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Epidemiological Evidence of the Recent Surge in MS in Asia and Australia: A Systematic Review

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Abstract

Context: Recently, the incidence and prevalence of multiple sclerosis (MS) have increased drastically in different regions of the world, including Asia. The present study aimed to systematically review the recent MS epidemiology in Asia, New Zealand, and Australia.

Methods: A systematic literature search was performed in Medline and Embase databases to retrieve the available studies regarding MS epidemiology in Asia, New Zealand, and Australia.

Results: Most of the studies were performed in hospital settings. The female-to-male ratio in the sample populations varied from 1.5:1 in Turkey to 5:1 in Malaysia. The total mean age at the onset of MS varied from the minimum of 28 years in Hong Kong to the maximum of 36 years in the United Arab Emirates. Among 16 pertinent studies in this regard, seven addressed the incidence rate of MS, and 13 addressed the prevalence of the disease. The highest prevalence rate was reported to be respectively 124.2 and 148.06 in Australia and Iran versus 2.73 in Malaysia (06 per 100,000 population), while a higher incidence rate was estimated at 6.88 and 6.7 per 100,000 population in Kuwait and Australia, respectively compared to the lower incidence rate per 100,000 population in China (0.2 in females, 0.12 in males).

Conclusions: According to the results, the prevalence of MS has increased in Asia, while the prevalence of MS in this continent is lower compared to the rates reported in Australia, Europe, and North America.

Keywords: Multiple Sclerosis, Epidemiology, Prevalence, Incidence, Asia, Australia

1. Context

Multiple sclerosis (MS) is considered to be the most prevalent neurological disorder, which primarily affects the central nervous system in young adults (1). MS has wide-ranging effects and is the leading cause of disability among adults and young working-age population; consequently, MS decreases the quality of life of the patients (2). Ample evidence suggests that the prevalence of MS has increased worldwide (3, 4), with the number of the patients rising from 2.1 million in 2008 to 2.3 million in 2013 (4). In 2016, statistics indicated the number of MS patients to be 2,221,188 worldwide, which corresponded to the prevalence rate of 30.1 per 100 000 population (95% CI: 27.5 - 33.0) (2). Furthermore, the prevalence of MS increased from 1970 to 2015 in the Middle East and north Africa (MENA region). In 2016, the lowest and highest prevalence of MS in Eastern Mediterranean countries was reported in Somalia (2.66 per 100,000) and Iran (72.11 per 100,000), respectively (5).

Asia has an outstanding geographical, ethnic, and cultural diversity, and more than half of the world's population inhabits this region (6). Although Asia was considered as a low-risk zone for MS in the past, the epidemiological status of MS in Asia has changed in recent decades (7). Several studies addressing the epidemiology of MS have been performed in North America and Europe, providing significant insight into MS epidemiology, such as the increasing prevalence and incidence of the disease (8).

Limited epidemiological studies have been conducted in Asia, Australia, and New Zealand in this regard. As such, we have performed a systematic review of the studies on the incidence and prevalence of MS in Asia, Australia, and New Zealand. According to a systematic review by the authors of the present study, the highest prevalence of MS was reported in Japan (East Asia; 16.2 in 2011), Turkey (Middle East; 101.4 in 2003) (3, 9), and New Zealand (15 in 2001) per 100,000 population (10).

In recent decades, the growing number of the patients affected by MS indicates that the prevalence and incidence of the disease may be comparatively higher in specific eth-

nic groups or residents of particular regions (3, 10). Numerous researchers have also recognized the trends of the prevalence and incidence of MS in various regions in Asia. For instance, a study comparing the prevalence and incidence rate of MS between different Asian countries indicated the highest prevalence rate in Turkey and Iran (3, 9).

Considering the increasing incidence and prevalence of MS, the present study aimed to review the available epidemiological data regarding the most recent changes in the incidence and prevalence patterns of MS in select countries.

