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Incidence of multiple sclerosis in Iran: a nationwide, population-based study

A. Hosseinzadeh [a], M.R. Baneshi [a], B. Sedighi [b], J. Kermanchi [c], A.A. Haghdoost [d,*]

[a] Modeling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
[b] Neurology Research Center, Kerman University of Medical Science, Kerman, Iran
[c] Deputy of Curative Affairs, Ministry of Health and Medical Education (MOHME), Tehran, Iran
[d] HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

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ABSTRACT

Objectives: The incidence of multiple sclerosis (MS) is not well known in Iran. This study was conducted to estimate the trends in annual MS incidence in Iran from March 21, 2010, to March 20, 2016.

Study Design: Longitudinal study.

Methods: In this longitudinal study, data for all MS patients fulfilling McDonald criteria were obtained from a national registry, coordinated by the Ministry of Health (MOH). In Iran, all MS patients are eligible to receive public care and treatment services based on their records in this registry, and thus nearly all MS patients are registered in this database. The annual incidence rates were calculated based on year of diagnosis and were standardized using the World Health Organization (2000–2025) population as a standard.

Results: In this registry, 36,287 (8202 [22.6%] males and 28,085 [77.4%] females) confirmed MS cases were registered by the MOH between 2010 and 2016. The female-to-male ratio was 3.11. The mean age of patients was 31.6 ± 0.9 years at the time of diagnosis. It was 31.3 ± 0.8 and 32.3 ± 0.9 for females and males, respectively. Overall incidence rate was 6.7/100,000 population (95% confidence interval [CI]: 6.2–7.2); 10.5 and 3.0 in females and males, respectively. The age-adjusted incidence rates increased significantly from 4.4 (95% CI: 4.3–4.6) in 2010 to 5.8 (95% CI: 5.7–6.0) in 2016, with its peak at 6.5 (95% CI: 6.3–6.6) in 2014.

Conclusions: This study revealed that Iran is a high-risk area for MS disease and that MS incidence and female-to-male ratio are more or less comparable with the dominant patterns in developed countries. Also, this study showed that the incidence trend of MS in Iran is similar to regional and global observed patterns.

* *Corresponding author*. Kerman University of Medical Science, Haght Bagh high way, Kerman, Iran. Tel. : +98 913 343 9427.
E-mail address: ahaghdoost@kmu.ac.ir (A.A. Haghdoost).

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Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system with unknown etiology.[1] Disease onset usually occurs in young adults and is more common in females.[2] Despite its relatively low prevalence, MS has a considerable economic and social impact, as it occurs at young age, and it is the major cause of non-traumatic disability in young adults.[3,4] This disease affects over 400,000 Americans and approximately 2.3 million people worldwide.[5] The healthcare costs in the United States associated with MS range from $8528 to $54244 per patient-year at 2011 prices.[6]

Previous studies revealed that MS incidence increased with the distance from the equator.[7] Thus, the highest prevalence of MS has been reported in Northern Europe and the lowest in Asia and Africa.[8] Recent studies, however, suggest that the epidemiology of MS has changed, and the latitude gradient in the MS incidence is disappearing.[7,9] Thus, many exceptions have been observed in areas previously considered as low-risk for MS.[10,11] The low-frequency areas, based on the Kurtzke classification, are regions where MS prevalence is less than five per 100,000 population.[12] Based on this classification, Asia and Africa are in the low-frequency areas, and MS prevalence and incidence is expected to be low in these geographic areas. However, recent studies have shown that the prevalence and incidence of MS is increasing in these geographic areas.[13] This increase, however, has not occurred in the same way in all areas. Epidemiological studies have revealed that the areas with relatively high initial incidence rates tend to remain stable, whereas those with low initial rates, such as Southern Europe, tend to show increasing rates over time.[14]

In previous epidemiological studies, the increasing prevalence of MS in a geographical area was assumed to be secondary to migration, population age structure, improved case ascertainment, and increased survival.[15] However, recently, it has been found that the increasing prevalence is due in part to increased incidence and lifestyle changes.[16–19] Iran, as an in transition country, is currently experiencing population aging and rising prevalence of Western lifestyle.[20] Thus, similar to other parts of the world, it is expected that the epidemiology of MS will change in Iran.

