick (1989) [51]	Yes	Yes	NR	NA	Yes	Yes	Yes	Yes	6/7
Wynn (1990) [35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8
Hopkins (1991) [52]	Yes	Yes	NR	NA	Yes	Yes	Yes	Yes	6/7
Mayr (2003) [14]	Yes	Yes	Yes	Yes	Yes	NC	Yes	Yes	7/8
Neuberger (2004) [53]	Yes	Yes	NR	NA	Yes	Yes	Yes	Yes	6/7
Cowen (2007) [37]	Yes	Yes	NR	NA	NC	Yes	Yes	No	4/7
Williamson (2007) [25]	Yes	Yes	NR	NA	Yes	Yes	Yes	Yes	6/7
Turabelidze (2008) [54]	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	7/7
Noonan (2010) [15]	Yes	Yes	NR	NA	Yes	Yes	Yes	Yes	6/7
Cabre (2001) [55]	Yes	Yes	NR	NA	Yes	Yes	Yes	Yes	6/7
Cabre (2005) [16]	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	7/7
Cabre (2009) [59]	Yes	Yes	NR	NA	Yes	NR	Yes	Yes	5/7
Central and South America									
Callegaro (1992) [56]	Yes	Yes	NR	NA	Yes	Yes	Yes	No	5/7
Callegaro (2001) [57]	Yes	Yes	NR	NA	Yes	Yes	Yes	No	5/7
Toro (2007) [8]	Yes	No	NR	NA	Yes	Yes	Yes	Yes	5/7
Melcon (2008) [17]	Yes	Yes	NR	NA	Yes	Yes	Yes	No	5/7
Cristiano (2009) [58]	Yes	Yes	NR	NA	NC	NC	Yes	NC	3/7
Gracia (2009) [7]	Yes	No	NR	NA	No	Yes	Yes	Yes	5/7

NR = Not reported; NA = not applicable; NC = not clear.

ciation [4, 22, 23]. A recent meta-analysis evaluating prevalence estimates from 59 countries found a statistically significant latitudinal gradient for prevalence even after age standardization and adjustment for prevalence year [24]. Interestingly, a previous review of the prevalence of MS in Canada, which included several of the studies reported in the current review, found no striking evidence of a latitudinal or longitudinal gradient [4]. Similarly, Melcon et al. [17] found no south-north gradient in prevalence within the Argentine Patagonia. Prevalence was much lower in South America compared to North America, despite the studied regions being similar distances from the equator. This may be due to variations in the methodologies used, the quality of medical care and the differential population susceptibility to MS [21]. These conflicting findings further support the notion that although an important factor, geography alone cannot predict the prevalence or risk of MS.

Despite evidence indicating that the risk of MS differs between ethnicities, only 4 studies reported results for specific ethnic groups; an American study examined prevalence among Hispanics, non-Hispanic Blacks and non-Hispanic Whites living in the same region [25], and 3 studies from Canada reported prevalence or incidence rates for Aboriginal populations [12, 26, 27]. Although there was considerable variability between the studies (probably due to differences in prevalence period, characteristics of the denominator and case ascertainment methods), the prevalence reported among Aboriginal groups was much lower than among non-Aboriginal populations in Canada, which is consistent with that shown in the previous literature both in Canada and elsewhere [28, 29]. Similarly, the prevalence reported for the Hispanic and non-Hispanic Black groups was lower than that reported for the non-Hispanic White group in Texas [25]. Population genetics is, therefore, an important consideration when examining regions or populations comprised of various ethnicities and ancestries.

Prevalence appeared to increase over time. While it has been previously suggested that the prevalence of MS has increased in recent years [30], this is likely due to a longer life expectancy in people with MS and is not necessarily an indicator of an increased risk of the disease [23]. Increases in prevalence also occur with repeated surveys in the same region [23] and are a reflection of advances in the recognition and diagnosis of the disease [31, 32], increased access to neurologists, and improved methods of case ascertainment [4]. Although incidence is a better measure of increased disease risk [21, 23], most of the identified studies only examined prevalence.