2. Methods

2.1. Search Strategy

To determine the updated epidemiology of MS in Asian countries, Australia, and New Zealand, a systematic literature search was performed in Medline and Embase databases, which allowed access to the publications available to Tehran University of Medical Sciences during January 1, 2015-September 1, 2018. In addition, various keywords were used to facilitate the search process, including epidemiology, multiple sclerosis, prevalence, incidence, and names of target countries (similar to our previous systematic reviews) (3, 9).

2.2. Article Screening and Selection Criteria

Computer databases were utilized to identify the population-based studies containing the epidemiological data of MS, and we only selected the articles published in English language. Cross-sectional and cohort studies were included in the review, and the potentially relevant titles and abstracts of the documented studies by the databases were reviewed as well.

2.3. Eligibility Criteria

This comprehensive systematic review was planned in advance, and the full text of the initially eligible studies were reviewed based on the eligibility criteria, as follows: (1) studies addressing human MS patients living in Asian countries, Australia, and New Zealand; (2) studies containing data on the prevalence, incidence, and number of the MS cases in the target countries; (3) studies regarding the diagnosis of MS patients based on the McDonald MS diagnostic criteria (11); (4) studies not limited to a specific gender or age groups; and (5) studies available in the full-text form. Two experts reviewed the abstracts of the identified articles, and only the studies confirmed by both reviewers based on the eligibility criteria were selected for the systematic review.

2.4. Protocol and Registration

The flow diagram of the article selection process was based on the PRISMA flow diagram (Figure 1) (12). In the current review, the classification of the Asian countries was based on the World Bank documents and Global Burden of Diseases (GBD) framework. We evaluated various countries that were divided into five geographical areas (7), including Japan, South Korea, China, North Korea, Hong Kong, and Taiwan (East Asia), Cambodia, Indonesia, Laos, Malaysia, Maldives, Myanmar, Philippines, Sri Lanka, Thailand, Vietnam, Singapore, and Brunei (Southeast Asia), Bangladesh, Bhutan, India, Nepal, and Pakistan (South Asia), Afghanistan, Bahrain, Iran, Iraq, Jordan, Kuwait, Lebanon, Palestine, Oman, Qatar, Saudi Arabia, Syria, Tunisia, Turkey, and the United Arab Emirates (Middle East), and Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, and Uzbekistan (Central Asia). Australia and New Zealand were also included in the study.

The collected data addressing different countries in the specified categories of regions were evaluated based on our previous systematic reviews (3, 9). In addition, the abstracts of the selected articles were screened by two expert reviewers to ensure that the initially selected articles met the eligibility criteria. If the eligibility of the selected abstracts was not initially confirmed, a full-text review would be performed.

2.5. Data Extraction and Quality Assessment of Articles

Both reviewers approved the quality of the selected articles for the extraction of pertinent data using a data extraction form. The following criteria considered in the decision-making regarding the eligibility of the studies: (1) date of study conduction; (2) study setting; (3) diagnostic criteria; (4) number of identified cases; (5) gender ratio (female-to-male); (6) mean age at disease onset; (7) prevalence per 100,000 population; (8) incidence per 100,000 population; and (9) quality score of each study. Duplicate publications and the studies not adhering to the mentioned criteria were excluded. The extracted data were meticulously investigated by the third reviewer.

The methodological quality of the reviewed and modified studies was also confirmed using the checklist of strengthening the reporting of observational studies in epidemiology (STROBE) (13). Given the growing number of epidemiological evidence, more specific, organized, and updated research is required on the subject.

