Temporal trends in the incidence of multiple sclerosis

A systematic review

Alvaro Alonso, MD
Miguel A. Hernán, MD

Address correspondence and reprint requests to Dr. Alvaro Alonso, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, West Bank Office Building, 1300 S 2nd St, Suite 300, Minneapolis, MN 55454
aalogut@alumni.unav.es

ABSTRACT

Background: Multiple sclerosis (MS) has been traditionally considered to be more frequent in women and in regions more distant from the equator. However, recent reports suggest that the latitude gradient could be disappearing and that the female-to-male ratio among patients with MS has increased in the last decades. We have conducted a systematic review of incidence studies of MS to assess the overall incidence of MS and explore possible changes in the latitude gradient and the female-to-male ratio over time.

Methods: Systematic review of incidence studies of MS published in Medline between 1966 and February 2007. Age- and sex-specific incidence rates were collected from eligible publications. We computed age-adjusted rates using the world population as standard, and assessed differences in rates according to latitude and period of case ascertainment. Additionally, we evaluated the association between period of case ascertainment and the female-to-male ratio.

Results: The overall incidence rate of MS was 3.6 cases per 100,000 person-years (95% CI 3.0, 4.2) in women and 2.0 (95% CI 1.5, 2.4) in men. Higher latitude was associated with higher MS incidence, though this latitude gradient was attenuated after 1980, apparently due to increased incidence of MS in lower latitudes. The female-to-male ratio in MS incidence increased over time, from an estimated 1.4 in 1955 to 2.3 in 2000.

Conclusion: The latitude gradient present in older incidence studies of multiple sclerosis (MS) is decreasing. The female-to-male MS ratio has increased in the last five decades.

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GLOSSARY

MS = multiple sclerosis; **NHS** = Nurses' Health Study.

Multiple sclerosis (MS) is a chronic inflammatory disease of the CNS with unknown etiology. It is the most frequent nontraumatic disabling neurologic disease among young adults, with 12,000 new diagnoses per year in the United States alone.[1] Early studies of MS established that the incidence of the disease increased with the distance from the equator[2-4] and it is widely accepted that the incidence of MS is about twice as high in women compared to men.[5] However, these classic tenets of the epidemiology of MS may be questionable.

Recent evidence suggests that the latitude gradient of MS incidence may be decreasing,[6-8] or even that it never existed in certain areas,[9] and two reports indicate that the female-to-male ratio of MS might have increased over time.[10,11] Confirming these trends would offer interesting clues to the etiology of MS. For example, genetic explanations for the latitude gradient and the sex ratio would need to be greatly qualified or rejected, whereas infectious or lifestyle explanations would appear stronger.

Although some systematic reviews on the worldwide and regional incidence of MS have been published,[1,9,12,13] none of them studied temporal changes in the latitude gradient or the sex ratio. We conducted a systematic review of published studies that provided age- and sex-

From the Division of Epidemiology and Community Health (A.A.), School of Public Health, University of Minnesota, Minneapolis; and Department of Epidemiology (M.A.H.), Harvard School of Public Health, Boston, MA.

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specific incidence rates of MS. Our objective was to evaluate temporal changes in the incidence of MS by latitude and sex.

METHODS **Literature search.** We conducted a search in Medline and EMBASE including the period 1966 to February 1, 2007, for the keywords "multipie sclerosis AND incidence" in Medical Subjects Headings and free text. We screened all abstracts from the retrieved articles published in English and obtained the full text of those that could meet the inclusion criteria. We also examined the references in the articles meeting inclusion criteria, as well as previous reviews on the incidence of MS. Studies were included if they provided original data, specified the period of case ascertainment and the criteria for MS diagnosis, defined the study population, and reported age- and sex-specific incidence rates of physician-diagnosed MS. To improve the comparability between reports conducted in populations with different age structure, we excluded studies that did not provide age- and sex-specific incidence rates.

Data collection. From each individual study, we gathered the following information if available: first author, year of publication, period of case ascertainment, geographic area (Northern Europe, Southern Europe, North America, Australia and New Zealand, or Other), mean latitude for the study area, diagnostic criteria used for MS diagnosis, inclusion of suspect or possible cases, size of the study population, number of MS cases (total and by sex), method of case ascertainment, use of date of first symptoms or diagnosis to define incidence time, and age- and sex-specific incidence rates. In each study, the study period was defined as the mean of the first and last years of case ascertainment, and the sex ratio was calculated as the ratio of MS age-standardized incidence among women divided by that incidence among men. We defined dichotomous variables for study period (<1980, ≥ 1980) and latitude zone (<50, ≥ 50 degrees) using the median values as cutoff points.

