ORIGINAL ARTICLE

Temporal trends of incidence and prevalence of multiple sclerosis in Razavi Khorasan Province, Northeast Iran

Mohammad Sarmadi [1,2] • Hanie Saravani [3,4] • Omid Azizi [2,5] • Fereshteh Najafi [6] • Mostafa Hadei [7] • Jalil Momeni [8] • Edris Bazrafshan [1,2]

Abstract

Objectives The prevalence of multiple sclerosis (MS) in the Persian Gulf countries has been significantly increasing during the past decades. This study was conducted for investigating the prevalence and incidence of MS in Northeast Iran (Khorasan Razavi province).

Methods This cross-sectional study was conducted during 1 January 1988 and 23 September 2018. All patients with a clinically definite diagnosis of MS according to the McDonald criteria (2005) and MRI along with the medical diagnosis, recorded in the Khorasan MS society, were considered for calculation of crude and age-standardized prevalence, and incidence rates of MS. The periodic incidence rates were calculated based on the year of onset of MS. Also, we calculated gender ratios for prevalence and incidence rates.

Results The mean age-standardized prevalence and incidence rates of MS in the Khorasan Razavi were 8.69 (95% CI 8.05–9.41) per 100,000 (3.99 (95% CI 3.39–4.74) for males, 13.49 (95% CI 12.37–14.76) for females). Age-standardized prevalence was 48.87 (95% CI 48.37–49.35) per 100,000 (22.47 (95% CI 22.01–22.93) for males, 75.65 (95% CI 74.80–76.51) for females). Also, the mean incidence and prevalence for Mashhad County as capital of province were 11.38 and 59.09 per 100,000 populations, respectively. The female/male ratio was 3.33 for all age groups.

Conclusion Our results showed that this region is a high-risk area for MS like central region of Iran. Our results revealed that the prevalence and incidence of MS in the study area have increased during the recent decades with a sharp slope.

Keywords Multiple sclerosis · Prevalence · Incidence · Epidemiology

Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by inflammation, demyelination of neurons, and damage to the central nervous system (CNS) [1]. MS is more prevalent among young people and women [2–4]. The etiology of this disease has been not known exactly, and it seems that it can be developed under the effect of several factors such as environmental and genetic factors [5–8]. According to previous studies, Epstein-Barr virus (EBV), vitamin D deficiency, and smoking are best documented as related with an increased risk of MS [9–12]. On the other hand, researchers believed that the risk of MS is related to body mass index (BMI) [13].

✉ Mohammad Sarmadi
  sarmadim1@thums.ac.ir; msarmadi2@gmail.com

1 Department of Environmental Health Engineering, School of Health, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran

2 Health Sciences Research Center, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran

3 Student of Emergency Nurse, School of Nursing and Midwifery, Birjand University of Medical Sciences, Birjand, Iran

4 Imam Ali Research Hospital, School of nursing and midwifery, Zahedan University of Medical Sciences, Zahedan, Iran

5 Department of Laboratory Sciences, School of Paramedical Sciences, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran

6 Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

7 Department of Environmental Health Engineering, School of Public Health, Tehran University of Medical Science, Tehran, Iran

8 Student Research Committee, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran

Among the countries of the Middle East, Iran has been one of the interesting countries for researchers to conduct MS-related epidemiological studies. Most new methodologically well-designed studies such as cohort ones clearly have showed that the MS distribution is much more complex than previously thought. According to the MS geographical gradient hypothesis proposed by Kurtzke, Iran is located in an area with a low prevalence (less than 5 per 100,000), while in a recent study conducted by Azami et al., the prevalence of this disease was reported to be high (30 per 100,000) [14], even a prevalence ratio of more than 100 per 100,000 population has been reported in some studies [15, 16].

In addition, the incidence rate of the disease varies in different parts of Iran. For example, in Isfahan and Sistan and Balouchestan provinces, the incidence rate of MS has been reported to be 9.1 and 0.62 per 100,000 population, respectively [17, 18]. In a national population-based study by Hosseinzadeh et al., the overall incidence rate in Iran was 6.7 per 100,000 population (10.5 and 3 for female and male, respectively) [19].

The reasons for the high prevalence of MS in Iran are unclear. Increasing rates of urbanization, modernization, and industrialization and development of diagnostic facilities, lifestyle changes, air pollution, etc., have been introduced as factors affecting the high prevalence of this disease in Iran [6, 20–22]. In addition, most of the studies in Iran have been conducted in the central regions, especially the two cities of Isfahan and Tehran, which are well known in terms of the MS prevalence. However, other areas of Iran, especially the northeast, where the important metropolis of Mashhad (in terms of tourism and weather conditions) is located, have not received much attention. Therefore, the present study is designed to investigate the trend of prevalence and incidence of multiple sclerosis in Khorasan Razavi province during the last three decades.