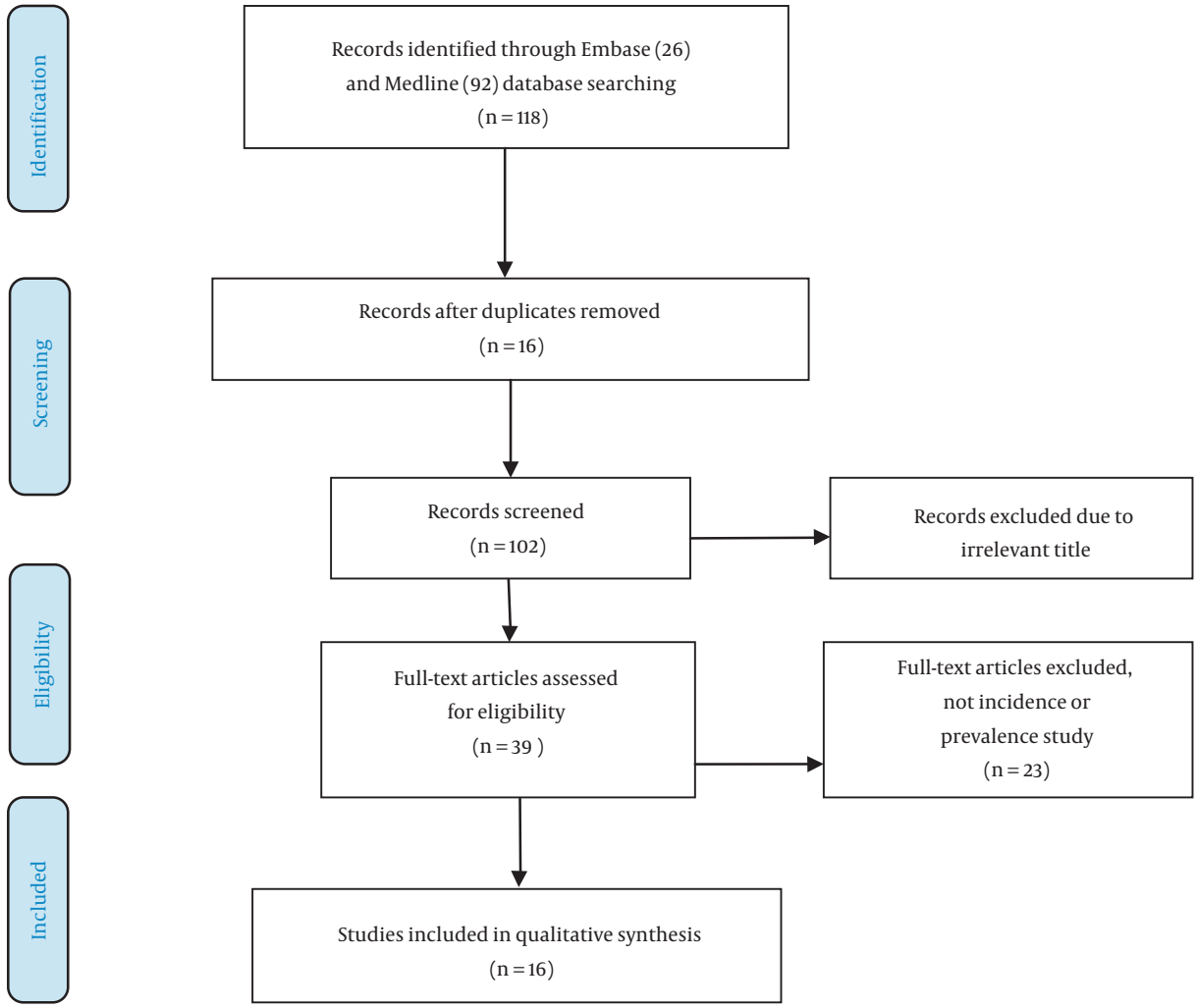

Figure 1. PRISMA flow diagram

3. Results

The thorough database search resulted in 118 citations (including 16 duplications) in the original sources. After screening 102 titles and abstracts, 39 studies were considered to be relevant to the epidemiological studies of MS in the selected countries and eligible for full-text screening. After performing full-text reviews, 16 articles that met the eligibility criteria were selected for data extraction and analysis of the incidence and prevalence of MS (Figure 1).

The final data were obtained from the studies addressing the prevalence and incidence rates of MS in 10 countries, including Japan (14), China (15-17), and Hong Kong (18) in East Asia, Malaysia (19) in Southeast Asia (Table 1), India (20) in South Asia, Iran (21-24), Kuwait (25), the United Arab Emirates (26), and Turkey (27, 28) in the Middle East, and Australia (29) (Table 2). McDonald criteria for MS were used as the diagnostic criteria in the selected studies.

