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## Is it time for a new global classification of multiple sclerosis?

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#### ABSTRACT

*Background:* The geographic distribution of multiple sclerosis (MS) is classically divided into three zones based on frequency that were established by Kurtzke in the early 1970s. In recent years, an increasing number of epidemiological studies have shown significantly higher MS prevalence and incidence rates.

*Objective:* The aim of this study was to review and update the geographic distribution of MS using incidence, prevalence and disease duration from the latest epidemiology surveys.

*Methods:* We conducted a systematic review of articles on MS epidemiology published between January 1, 1990 and December 31, 2012.

*Results:* MS studies were grouped by continent: the Americas, Europe, Asia, Australia/New Zealand, and Africa. A total of 101 studies were identified according to the inclusion criteria, and 58 reported incidence estimates. Globally, the median estimated incidence of MS was 5.2 (range: 0.5–20.6) per 100,000 p-yrs, the median estimated prevalence of MS was 112.0 (with a range of 5.2–335) per 100,000 p-yrs, and the average disease duration was 20.2 years (range: 7.6–36.2).

*Conclusion:* In the past few decades, the global prevalence and incidence patterns of MS have changed dramatically. Regardless of the reason of increasing prevalence and incidence rate, we suggest the need for a novel classification system based on global MS disease burden. Adopting such a system would improve economic efficiency and prioritization in health policy planning for MS.

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#### 1. Introduction

An increasing number of multiple sclerosis (MS) epidemiology studies in recent years have shown that some populations have significantly higher prevalence and incidence rates than others. As early as the 1920s, epidemiologists have suggested that MS patterns are not uniform worldwide. In 1921. Charles Davenport introduced the north-south gradient of MS, which reflected that individuals with Scandinavian ancestry are at a higher risk for MS [1]. In 1975, Kurtzke established conclusive categories for describing MS prevalence. He divided MS prevalence into three geographic zones of MS frequency: high prevalence (30 or more cases per 100,000 pop.), which included most of Europe, the northern US, Canada, southern Australia, and New Zealand; medium prevalence (5 to 29 cases per 100,000 pop.), which included the southern US, southern Europe, northern Australia, and parts of Latin America; and low prevalence (less than 5 cases per 100,000 pop.), which included Asia, Africa, and South America. Despite being established in the early 1970s, these classifications of MS prevalence remain widely used [2].

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In the past two decades, several studies have suggested that MS prevalence and incidence have been increasing in southern Canada, the northern US, and north, south, and southeast Europe. Based on this new data, the geographical areas previously categorized as low or medium MS prevalence have turned into high prevalence areas. Moreover, MS incidence in some high prevalence areas continues to increase. In this study, we reviewed the current literature of the geographic distribution of MS.

#### 2. Methods

#### 2.1. Data collection

We conducted a systematic review of articles published worldwide on MS epidemiology to determine the global distribution of MS. We reviewed MS articles published in international scientific peerreviewed literature and surveys from the past two decades [3] between January 1, 1990 and December 31, 2012. In countries where multiple epidemiology MS studies had been conducted, data from the most recent studies were preferentially used.

We performed an online search of PubMed (http://www.pubmed. org) and EMBASE (http://www.embase.com) for any English publications and LILACS (http://www.bireme.br) for any Spanish publications with the following keywords: multiple sclerosis, prevalence, incidence, epidemiology, or worldwide epidemiology. In addition, we included relevant information from the World Health Organization (WHO), Multiple Sclerosis International Federation, and the 2008 Multiple Sclerosis Resources in the World [4]. More than 150 surveys of MS epidemiology were analyzed. Clusters of MS in small towns were excluded.

We summarized the following information from each study: survey location, latitude, population size and/or number of cases, incidence rate (95% confidence interval [CI]), prevalence rate (95% CI), female–male ratio, and prevalence year or period. Studies were grouped into five continents: America, Europe, Asia, Australia/New Zealand, and Africa.

#### 2.2. Quality evaluation

We included cross-sectional (prevalence studies), longitudinal (incidence studies), population-based, and cohort studies as well as studies using the capture–recapture method; we also included the Rochester Epidemiology Program Project, which collected MS incidence, prevalence, and other related data. MS cases were included if they were classified according to validated criteria (i.e., the Poser criteria or McDonald 2001, 2005, and 2010) [5,6] and had estimated 95% Cls or when the number of MS cases or population denominator were reported.

#### 3. Results

Estimates of MS prevalence were more common than estimates of MS incidence; 101 studies met the inclusion criteria, and 93 of the 101 studies reported MS prevalence while 58 reported MS incidence. The studies reviewed here were considered representative of the current MS literature. MS prevalence and incidence tended to be higher in more recent studies and in studies of North America and northwest Europe. MS prevalence was higher among women with a female–male ratio as high as 4.1 (USA) [11]. In Canada, the female to male incidence ratio has been increasing for at least 50 years and now exceeds 3.2:1. This change must have environmental origins even if it is associated with a gene–environment interaction [12]. The quality of more recent studies was generally higher; more recent studies also tended to use the McDonald criteria.