Methods

Study population

This is a cross-sectional study conducted on Khorasan Razavi province (Iran) during 1988 to 2018. The study is designed based on the STROBE protocol [23]. All methods were carried out in accordance with relevant guidelines. The Khorasan Razavi province with an area of 118,884 km^2 is located in northeastern Iran (36.2980° N, 59.6057° E) (Fig. 1). The province also shares a border with Afghanistan and Turkmenistan to the east, and it is the second largest province in Iran. Its total population in September 23, 2018 (in prevalence day), was reported to be 6,434,501, according to the Statistical Centre of Iran [43]. The province consists of 28 counties, 73 cities, and 3281 villages, and its center is the city of Mashhad (the capital

of Razavi Khorasan province). Unfortunately, data from the two counties (Sarakhs and Bajestan) were not available, since MS Society has not established in these cities, and there were no reliable datasets. The population of the province is almost homogeneous culturally and racially. Figure 1 shows the Khorasan Razavi province along with its counties.

The data on the MS patients in the Khorasan Razavi province from January 1, 1988, to September 23, 2018, was collected. At county level, patients are registered at MS Society of each county. The patients were required to register at the MS Society in order to get their medications. In addition, they were asked to keep their personal information up to date and re-register every year. This information is continuously sent to the provincial and national MS Society. In addition, the Treatment Deputy of Medical Universities records the information of MS patients.

After removing the duplicate records and correcting for the residential address, the confirm data is sent back to each provincial MS Society. This dataset is the most reliable MS dataset in Iran and has been used in many national and provincial studies [25, 26]. In fact, all of the MS patients receive their medications through this registration system.

Data collection

The information was taken from the Khorasan MS Society and was coded to respect the individual identity of the patients. We used secondary data, so it is not required to consent of patient. Also, all data gathered based on some codes and we did not have access to the name of patient. In order to join the MS society, each patient must have provided a neurologist's confirmation based on the latest diagnostic criteria. MS confirmation has been approved by clinical finding, McDonald criteria (2005 and 2010), magnetic resonance imaging (MRI), evoked potential studies, and cerebrospinal fluid (CSF) examination [18, 26].

Demographic information of patients, number of patients, sex, city and county population, the diagnosis age, patient's age, residential area (urban or sub-urban), and other variables were collected in a checklist and entered to an SPSS file. Demographic information of the population was obtained from the Statistical Centre of Iran [43]. The MS Society of Khorasan was considered as one of the main sources for MS information.

Only people who are medically diagnosed with MS and are registered in the Khorasan MS Society are included in the study. Therefore, patients from other provinces who have been registered to receive medication or medical services in the MS Society in a short time period were excluded.