Tables 1 and 2 shows the data extracted from the selected articles, including the name of the first author, conduction of the study, study setting, sample size, female-to-male ratio, mean age at disease onset, and prevalence and incidence rates per 100,000 population. The main data source to obtain the characteristics of the MS patients in 38% of the studies was the national/regional MS registries. Furthermore, 37% and 25% of the data reported in the studies were obtained from a multicenter hospital setting and a single hospital setting, respectively.

With respect to the gender ratio, it must be considered that the large number of MS cases affected this ratio. The

Table 2. Baseline Characteristics of MS in South Asia, Central Asia, and Middle East

Country	First Author	Study Period	Study Setting	Number of Cases	Gender Ratio (F:M)	Mean Age at Onset ± SD	Prevalence per 100,000 (95% CI)	Incidence per 100,000 (95% CI)
India	Singhal et al. (20)	2011 - 2012	Single hospital-based (NewDelhi)	101	1.5:1	33.3 ± 9.28	-	-
Iran	Eskandarieh et al. (21)	1999 - 2017	Regional MS registry (Tehran)	19,902	3.03:1	28.64	148.06	-
	Mousavizadeh et al. (22)	1999 - 2016	Treatment surveillance system (Kohgiluyeh and Boyer-Ahmad)	421	3.3:1	29.78	60.14	-
	Eskandarieh et al. (23)	1999 - 2015	Regional MS registry (Tehran)	16,447	3.06:1	28.36	115.94	-
	Eskandarieh et al. (24)	1991 - 2014	Regional MS registry (Tehran)	15672	3.18:1	30.04	101.39	6.02
Kuwait	Alroughani et al. (25)	2010 - 2013	National MS registry	1176	1.8:1	35.40 ± 10.99	85.05 (82.80 -87.04)	6.88
Turkey	Boru et al. (27)	2014 - 2015	Door-to-door survey (Karabük-Akçakoca)	33	1.5:1	30.8 ± 9.1	95.9 Karabük; 6.1 Akçakoca	-
	Akdemir et al. (28)	2010 - 2011	Middle Black Sea Region	1,584	2.42:1	29.39 ± 7.6	43.2	-
United Arab Emirates	Schiess et al. (26)	2010 - 2014	Multicenter hospital-based (Abu Dhabi)	510	1.77:1	36 ± 11	57.09 (50 - 63)	6.0 (5.5 - 6.5)

Table 1. Baseline Characteristics of MS in East Asia, Southeast Asia, and Australia

Country	First Author	Study Period	Study Setting	Number of Cases	Gender Ratio (F:M)	Mean Age at Onset ± SD	Prevalence per 100,000 (95% CI)	Incidence per 100,000 (95% CI)
Japan	Houzen et al. (14)	2016	Multicenter hospital-based (Tokachi)	4827	3.57:1	32 ± 13	18.6	-
China	Chen et al. (15)	2012 - 2014	Single hospital-based (Beijing)	85	1.83:1	32	-	
	Liu et al. (16)	2013	Multicenter hospital-based (Shandong)	-	1.77:1	33.7 in females;36 in males	6.7 in females;3.7 in males	0.2 in females;0.12 in males
	Ma and Zhang (17)	2002 - 2012	Single hospital-based (Beijing)	264	2:1	33.9 ± 12.3	-	-
Hong Kong	Lau et al. (18)	2013 - 2015	Multicenter hospital-based	65	3:1	28	7.2	2.2
Malaysia	Viswanathan and Wah (19)	2013 - 2017	Single hospital-based (Kuala Lumpur)	767	5:1	29.0 ± 9.9	2.73	0.55
Australia	Ribbons et al. (29)	2011	Multicenter hospital-based (Newcastle)	-	3:10:1	-	124.2	6.7 (106.3 - 142.5)

Abbreviations: F:M, female-to-male ratio; CI, confidence interval; SD, standard deviation.

results of the studies regarding the female-to-male ratio in East Asia varied from 3.57:1 in Japan to 2:1 in China (Table 1). In Southeast Asia and South Asia, the gender ratio has been reported to be 5.1:1 in Malaysia and 1.5:1 in India, respectively. Furthermore, the findings regarding the gender ratio in the Middle East indicated the value of 3.03:1 in Iran and 1.77:1 in the United Arab Emirates (Table 2). To summarize, it could be stated that the female-to-male gender ratio varied from the maximum of 5:1 in Malaysia (Table 1) to the minimum of 1.5:1 in Turkey in different studies conducted in Asia (Table 2). Overall, the female-to-male ratio of 2.61:1 could be estimated in the MS patients in Asia based on the reviewed data of the studies in this regard.