Investigations of MS incidence and prevalence in regions previously considered as low-risk areas are interesting and may contribute to our understanding of the cause of the disease. To date, most of the previously published studies in Iran on MS incidence were performed in a city or on a regional scale. Based on the findings of these studies, MS incidence in some provinces, including Tehran and Isfahan, has increased.[21–23] To the best of our knowledge, only one reliable study has estimated the national incidence of MS in Iran.[24] However, in the aforementioned study, the trend of MS incidence was not investigated.

As the incidence rate is a more valuable index to express recent changes of the developing risk of a disease, this study aimed at determining the incidence trends of confirmed MS in Iran at the national level between 2010 and 2016. In addition, this study investigated the female-to-male ratio trends of MS in Iran.

Methods

This longitudinal study carried out based on analysis of the data from the monitoring and treatment surveillance system for the MS patients in Iran, from 2010 to 2016. Because of the high therapeutic cost of patients with MS in Iran, the Iranian government pays a considerable amount of treatment costs for MS patients. As a result, there is a population-based computerized registry in each province, coordinated by the Ministry of Health (MOH), to register the information of MS patients under treatment. In this system, only those patients with clinically confirmed MS who have fulfilled the McDonald criteria and whose diagnosis have been approved by a neurologist are registered. For enrollment in this system, patients should refer to the Office of Special Diseases affiliated to any medical sciences universities. In this office, each patient should present the approval letter, fill out a demographic questionnaire (name, birth date, gender, type of MS, marital status, education level, insurance, etc.) and be interviewed by a trained general practitioner who records the date of onset and diagnosis, presenting symptoms, medical history, and disability levels. Then, each patient receives an identification card with a unique code.

In almost all parts of Iran, patients have access to neurologists and those in deprived areas are referred to higher levels through the referral system in primary care levels.[25] Moreover, all MS patients are eligible to receive public care and treatment services based on their records in this registry. Therefore, nearly all MS patients are registered in this database. However, a small number of patients who have not been registered yet may remain underestimated. Registration of MS patients in Iran began in 2005.[3]

The Ethics Committee of Medical Research at Kerman University of Medical Sciences approved this study. To reduce bias, the incidence cases were determined according to the date of diagnosis. The annual incidence rates were calculated from March 21, 2010, to March 20, 2016. March 21 is the beginning of the Persian New Year. Age-specific and gender-specific incidence rates were computed as the newly diagnosed cases in per 100,000 population.

To remove the effect of different population age structures in different years, we adjusted incidence rates by the direct method standardization using 10-year age grouping of the 2000–2025 World Health Organization population as a standard. Moreover, 95% confidence interval (CI) was calculated for the standardized incidence rates using Poisson distribution method. The Poisson regression model was used to analyze each year's trend of MS incidence. Calendar year, as the continuous variable, was used in the model for linear trend, and an interaction term with sex cross-product year was used to test the difference in the trends between males and females. All analyses were performed using Microsoft Excel 2010 and Stata, version 12.0.

Results

A total of 36,287 newly diagnosed cases (8202 [22.6%] males and 28,085 [77.4%] females) were registered in the MS registry

system of MOH from March 21, 2010, to March 20, 2016. This number increased gradually from 3654 in 2010 to 5570 in 2016. The mean age at the time of diagnosis was 31.3 ± 0.8 years for females, 32.3 ± 0.9 years for males, and 31.6 ± 0.9 years overall. MS incidence was more in females than in males in all age groups. The highest incidence rate was observed in the age group of 30–40 years and the lowest in the age group of ≥60 years (Table 1).

The mean age at diagnosis increased significantly from 30.4 ± 9.1 in 2010 to 32.9 ± 9.1 in 2016 (Fig. 1a). During the same period, the female-to-male (F/M) ratio of MS incidence decreased from 3.6 in 2010 to 3.3 in 2016 ($P < 0.001$) (Fig. 1b).