The age- and sex-specific prevalence and incidence rates (per 100,000 populations) were calculated along with a 95% confidence interval (95% CI). Age of onset in the patients was from 13 to 72 years old. Since the age at onset in MS has been
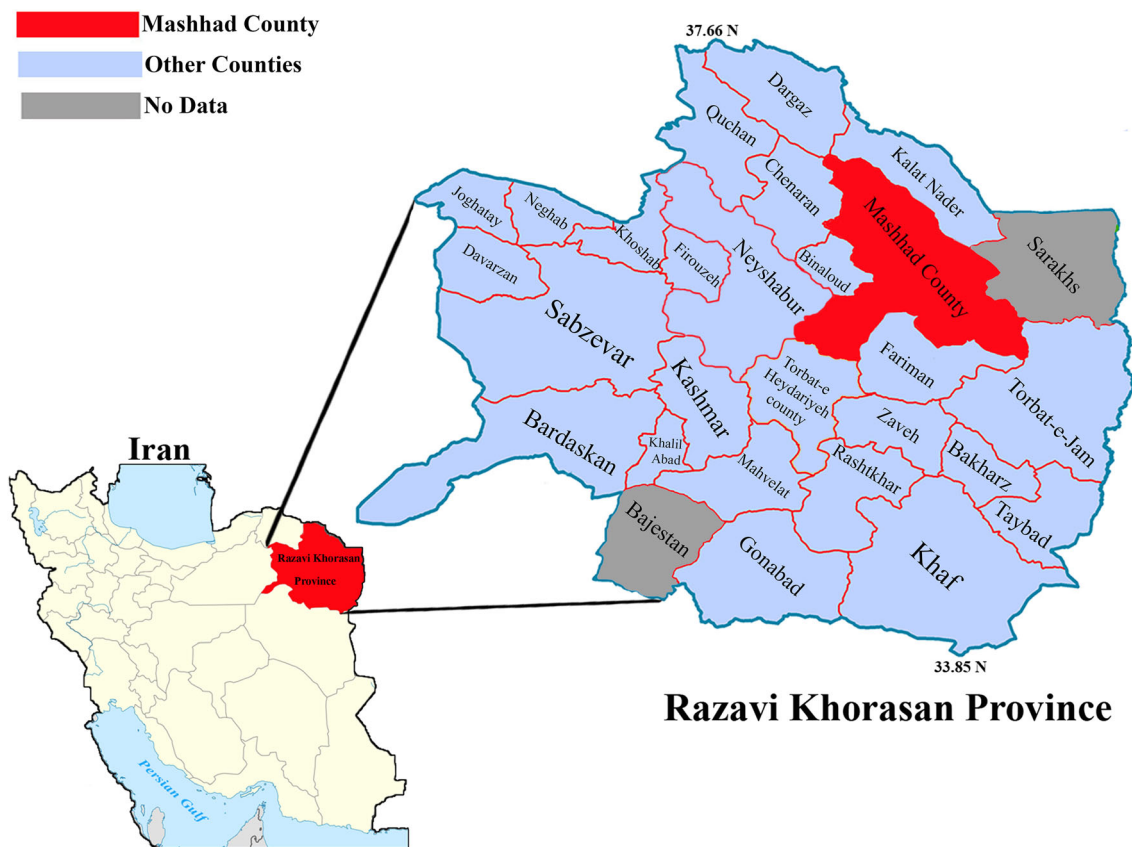
Fig. 1 Location of Khorasan Razavi province and its 28 counties

reported periodically, the mentioned period was divided into 5-year periods. The prevalence and incidence of the disease were calculated based on the age at the onset in MS and the population of city in that year. According to the age group of patients, the prevalence was calculated and reported at different ages. The data of 3707 MS patients registered in the MS Association was extracted alongside with their demographic data; however, some of them did not meet the study criteria. We confirm that all methods were carried out in accordance with relevant guidelines and regulations. This study has been approved by the Ethical Committee of Torbat Heydariyeh University of Medical Sciences (IR.THUMS.1398.021).

Statistical analysis

Age- and sex-specific prevalence between the January 1, 1988, and September 23, 2018, were calculated based on the age at onset in MS and the population number in 2018. The number of patients resided in Khorasan Razavi province until September 2018 was divided to the population to obtain prevalence. Crude sex and age area-specific prevalence were calculated as the number of cases on prevalence day per 100,000 inhabitants.

In addition, age-standardized prevalence was calculated using the standard population of Iran in 2016 [43]. The incidence was calculated for 5-year periods based on the age at onset in MS. For this, the number of new cases of MS in each period was divided to the population in that period. The average of incidence for the Khorasan Razavi province (except for Sarakhs and Bajestan counties), Mashhad county, and other counties of the province are reported. Confidence interval for different groups was calculated using Poisson's analysis. Significant differences between the groups were tested by unpaired t-tests and the Chi-square test or Fisher exact test, as appropriate. $P < 0.05$ were considered statistically significant. SPSS (version 16) and STATA (version 14) were used for data analysis. Patients with incomplete information in terms of age, sex, or diagnosis date were treated as missing data but they were not removed from the study.

Results

A total of 3707 patients with MS have been registered by MS Society until September 23, 2018. Of these, 741 patients were excluded from the study. These patients were specifically from other provinces and have traveled to Mashhad only for a limited period of time or have referred from other cities to the Khorasan MS Society to get medication.