Several studies have reported changes in the sex ratio of MS over time which may be a reflection of an increasing incidence of the disease in women [20, 23, 30, 33]. A recent meta-analysis found nonsignificant increases in the female/male ratios of MS prevalence over time, although the authors acknowledge that the discrepancy may be due to different methods used [24]. Results from 2 studies from Alberta, Canada using the same ascertainment methods in different time periods, indicate an increasing female/male MS prevalence ratio: 2.0 in 1984–1989 [34] to 2.6 in 1994–2002 [26]. Conversely, results from the studies of Olmstead County, Minn., USA suggest a decline in the sex ratio from 2.9 in 1985 [35] to 2.2 in 2000 [14]. However, because most studies in this review did not report age-standardized rates by the sexes, it is difficult to identify trends or make direct comparisons.

Case ascertainment varied greatly across studies and is likely a reflection of the resources available to researchers in each region. While chart reviews are often considered the gold standard for identifying cases of MS [36], they are resource intensive, complicated by privacy requirements, and not practical to conduct at a population level in large jurisdictions [9, 37]. Self-reported or community-based case ascertainment may identify those individuals with MS who do not regularly utilize medical services but are limited by the potential for recall bias and diagnostic inaccuracy [9]. In countries with universally funded health care systems such as Canada and many European nations, administrative health care databases can provide a practical and often population-based alternative to the traditional multiple sources of case ascertainment [38]; these have been used successfully in epidemiological studies of other chronic conditions [39–41] but require validation prior to use. Few studies of MS relied solely on administrative data to estimate prevalence, but this may increase now that case definitions for MS using administrative health data have been developed and validated [36, 38]. However, not all regions have access to population-based administrative databases or may be limited by the data available within the databases. In those regions, it will be more challenging to achieve population-based studies with standardized methods. Regardless of the sources used, researchers should consider the use of capture-recapture methodology to evaluate the completeness of the ascertainment and to correct for underascertainment [42–44]. Another option includes the designation of MS as a reportable condition or the development of a national or international registry [36, 37, 45]. Experience with such endeavors is growing and successful registries are emerging in other rare diseases [46]. While these may improve data consistency, they are costly and often rely on voluntary reporting. Given the advantages and limitations of each, and the resource variability among regions, it is difficult to propose one ideal method for MS case ascertainment; however, we suggest that this is a public health concern that should be addressed at national level.

Although study quality generally appeared adequate, lack of uniform methodologies (including case definitions and case ascertainment strategies) and inconsistent reporting of standardized rates made it difficult to combine data and compare studies. Therefore, this review remains primarily descriptive. A further limitation is that we only included full-text articles published in English or French, allowing for potential publication bias. Three studies were excluded based on language, and all were from South American countries (Argentina, Brazil and Colombia). Although all three countries also had studies

published in English that were included in the review, they measured different regions; therefore, it is possible that these exclusions could affect our results. The quality assessment was based on a tool designed specifically for this study and required some subjective judgments. However, this is still one of the first reviews [4] to assess the quality of studies included in a review of MS incidence or prevalence. Also, the use of independent reviewers allows us to have confidence in our assessments.

Conclusion

This review provides an updated overview of the incidence and prevalence of MS in the Americas, and highlights the gaps that still exist in the epidemiological knowledge of MS in both developed and developing countries. As the most common cause of nontraumatic disability in young adults [1, 2], it is alarming that technologically advanced countries such as the USA lack information on the prevalence and incidence of MS. Just as troublesome are the inconsistencies in the methodologies and quality of epidemiological studies that have been conducted. There is a need for future studies of MS prevalence and incidence to include uniform case definitions, comparable methods of ascertainment and standardized results, as well as coverage on a more national level in all regions evaluated. It is also important that researchers consider not only the sex distribution, but also the ethnic make-up of the populations being studied, as both can affect prevalence and incidence rates. Finally, such studies will support work evaluating the attributable risk of potential etiological factors for MS, including population lifestyle habits such as smoking, sun exposure or vitamin D status. Efforts such as these will help facilitate future global comparisons of the incidence and prevalence of MS, which are essential for understanding the economic and societal burden as well as advancing knowledge in the etiology, management and treatment of the disease.

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