Statistical analysis. For each study, we computed age-standardized incidence rates separately in women and men using the world population as reference.[14] We computed the mean age-standardized incidence including all studies and by study period and latitude zone. We also summarized incidence rates in each study by calculating the lifetime probability of receiving an MS diagnosis (lifetime risk).[15]

We used regression analysis to estimate the association of (log) MS incidence with latitude and period of case ascertainment (both considered as continuous variables). Similarly, we regressed the (log) female-to-male ratio on the study year. Each study was weighted by the inverse of the variance of its incidence rate, defined as the number of MS cases over the square of person-years of follow-up.[16]

RESULTS Our initial search retrieved 3,313 references in Medline and 1,253 in EMBASE. Of these, 28 articles provided age- and sex-specific incidence rates.[6,17-44] Six of them reported MS incidence separately for more than one population or for different periods of time for the same population[18,19,21-23,32] so, for the purposes of this analysis, we considered them as separate studies. We excluded one study[44] because it provided age-specific incidences that were all lower than the overall incidence. Therefore, our analysis included 38 studies: 19 conducted in northern Europe (Nordic countries and the United Kingdom), 12 in southern Europe, five in Australia, and two in the United States. Three studies (two in the United Kingdom, one in the United States) reported MS incidence only among women.[6,25,26] Table 1 lists the studies included in the systematic review, and their corresponding MS incidence rates and lifetime risk.

Among women, the weighted mean incidence rate of MS was 3.6 (95% CI 3.0, 4.2) cases per 100,000 person-years (nonweighted: 5.3, 95% CI 4.5, 6.1) and the lifetime risk was 2.5‰ (nonweighted: 3.7‰). Among men, the corresponding figures were 2.0 (95% CI 1.5, 2.4; nonweighted: 2.8, 95% CI 2.3, 3.3) for incidence and 1.4‰ (nonweighted: 2.0‰) for the lifetime risk.

Incidence rates were greater at higher latitudes, both in women and men (figure 1). For each increment in 10 degrees of latitude, MS incidence increased 30% in women and 50% in men (table 2). This latitude gradient was slightly weaker when we restricted our analysis to studies conducted in Europe (31 studies). After adjustment for latitude, we did not observe any significant association between the study year and the incidence of MS (table 2).

The mean MS incidence rates by study period and latitude zone are shown in table 3. Compared with studies conducted before 1980, the MS incidence was generally higher after 1980, especially in lower latitudes. As a consequence, the incidence rate ratio for high vs low latitude was higher, both in women and men, before 1980 than after 1980. In fact, latitude was clearly associated with MS incidence only before 1980, when a 10-degree increment in latitude was associated with a 31% increase (95% CI: 17% to 47%) in MS incidence among women and 54% (95% CI: 35% to 77%) among men. After 1980 the corresponding numbers were 15% (95% CI: −9% to 44%) in women and 11% (95% CI: −13% to 41%) in men.

We found an association between study year and sex ratio: for each 5-year period, the female-to-male incidence ratio increased 6% (95% CI: 3% to 10%) on average, from a predicted mean sex ratio of 1.4 in 1955 to 2.3 in 2000. These results did not materially change when the model included a quadratic term for the study year. The increase in the sex ratio was apparent when we examined separately studies conducted in the same region over different periods of time (figure 2).

DISCUSSION Our findings suggest an attenuation of the latitude gradient in MS incidence over the last