The remaining cases (2966 cases, 685 men and 2281 women, mean age 37.07 ± 9.67) were evaluated in this study. Figure 2 clearly shows that during the 5-year periods between

1988 and 2018, the number of patients in Khorasan Razavi province, as well as in Mashhad and other counties, has increased significantly, so that the highest number of patients was observed in the period 2013–2018 (1381 cases, 1078 females and 303 males). The results showed that there is a significant difference between the number of patients in Mashhad county and other counties of the province ($P <$
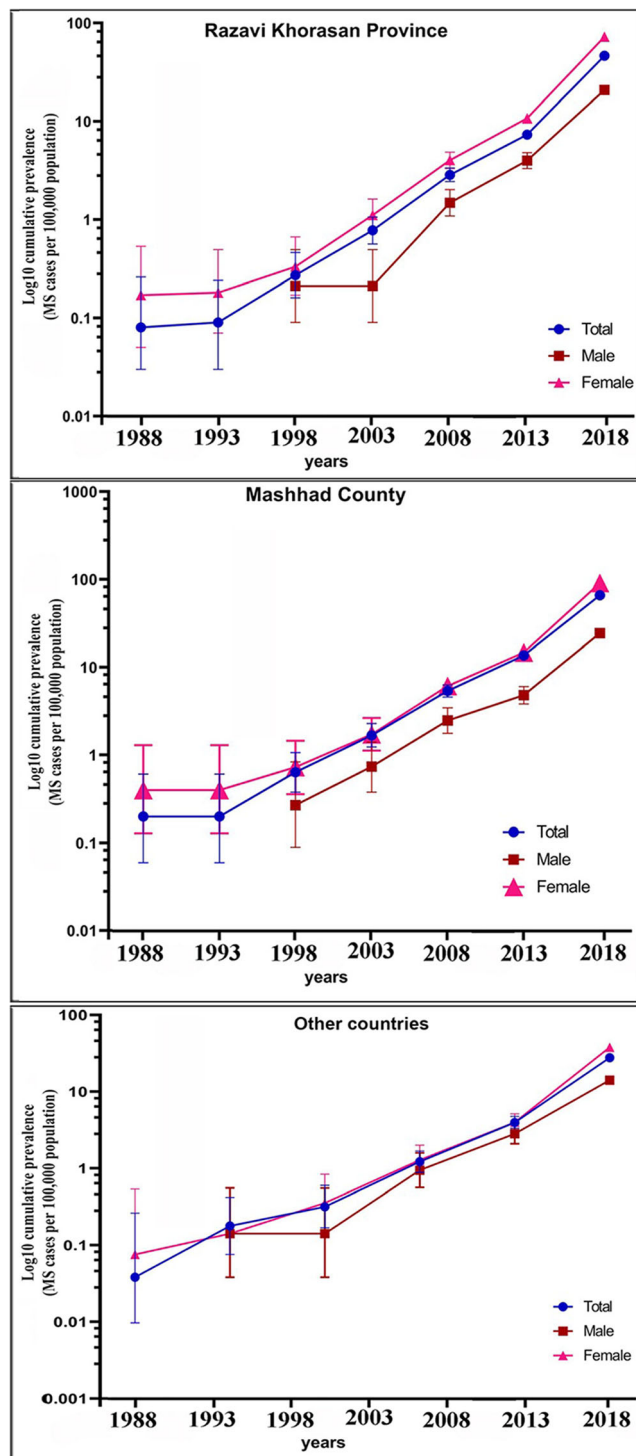

Fig. 2 Cumulative prevalence of MS patients in six 5-year periods

0.05). It is also clear that an increase in the prevalence of female with MS is occurring at a much higher slope than in men (Fig. 2).

The crude prevalence of MS stratified in terms of age for Khorasan Razavi province, Mashhad County, and other counties has been presented in Table 1. The overall crude prevalence in the Khorasan Razavi province with a population of 6,307,867 was 47.02/100,000 population (95% CI 45.36–48.74). Also, overall crude prevalence for Mashhad county and other counties of Khorasan Razavi province were 58.51/100,000 population (95% CI 56.01–61.11) and 32.98/100,000 population (95% CI 30.93–35.16), respectively. A significantly higher prevalence was showed in females than in males in all of the age groups ($P < 0.001$). The age-adjusted prevalence standardized to the Iran population were 48.87 per 100,000 population (95% CI 48.37–49.35), 59.05 per 100,000 population (95% CI 58.52–59.59), and 35.6 per 100,000 population (95% CI 35.19–36.02) for Khorasan Razavi province, Mashhad county, and other counties, respectively (Table 1).

The incidence rates of MS in the Khorasan Razavi province, Mashhad County, and other counties during 5-year periods are presented in Table 2. High rates of incidence can be observed in case of Mashhad County for female (46.2 per 100,000) during the 2013–2018 period. The overall incidence of MS in Mashhad was 11.38 per 100,000. Also the sex-specific average of incidence rate in each period has been shown.