During the study, the age-adjusted mean annual incidence of MS was 6.7 per 100,000 population (95% CI: 6.2–7.2). It was higher in females (10.5 [95% CI: 9.6–11.4]) than in males (3.0 [95% CI: 2.5–3.4]). The age-adjusted incidence rates increased significantly from 4.4 (95% CI: 4.3–4.6) in 2010 to 5.8 (95% CI: 5.7–6.0) in 2016, per 100,000 population, with its peak (6.5 [95% CI: 6.3–6.6]) in 2014 (Fig. 2). During the same period, the age-adjusted incidence rate significantly increased from 1.8 (95% CI: 1.7–1.9) to 2.7 (95% CI: 2.5–2.8) ($P < 0.001$) in males and from 7.6 (95% CI: 7.4–7.9) to 9.1 (95% CI: 8.8–9.4) in females ($P < 0.001$), per 100,000 population. The likelihood ratio test revealed that the trend of MS incidence was significantly different between males and females ($P < 0.003$).

Discussion

Our study revealed that MS incidence increased significantly from 4.9 in 2010 to 6.7 in 2016, per 100,000 population. At the beginning of 2010, MS incidence was relatively low, but it gradually increased and reached its peak (7.5) in 2014 per 100,000 population. To the best of our knowledge, no reliable study has previously investigated the trend of MS incidence in Iran. However, previous studies in some provinces of Iran, such as Tehran and Isfahan, have reported an increasing trend in MS incidence.[21,24] Also, similar to our findings, an increase in MS incidence has been reported from Greece,[13] Norway,[26] Sardinia,[11] Kuwait,[27] and Japan.[28] MS incidence in Greece increased from 2.71 in 1984-89 to 10.73 in 2001–2006, and it increased from 10.2 in 2003–2007 to 13.1 in 2008–2013 in Norway, per 100,000 population. Similarly, the incidence rate rose from 0.17 in 1980–1989 to 0.77 in 2000–2009 in Japan, per 100,000 population. However, the results of a population-based study have revealed that the incidence rate of MS has been stable in Saskatoon, Canada, for 35 years.[29]

In recent years, Iran has experienced significant growth in the field of medicine and access to health services, and patients, even in the deprived areas, have access to neurologists and health services through the referral system.[25] Therefore, the increase in MS incidence in Iran might be the result of improved diagnosis criteria (availability of magnetic resonance imaging [MRI] and paraclinical tests), general knowledge or awareness of the disease and its therapies, and an increasing proportion of people with only minor symptoms and signs who have been diagnosed with MS. If easy access to MRI and/or diagnostic awareness has caused the observed increase, then, the incidence of MS would stabilize or decrease in the coming years.[30]

In this study, the overall mean age at diagnosis was 31.5 years, which is higher than 26 years reported in Kuwait, 26.66 years in the United Arab Emirates, and 27 years in Pakistan.[27,31,32] However, it is lower than 38.3 years reported in Oslo, Norway, 36.2 in the Olmested County, USA, and 38.1 in Western Greece.[13,14,33] Considering that presently the population growth rate is decreasing in Iran, it seems that the average age of MS incidence in Iran is increasing and approaching that of developed countries.

In this study, the mean annual incidence of MS was 6.7 in the total population, 3.0 in males and 10.5 in females, per 100,000 population. These figures place Iran in the high-risk area for MS. The high incidence of MS in Iran may be because of the genetic predisposition of Iranians to MS. A study conducted on migrant Iranians in Bombay, India, has shown that the prevalence of MS in migrant Iranians is higher than the general population.[34] Also, among the Indian immigrants to England, the rate of MS was higher in Parsis than in

Table 1 – Age standardized incidence rate of multiple sclerosis by age group between 2010 and 2016 in Iran (per 100,000 population).