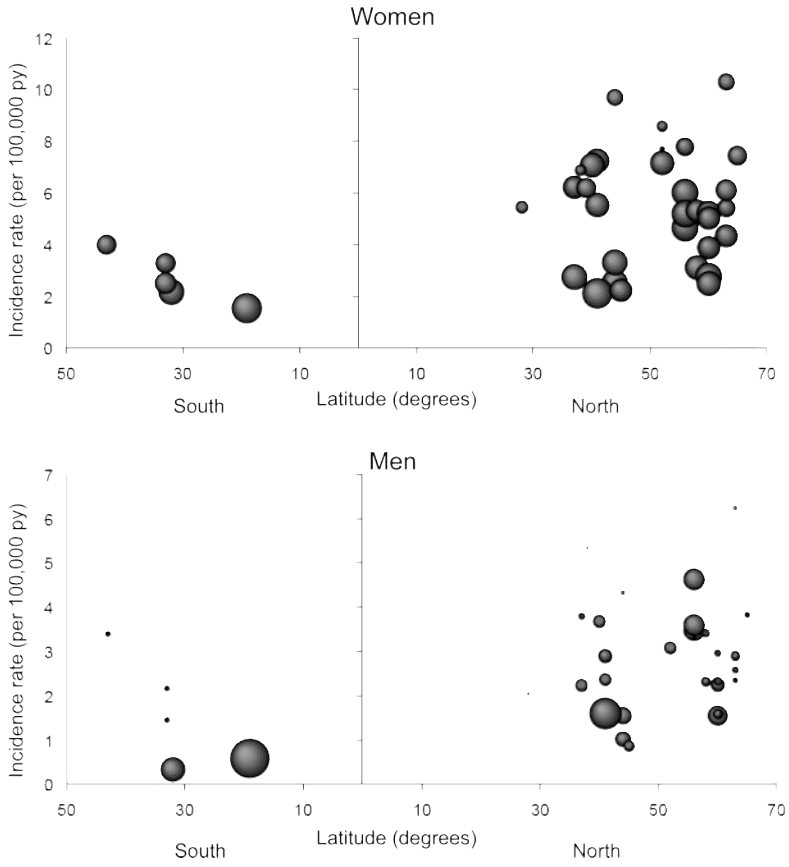
Table 1 Age-standardized incidence rates (per 100,000 person-years) and lifetime risk of multiple sclerosis (MS) in published studies reporting age- and sex-specific incidence rate of MS

Year of publication	Years of case ascertainment	City/region/country	Latitude	No. MS cases	Age-adjusted rates		Lifetime risk (‰)	
					Women	Men	Women	Men
2003[17]	1988–1997	Vasterbotten, Sweden	65 N	133	7.4	3.8	5.2	2.6
1984[18]	1964–1978	Vaasa, Finland	63 N	211	4.3	2.9	3.0	2.0
2000[19]	1979–1993	Seinajoki, Finland	63 N	240	10.3	6.2	7.8	4.9
2000[19]	1979–1993	Vaasa, Finland	63 N	90	5.4	2.3	4.1	1.9
2004[20]	1979–1998	Central Finland	63 N	231	6.1	2.6	4.5	1.9
1984[18]	1964–1978	Uusima, Finland	60 N	337	2.8	1.5	1.8	1.0
2000[19]	1979–1993	Uusima, Finland	60 N	736	5.2	2.2	3.8	1.6
1984[21]	1953–1962	Hordaland, Norway	60 N	65	2.5	1.6	1.7	1.1
1984[21]	1963–1972	Hordaland, Norway	60 N	113	3.9	3.0	2.5	2.0
1984[21]	1973–1982	Hordaland, Norway	60 N	133	5.0	2.3	3.5	1.6
1990[22]	1950–1964	Gotheburg, Sweden	58 N	253	5.3	3.4	3.6	2.3
1990[22]	1974–1988	Gotheburg, Sweden	58 N	166	3.1	2.3	2.2	1.6
1992[23]	1950–1959	Denmark	56 N	1801	6.0	4.6	4.1	3.2
1992[23]	1960–1969	Denmark	56 N	1801	4.6	3.5	3.2	2.4
1992[23]	1970–1979	Denmark	56 N	1801	5.2	3.6	3.7	2.5
2004[24]	1989–1998	Glasgow, Scotland	56 N	96	7.8	3.3	5.6	2.4
1993[25]	1968–1991	Britain	52 N	63	7.7	.	5.4	-
1998[26]	1968–1996	Britain	52 N	114	8.6	.	6.1	-
2007[27]	1993–2000	Britain	52 N	642	7.2	3.1	5.5	2.5
1989[28]	1961–1972	Istria, Yugoslavia	45 N	32	2.2	0.9	1.5	0.6
1995[29]	1985–1990	Reggio-Emilia and Modena, Italy	44 N	103	2.5	1.0	1.7	0.7
1996[30]	1965–1993	Ferrara, Italy	44 N	252	3.3	1.5	2.2	1.0
2003[31]	1985–2000	Olmsted Co., MN	44 N	132	9.7	4.3	7.0	3.4
1988[32]	1971–1981	Hobart, Australia	43 S	57	4.0	3.4	3.0	2.3
1996[33]	1961–1991	NW Sardinia, Italy	41 N	277	5.5	2.4	3.6	1.6
2001[34]	1968–1997	Sassari, Sardinia, Italy	41 N	637	7.2	2.9	4.7	1.9
1990[35]	1970–1984	Northern Greece	41 N	638	2.1	1.6	1.4	1.1
2000[36]	1955–1995	Nuoro, Sardinia, Italy	40 N	469	7.1	3.7	4.8	2.4
1999[6]	1976–1995	United States	39 N	361	6.2	.	5.0	-
2001[37]	1986–1995	Enna, Sicily, Italy	38 N	16	6.9	5.3	4.2	3.3
2001[38]	1975–1994	Catania, Sicily, Italy	37 N	170	2.7	2.2	1.8	1.5
2005[39]	1990–1999	Catania, Sicily, Italy	37 N	155	6.2	3.8	4.4	2.7
2007[40]	1993–2002	Caltanissetta, Sicily, Italy	37 N	56	12.4	7.0	8.7	4.8
1988[32]	1971–1981	Newcastle, Australia	33 S	29	2.5	2.2	1.7	1.5
2003[41]	1986–1996	Newcastle, Australia	33 S	32	3.3	1.5	2.6	1.1
1988[32]	1971–1981	Perth, Australia	32 S	106	2.2	0.3	1.5	0.4
2005[42]	1998–2002	Las Palmas, Spain	28 N	17	5.5	2.0	3.8	1.2
1987[43]	1971–1981	Queensland, Australia	19 S	197	1.5	0.6	1.1	0.4
Total					3.6	2.0	2.5	1.4