Table 1 shows the mean age at disease onset in different Asian countries. The mean age at MS onset has been reported to be 32 $\pm$ 13 years in Japan, while the minimum mean age of 32 years was reported in 2014, and the maximum mean age was estimated at 33.9 $\pm$ 12.3 years in 2012 in China; in addition, the mean age at MS onset in the patients in Hong Kong has been estimated at 28. Table 2 shows the mean age of MS patients at disease onset. Accordingly, the minimum mean age was 28.36 years in 2015 in Iran, and the maximum mean age has been reported to be 36 $\pm$ 11 years in the United Arab Emirates. Moreover, the total mean age at disease onset has been estimated at 31.64 years in the selected countries, with the minimum mean age of 28 years in Hong Kong (Table 1) and the maximum mean age of 36 years in the United Arab Emirates (Table 2).

According to our findings, the number of the studies addressing the prevalence rate of MS was more than those examining the incidence rate of the disease in Asian countries. In this regard, 13 studies reported the prevalence rate of MS, while only seven studies reported the incidence rate of MS. The reported prevalence rate of MS is within the range of 2.73 - 18.6 cases per 100,000 population in Southeast and East Asia, while the estimated value for Australia is 124.2 (Table 1). The reported prevalence rates of the disease are higher in the Middle East, ranging from 148.06 in Iran to 43.2 in Turkey per 100,000 population (Table 2). To address the prevalence of MS in Tehran (Iran), the data retrieved from the regional MS registry indicated the annual increase of MS prevalence from 101.39 in 2014 to 148.06 in 2017 (Table 2). Notably, the data on the reported prevalence and incidence of MS in South Asian countries were not available.

The reviewed data on the incidence rate of MS revealed the statistically low values of 0.2 and 0.12 in the women and men in China, respectively. Moreover, the highest incidence rates of MS were 6.7 in Australia per 100,000 population per year during the period of the reviewed studies (Table 1). The incidence rate of MS in the Middle East is rather comparable between different nations and reported to be 6.88 per 100,000 population in Kuwait and six per 100,000 population in Iran and the United Arab Emirates. However, the incidence rate of MS in Japan, India, and Turkey has not been reported in any studies, and no MS epidemiology studies could be identified in these countries.

4. Discussion

Our study aimed to present the inclusive surge and a systematic review of 16 epidemiological studies of MS in Asia. Most of the countries in the examined regions published no epidemiological data on MS during 2015 - 2018. Based on the existing data, the epidemiology of MS has changed in recent decades, and the incidence and prevalence of the disease have increased significantly in Asia (3, 9). Furthermore, the systematic review data indicated a significant increase in the risk of MS globally (14, 30).

Evidence in this regard has several limitations, which could influence the mean age at MS onset, gender ratio, and MS prevalence and incidence rates. Countrywide epidemiological studies are rare, and the only reports among Asian countries are from Kuwait. Moreover, the indeterminate quality of the presented data, small sample size of the studies, and differences in the publication methods (31) were among the other limitations of the reviewed studies. Another limitation is that only a few studies have estimated the incidence rate compared to the prevalence rate of MS per 100,000 population.