Age group (yr)	Gender	2010	2011	2012	2013	2014	2015	2016	Slope	P-value	Annual incidence rate
<19	Male	0.5	0.6	0.7	0.6	0.5	0.6	0.4	−0.03	0.21	0.5
	Female	2	2.5	2.5	2.5	2.4	2.1	1.7	−0.03	0.01	2.2
	Total	1.1	1.5	1.6	1.5	1.4	1.3	1.1	−0.02	0.04	1.3
20–29	Male	4.0	4.7	5.6	6.0	6.5	6.3	5.4	0.06	0.01	5.4
	Female	14.6	18.7	22.2	22.3	23.8	20.6	19.8	0.02	0.01	20.7
	Total	9.3	11.5	13.7	14.0	15.1	13.4	12.5	−0.01	0.92	11.2
30–39	Male	4.0	5.6	5.9	5.5	6.7	6.5	5.9	0.05	0.01	5.8
	Female	19.5	21.2	21.2	20.8	21.8	21.6	20.9	0.01	0.17	21.1
	Total	10.7	13.3	13.4	13.1	14.1	13.9	13.3	0.06	0.01	15.0
40–49	Male	2.6	4.1	4.1	4.1	4.3	4.4	4.3	0.05	0.01	4.0
	Female	10.5	12.2	12.4	13.6	13.8	13.1	13.5	0.03	0.01	12.7
	Total	6.1	8.1	8.2	8.8	9.0	8.7	8.8	0.05	0.01	8.7
50–59	Male	0.6	1.2	1.5	1.2	1.8	1.7	2.0	0.14	0.01	1.5
	Female	3.4	3.0	2.4	3.4	3.6	4.0	4.6	0.08	0.01	3.4
	Total	1.7	2.1	1.9	2.3	2.7	2.9	3.3	0.13	0.01	2.5
>60	Male	0.07	0.17	0.06	0.20	0.28	0.36	0.25	0.21	0.01	0.2
	Female	0.5	0.4	0.2	0.4	0.6	0.4	0.5	0.02	0.72	0.4
	Total	0.1	0.2	0.1	0.2	0.3	0.4	0.2	0.11	0.01	0.3

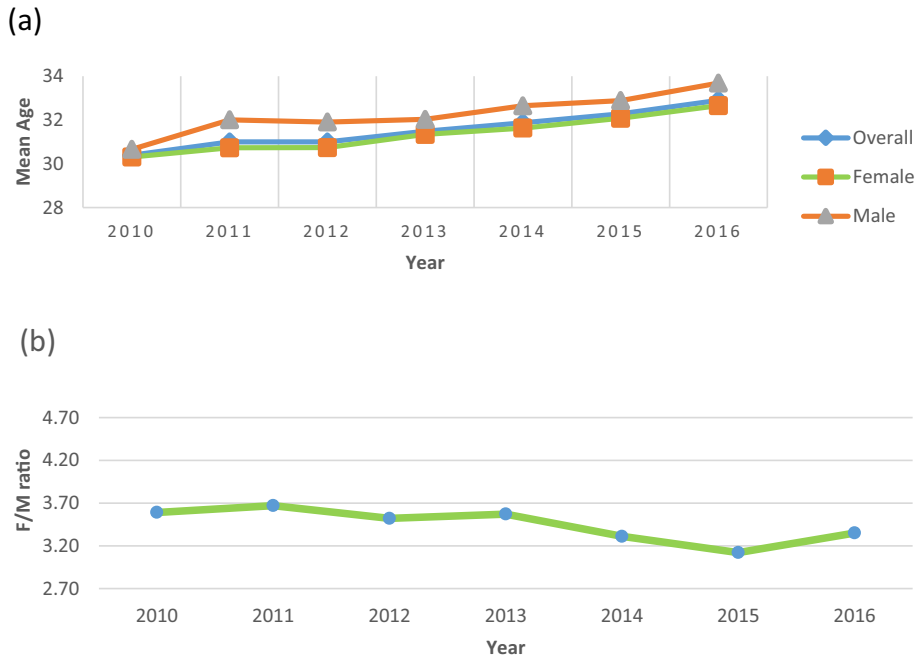

Fig. 1 – The trend of mean age in diagnosis multiple sclerosis (a) and F/M ratio (b) from 2010 to 2016 in Iran. F/M, female-to-male.