25 years, apparently as a result of increased incidence of MS in regions closer to the equator, and an increase of the female-to-male ratio of MS over time.

The existence of a latitude gradient in the distribution of MS was an early finding in the epidemiologic study of this disorder. Two seminal studies, one

Figure 1 **Age-adjusted incidence rate of multiple sclerosis by latitude in 38 different incidence studies**



Each observation corresponds to the incidence in one study. Size of each observation is proportional to the inverse of its variance.

conducted among US veterans and the other in different populations from Australia and New Zealand, found a higher frequency of MS in regions farther from the equator.[3,4] These studies, together with observations from migrant populations,[45,46] make it unlikely that the latitude gradient is fully explained by the genetic composition of the population or, as some authors have argued,[9] by differential diagnosis of MS in contiguous regions.

More recent reports, however, pointed to an attenuation of the latitude gradient. An analysis from the Nurses' Health Study (NHS) and NHS II cohorts assessed MS incidence among US female nurses born between 1921 and 1946 (NHS) and between 1947 and 1964 (NHS II). In the NHS, women born north of 41–42 degrees North latitude had a risk of developing MS 3.5 times higher than women born south of 37 degrees North latitude. In contrast, in the NHS II, being born in the north was not associated with a higher incidence of MS.[6] Similarly, an extension of the study conducted among US war veterans by Kurtzke et al. in 1979 showed that the north to south relative risk in the United States declined from 2.6 for veterans from the Second World War and the Korean Conflict to 2.0 for those from the Vietnam War and the Gulf War.[7] Our results confirm the attenuation of the latitude gradient, and extend this finding outside the United States.

The observed change in the latitude gradient suggests that, in addition to genetic determinants, one or more environmental factors play a role in the etiology of MS. Vitamin D and sun exposure (highly correlated), and infections have been suggested as potential candidates.[8,47] Several studies have observed an inverse association between vitamin D (both dietary intake and blood levels) and the risk of developing MS.[48,49] Changes in lifestyle associated to decreased sun exposure, and therefore lower synthesis of vitamin D, could account in part for the attenuation of the latitude gradient. Another potential explanation for the change in the latitude gradient is a change in the timing of exposure to infections in early life. According to the so-called hygiene hypothesis, an increased exposure to infections during childhood reduces the risk of autoimmune disorders, possibly including MS. Individuals in the southern regions of Europe and the United States have been traditionally more exposed to infections at young ages,[50] but recent improvements in socioeconomic conditions and lifestyle modifications might have eliminated this earlier exposure.