Most of the reviewed studies were conducted in multicenter hospital settings, with the exception of Kuwait and Iran, which were performed based on regional and national registry systems. Several studies have indicated the increased female-to-male ratio in MS cases over the past decade, which could be attributed to the increased incidence of MS among women compared to men (32). According to a review article addressing the epidemiology of MS in Europe, the female-to-male ratio in MS cases varies from 1.1:1 to 3.4:1 (33). In addition, the female-to-male ratio varied and slightly increased over time in different studies conducted in a specific region (from 1:1 in 1955 to 3.57:1 in 2016 in Japan, from 1.2:1 in 2006 to 2:1 in 2012 in China, from 2.9:1 in 1987 to 3:1 in Hong Kong, from 0.7:1 in 1988 to 1.5:1 in 2012 in India, from 2.5:1 in 2011 to 3.03:1 in 2017 in Iran, from 1.3:1 in 1988 to 1.8:1 in 2013 in Kuwait, from 1.56:1 in 2013 to 2.42:1 in 2011 in Turkey, and from 1.18:1 in 1961 to 3.10:1 in 2001 in Australia) (33). Furthermore, the results of a systematic review addressing 123 studies conducted in Europe estimated higher rates of MS incidence among women with the ratio of 3:1 (4).

Compared to men, women are often at a higher risk of autoimmune diseases. However, the increased female-to-male ratio in MS incidence could be attributed to environmental risk factors and the modern lifestyle mostly favored by women, especially in recent decades. Hormonal, social, and nutritional factors leading to vitamin D deficiency should also be taken into account in this regard (23, 34).

Compared to previous studies, the findings of the current research indicated that the mean age at the disease onset decreased in MS patients, with the exception of the mean age at MS onset in Japan, Kuwait, and the United Arab Emirates. Differences in diagnostic criteria and methods may lead to the earlier diagnosis of MS in the course of the disease, thereby decreasing the mean age at disease onset (35).

The prevalence and incidence rates of diseases are considered to be essential concepts in epidemiological studies. Several studies conducted in different countries have shown a significant increase in the incidence and prevalence of MS in recent decades as observed in the reported data of Japan, China, Korea, Hong Kong, Taiwan, Malaysia, Iran, Kuwait, and the United Arab Emirates (3, 9).

According to our findings, the incidence and prevalence rates of MS are higher in Nordic countries compared to Europe and Asia (3, 4, 9). On the other hand, the reported incidence and prevalence of MS in Asia are significantly lower than the reported data in Europe and North America (36). The incidence and prevalence of MS across America show the higher heterogeneity of the studies in this regard, even when stratified by country. The highest prevalence rate has been observed in Olmsted County (Minnesota) with the age-standardized rate of 191.2 per 100,000 population (36).

Based on the Kurtzke classification of MS prevalence into three geographical zones, the countries in East Asia (Japan, China, and Hong Kong) have a moderate prevalence rate of MS similar to the rate reported in Southern Europe and the United States. Furthermore, Malaysia (Southeast Asia) has the lowest prevalence of MS similar to the rate reported in Africa. On the other hand, Australia, India, and the countries in the Middle East have reported the highest prevalence rate of MS (e.g., Canada and Europe) (37).

According to the results of the present study, the highest prevalence of MS was reported in the Middle East and Australia, while the lowest prevalence was reported in the countries in East Asia. The results of a systematic review addressing MS patients in New Zealand indicated a significant increase in the prevalence of MS, which has remained constant (38).

The rising trend of MS prevalence and incidence might reveal the influence of modified diagnostic criteria, improved medical care and treatment outcomes, and extended survival (29). The possible reasons for the growing incidence and prevalence of MS might be genetic and environmental risk factors, as well as awareness and information about MS, which have been promoted in recent decades (22). Notably, Asians have different ethnicities, environments, lifestyles, and genetic compositions, which could be considered as the influential factors in the difference in the prevalence and incidence rates of MS between various countries (39).

5. Conclusions

The present study provided an updated systematic review of the epidemiological characteristics of MS in Asia and Australia. According to the results, the incidence and prevalence of MS have not been well-documented in most of the countries in Asia, while epidemiological evidence suggests the increasing prevalence of MS in many countries of this continent. Therefore, further epidemiological studies are required to shed light on MS epidemiology. Furthermore, population-based registries and using standardized, uniform data collection methods and outcome metrics could improve the quality and comparability of such studies and increase our knowledge of global and regional MS epidemiology.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

Authors' Contribution: SE and MS conceived and designed the study, data collection and extraction. The manuscript was drafted by SE and MS. All authors read and approved the final version of the manuscript.

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