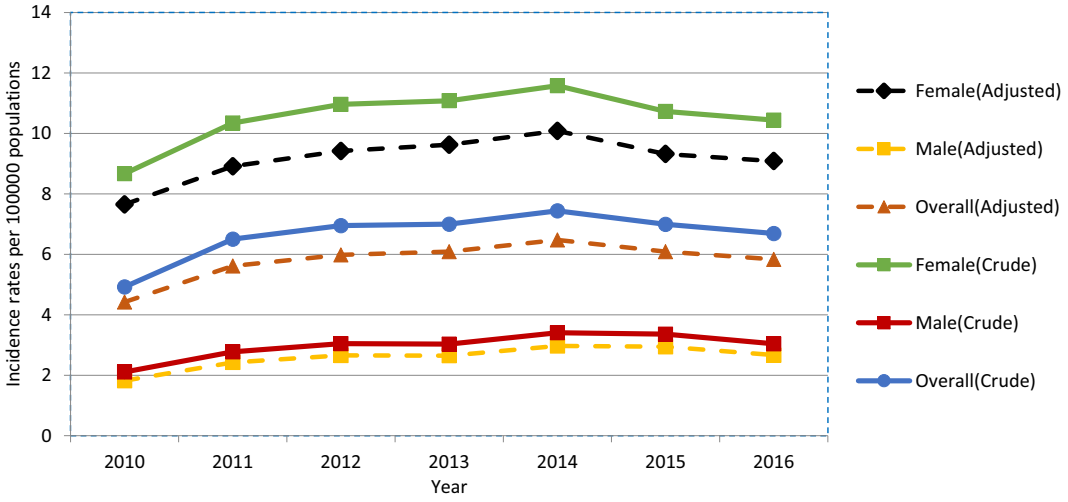

Fig. 2 – The incidence of new multiple sclerosis cases between 2010 and 2016 in Iran.

ethnic Indians.[34] In addition, findings from a study in Norway showed that the prevalence of MS is more common in immigrants from the Middle East (mainly from Iran) than in other non-Western immigrants.[35] Therefore, it can be assumed that Iranians have genetic predisposing factors that are triggered under specific environmental conditions. In addition, a part of the high incidence of MS among Iranians could be attributed to Iran's young population, as MS mainly affects young people.[1]

The incidence rate estimated in our study was higher than the incidence rate reported in the study of Etemadfar et al., in 2013.[24] Similarly, the annual incidence in the present study was significantly higher than the incidence rate estimated in the study of Elhami et al. for the period of 1989–2008.[21] We have no clear explanation for this difference; however, improved general awareness about the disease, along with an increase in the number of neurologists and access to MRI services, may have led to the early detection of MS.

Unlike previous studies in which geographical areas with latitudes lower than 42° have been reported as low-risk areas for MS,[36] our findings indicated that MS incidence in Iran is high, and its incidence rate is more or less comparable to the findings of studies conducted in Europe and North America.[9] MS incidence rate, for example, has been reported 7.6/100,000 in Iceland in 2002–2007.[37] Also, a population-based study from France reported an incidence rate of 7.6/100,000 for MS.[38] Another population-based study reported an

Table 2 – The incidence and F/M ratio of multiple sclerosis (per 100,000) in various part of Iran and some of other countries.