#### 3.1. Relevant findings

Globally, the median estimated MS incidence and prevalence were 5.2 (range: 0.5–20.6; Table 3) per 100,000 p-yrs and 112 (range: 5.2–335; Table 4) per 100,000 pop., respectively. The mean estimated MS incidence and prevalence were highest in North America (6.5/100,000 p-yrs and 126.0/100,000 pop., respectively), followed by northwest, north, southeast, and south Europe. MS incidence and prevalence was low in east and west Asia, South America, and North Africa.

Globally, the mean disease duration was 20.2 years (range of 7.6– 36.2; Table 5). The mean duration of the disease was highest in northwest Europe, followed by North America, north, southeast, and south Europe, and Australia.

#### 3.1.1. North America

Studies conducted after 1990 in *Canada* observed MS prevalence rates greater than 100/100,000 pop. A study of MS prevalence and incidence in Saskatoon, Canada identified 558 incident cases (female–male ratio: 2.6) between 1970 and 2004 using a population-based registry. The crude MS prevalence on January 1, 2005 was 298.3/100,000 pop., and the average annual incidence rate was 9.5/100,000 p-yrs. The high MS incidence observed in this study confirmed that individuals in Saskatoon are at a high risk for MS and showed that these rates were stable over three decades [7].

MS prevalence between 2000 and 2001 was computed in five regions (Atlantic Canada, Quebec, Ontario, the Canadian Prairies, and British Columbia) using data from the Canadian Community Health Survey. The overall prevalence of MS in Canada was 240/100,000 pop., ranging from 180 to 350 per 100,000 pop. in Quebec and Atlantic Canada, respectively [8]. Data from government health databases were also used to describe MS incidence among First Nations aboriginal people in Alberta between 1994 and 2002. In 2002, MS incidence among First Nations people was 7.6/100,000 p-yrs compared to 20.6/100,000 p-yrs among the general population. MS incidence in females was higher than that in males for both First Nations people (female-male ratio: 1.7) and the general population (female-male ratio: 2.5). These high MS incidence rates are consistent with the high prevalence rates reported for both groups in 2002: 99.9 and 335.0/100,000 pop. for First Nations people and the general population, respectively [9].

In the US, MS epidemiology data in Olmsted County, MN has been recorded for almost a century and showed that increasing MS prevalence is partially due to increasing incidence. All MS cases from 1985 to 2000 were identified using a centralized diagnostic index at the Mayo Clinic and the Rochester Epidemiology Program Project. Crude MS prevalence was 177/100,000 pop. on December 1, 2000, and MS incidence between 1985 and 2000 was 7.5/100,000 p-yrs [10].

A study of MS prevalence in three US communities between 1998 and 2000 found extremely different estimated overall MS prevalence rates in each area. Crude MS prevalence was lowest (47.8/100,000 pop.) in Texas (33° 30' N), intermediate (87.7/100,000 pop.) in Missouri (39° 07' N), and highest (112.4/100,000 pop.) in Ohio (41° 24' N). MS prevalence was much higher among women than men (female–male ratios of 4.1, 3.9, and 2.8 in Texas, Missouri, and Ohio, respectively) [11].

MS cases were also obtained for individuals who served in the military between 1990 and 2007 from the US Department of Defense and the US Department of Veterans Affairs. Definite MS (DMS) was confirmed in 2288 patients. The average annual, age-specific MS incidence was 9.6/100,000 p-yrs. Incidence was highest among Blacks (12.1/100,000 p-yrs) while incidence rates of 9.3 and 6.9 per 100,000 p-yrs were reported for Whites and individuals of other races, respectively. The finding that Blacks had the highest MS incidence (relative risk ratio of 1.27 for Black–White) was novel. Furthermore, MS incidence among females was almost three times higher than that among males (female–male ratio: 3.4) [13].

The first longitudinal study of MS incidence was conducted between 2000 and 2009 by the US Armed Forces. A higher incidence rate than in other populations was observed; 1827 incident MS cases occurred, resulting in an overall incidence of 12.9/100,000 p-yrs. Incidence was higher among Black non-Hispanics (18.3/100,000 p-yrs) than White non-Hispanics (12.5/100,000 p-yrs), which reaffirmed the novel racial MS incidence pattern in the US [14].

#### 3.1.2. Latin America and the Caribbean

We found 16 studies of MS prevalence in Latin American and the Caribbean, which reported low or medium MS prevalence rates. This suggests that the crude MS prevalence in this region is homogenous. MS distribution in LAC can be divided into two regions: (1) intertropical, which is bounded by the Tropic of Cancer (23.5° N) and the Tropic of Capricorn (23.5° S) and (2) the Southern Cone, which is comprised of the southernmost areas of South America that are south of the Tropic of Capricorn (23.5° S to 56° S). MS prevalence was highest in San Pedro Garza Garcia, Nuevo Leon, Mexico (30/100,000 pop.) with DMS confirmed in 38 patients [15]. The tropics, including Colombia and Ecuador, had the lowest average MS prevalence rates (less than 5/100,000 pop.). The very low MS prevalence in the tropics has been attributed to the combination of different ethnic groups and environmental factors. Several studies have also documented MS prevalence in north and south of the Equator and in the Southern Cone (Table 1) [16-32].

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