We also found an increase in the female-to-male ratio among MS cases. Two previous reports had detected this increase in North America. The Canadian Collaborative Project on Genetic Susceptibility to Multiple Sclerosis evaluated the MS sex ratio by year of birth among 27,073 patients with MS born between 1931 and 1980. The ratio was 1.90 for cases born in 1931–1935, and increased steadily to 3.21 for those born in 1976–1980.[10] Similarly, in 30,000 North American patients enrolled in the NAR-

Table 2 **Rate ratios (RR) of multiple sclerosis (MS) and 95% CI associated to change of latitude and period of case ascertainment**

	Women		Men	
	Crude	Adjusted*	Crude	Adjusted*
Latitude				
All studies	1.3 (1.2,1.4)	1.3 (1.2,1.4)	1.5 (1.4,1.7)	1.5 (1.4,1.7)
Only European studies	1.3 (1.1,1.5)	1.3 (1.0,1.5)	1.3 (1.0,1.5)	1.2 (1.0,1.5)
Period				
All studies	0.9 (0.8,1.1)	1.0 (0.9,1.2)	0.8 (0.6,1.1)	1.0 (0.8,1.1)
Only European studies	0.9 (0.8,1.1)	1.0 (0.9,1.2)	0.8 (0.7,1.0)	0.9 (0.8,1.1)

Values are RR (95% CI) of MS. RRs provided for increases of 10 units in the predictor variable.
*Regression model including latitude and period simultaneously as continuous variables.

Table 3 Mean incidence of multiple sclerosis (per 100,000 person-years) by study period and latitude

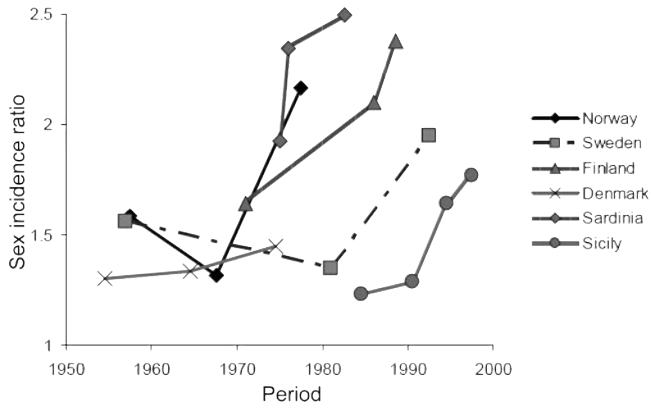
Latitude zone	Study year* <1980 (n = 19)	Study year* ≥1980 (n = 19)	Change in incidence rate <1980–≥1980, %
Women			
Overall	3.4	4.7	+38
≥50 (n = 19)	4.7	5.4	+15
<50 (n = 19)	2.4	4.1	+71
Latitude ratio†	2.0	1.3	
Men			
Overall (n = 35)	1.9	2.4	+26
≥50 (n = 17)	3.3	2.7	−19
<50 (n = 18)	1.1	2.1	+91
Latitude ratio†	3.0	1.3	

Cutoff points for latitude and period were the median values for each variable.
*Study year defined as the mean of first and last years of case ascertainment.
†Latitude ratio defined for each sex and study period as the ratio between mean incidence for studies conducted in latitude 50 or higher and the corresponding weighted mean for studies conducted below latitude 50.

COMS MS registry, the female-to-male ratio increased from approximately 2 for patients diagnosed in 1940 to 4 for those diagnosed in 2000.[11] Again, our study confirms these findings and extend them outside North America.

The observed rise in the female-to-male ratio cannot be easily explained by genetics or by new diagnostic technologies or increased awareness, which would apply to both sexes. Some possible environmental factors that could contribute to this change are smoking (which is associated with an increased MS risk[47] and whose prevalence increased among women during the 20th century), or reproductive factors (though there is no evidence for an increased MS risk associated with oral contraceptive use, pregnancy,[51] or a sexually transmitted agent).

Figure 2 Sex (female-to-male) incidence rate ratio of multiple sclerosis by study year and region



Study period was defined as the mean of the first and last year of the case ascertainment for that particular study. Only regions with information from three or more periods of time are included.

In contrast to our results, a previous systematic review concluded that there was not a true latitude gradient in the incidence of this disorder.[9] Two main reasons could explain the disagreement between our study and the older one. First, the previous review only included articles published between 1980 and 1998. Our review, on the other side, included articles published up to 2007. Second, we weighed study-specific incidence rates by the inverse of the variance, while the previous report did not attempt to correct for study size or number of MS cases included.

Our review has several limitations. First, the absence of incidence studies in Africa, Asia, and Central/South America makes it difficult to portray accurately the distribution of MS worldwide. Second, the lack of a uniform methodology in the studies included in our review may have introduced noise in our estimates. We tried to partially limit this problem by including only publications that provided age- and sex-specific incidence rates, which allowed us to compute standardized rates. Third, we could not differentiate between relapsing remitting and primary progressive MS. Finally, our review does not provide direct evidence regarding the causes of the attenuation in the latitude gradient or the increase in the female-to-male ratio.

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