Study	Year	Country/Region/City	Mean age at time of diagnosis (years)	F/M ratio	Annual incidence rate
Etemadifar [9]	2003–2010	Iran (Isfahan)	28.2	3.4	9.1
Present study	2010–2016	Iran (national wide)	31.5	3.1	6.7
Etemadifar [24]	2006–2013	Iran	–	3.3	5.8
Elhami [21]	2000–2008	Iran (Tehran)	29.1	3.1	4.8
Moghtaderi [39]	2009	Iran (south-eastern)	25.9	2.2	2.7
Hader [29]	1970–2004	Canada (Saskatoon)	32.4	2.6	9.5
Celius [33]	1992–1996	Norway (Oslo)	38.1	–	8.7
Granieri [40]	1990–2005	San Marino	31.7	2.6	7.9
Fromont [38]	2001–2007	France	–	2.7	7.6
Eliasdottir [37]	2002–2007	Iceland	36.3	3.0	7.6
Mayr [14]	1985–2000	USA	35.4	–	7.3
Inshasi [31]	2000–2007	United Arab Emirates	26.7	2.8	6.8
Alroughani [27]	2013	Kuwait	35.4	1.8	6.8

F/M, female-to-male.

incidence rate of 8.7/100,000 for MS in Oslo, Norway.[33] A study from Olmsted County, USA, also reported an incidence of 7.3/100,000 for MS.[14] However, we expect significantly higher MS incidence in Europe and North America than in Iran, as Iran is located in a low-risk area based on Kurtzke classification.[12] In addition, evidence suggests that MS incidence increases with the distance from the equator.[7] Table 2 presents MS incidence in different parts of Iran and other countries for comparative purposes.

The proximity of our findings with the reported results from European and North American countries may be because of genetic affinities, as some studies have recognized that Iranians are genetically close to the Europeans, who are an ethnic group susceptible to MS.[35,41] Moreover, as the criteria for the diagnosis and sensitivity of registry system in different studies may not be the same, comparing our findings with those of other studies should be done with caution.

In this study, the average F/M ratio of MS incidence was 3.1. This is similar to the 3.3 reported by Etemadfar et al. and 3.1 reported by Elhami et al.[21,24] Also, the F/M ratio calculated in our study is similar to that reported in Canada, but it is higher than Kuwait.[27,42] However, in recent years, the annual increase in MS incidence in Iranian males was found to be higher than in females, and the F/M ratio was slightly decreasing (Table 1). According to this finding, in Canada, an increase in MS incidence has been reported among males.[42] However, no solid evidence exists for the shift in F/M ratio, but change in lifestyle factors, such as increased smoking, changing the roles of women in the workplace, dietary habits, and the timing of childbearing years, may be involved.[30] However, differences in time of diagnosis and age of onset could potentially affect the sex ratio in the short-term if a relative delay is sex specific. Therefore, sex ratio is suggested to be a measure for long periods.

In this study, the peak of MS incidence was observed in the 30–39 years age group. Almost identical patterns in MS incidences by age were observed in Iceland (peak incidence in 35–39 years age group).[37] A Canadian study found a peak incidence in the 25–34 age group.[29] In a study conducted in Kuwait, the peak of MS incidence was reported in 20–29 age group.[27] In addition, MS incidence in all age groups was higher in females than in males. This finding, according to the reported results from other studies, confirms the high MS incidence among Iranian females. However, in recent years, MS incidence was higher among males compared with females.

The present study was performed only on patients who were registered for treatment in the MOH registration system. Because MS diagnosis is often difficult, the cases who have not yet been diagnosed by a neurologist or have not been registered for treatment may not be considered as a potential case. Therefore, our estimate may be less than the actual rate of MS incidence in Iran. However, the incidence rate obtained from our study is supported by the results of other studies, and there is no robust reason to believe that underestimation of MS incidence rate has changed over time.

Conclusion

This study provided evidence for an increase in MS incidence in Iran. However, controlling confounding factors, such as changing the ability to diagnose MS and completeness of ascertainment, are not possible, but examination of the demographic data suggest that this has occurred mainly as a result of increasing MS incidence among females. Nevertheless, in recent years, the annual percent change of MS incidence has occurred more in males, and it seems that sex-specific environmental factors have been operative in the past years. Therefore, further longitudinal studies can explain the reasons for these changes. In addition, the average age of MS incidence in Iran has been increasing and is approaching that of developed countries.

Author statements

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Ethical approval

The Ethics Committee of Medical Research at Kerman University of Medical Sciences approved this study.

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Competing interest

None to be declared.

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