The crude 5-year incidence of MS in this population was between 0.53 (95% CI 0.36–0.8) and 23.17(95% CI 21.98–24.42) per 100,000 (range 0.68–36.66 for female and 0.39–10.06 for male per 100,000). The age standardized rates (adjustment for the Iranian population) for total, males, and females were 3.99, 8.69, and 13.49 per 100,000, respectively. The incidence rate for females was 1.55 times higher than that for males.

The female/male ratio of MS prevalence for the whole province was 3.33. In case of Mashhad, this ratio was 3.56, indicating a higher ratio comparing to the whole province. The highest amounts of F/M ratio were observed for 19–30 and 31–45 age groups (Appendix Table 3). The mean age of patients in prevalence year and the age at onset in MS do not differ remarkably in different parts of the province; however, these were lower in Mashhad, comparing to the whole province and other counties (Appendix Table 4).

Discussion

The prevalence and incidence of MS in the Persian Gulf countries has been significantly increasing during the past decades [27–29]. Iran has been a region of interest for MS research because it is located in a low-risk area of MS, but in some areas, especially Tehran and Isfahan, the prevalence is very high. In

Table 1 Age, sex, and residence place-specific MS prevalence rates in Khorasan Razavi province (per 100,000 individuals in the population) on September 23, 2018

Age group	Male			Female			Total		
	Cases	Population	Prevalence (95% CI)	Cases	Population	Prevalence (95% CI)	Cases	Population	Prevalence (95% CI)
Khorasan Razavi Province[a]									
<18	9	1,050,129	0.86 (0.45–1.65)	22	1,002,908	2.19 (1.44–3.33)	31	2,053,037	1.51 (1.06–2.15)
19–30	153	681,746	22.44 (19.15–26.3)	602	680,260	88.50 (81.7–95.85)	755	1,362,005	55.43 (51.62–59.53)
31–45	353	786,246	44.90 (40.45–49.83)	1229	767,713	160.09 (151.39–169.28)	1582	1,553,960	101.80 (96.91–106.94)
46–60	156	421,732	36.99 (31.62–43.27)	393	426,401	92.17 (83.49–101.74)	549	848,133	64.73 (59.54–70.38)
>61	14	239,951	5.84 (3.46–9.85)	35	250,780	13.96 (10.02–19.44)	49	490,732	9.99 (7.55–13.21)
Total	685	3,179,803	21.54 (19.99–23.22)	2281	3,128,064	72.92 (69.99–75.97)	2966	6,307,867	47.02 (45.36–48.74)
Mashhad County[b]									
<18	5	554,375	0.90 (0.38–2.17)	16	531,529	3.01 (1.84–4.91)	21	1,085,904	1.93 (1.26–2.97)
19–30	113	374,364	30.19 (25.1–36.3)	431	387,489	111.23 (101.21–122.24)	544	761,853	71.41 (65.65–77.66)
31–45	231	446,663	51.72 (45.46–58.83)	887	438,705	202.19 (189.32–215.92)	1118	885,368	126.28 (119.09–133.89)
46–60	90	240,200	37.47 (30.48–46.07)	231	240,894	95.89 (84.3–109.08)	321	481,094	66.72 (59.81–74.43)
>61	6	126,783	4.73 (2.13–10.53)	20	128,806	15.53 (10.02–24.07)	26	255,589	10.17 (6.93–14.94)
Total	445	1,742,385	25.54 (23.27–28.03)	1585	1,727,422	91.76 (87.35–96.38)	2030	3,469,808	58.51 (56.01–61.11)
Other counties[c]									
<18	4	495,753	0.81 (0.30–2.15)	6	471,380	1.27 (0.57–2.83)	10	967,133	1.03 (0.56–1.92)
19–30	40	307,381	13.01 (9.55–17.74)	171	292,771	58.41 (50.28–67.85)	211	600,152	35.16 (30.72–40.24)
31–45	122	339,584	35.93 (30.09–42.90)	342	329,009	103.95 (93.5–115.56)	464	668,592	69.40 (63.37–76.01)
46–60	66	181,532	36.36 (28.56–46.28)	162	185,508	87.33 (74.87–101.86)	228	367,039	62.12 (54.56–70.73)
>61	8	113,168	7.07 (3.54–14.14)	15	121,974	12.30 (7.41–20.4)	23	235,143	9.78 (6.5–14.72)
Total	240	1,437,418	16.70 (14.71–18.95)	696	1,400,641	49.69 (46.13–53.52)	936	2,838,059	32.98 (30.93–35.16)

CI confidence interval

[a] Age-adjusted prevalence for the Iranian standard population (2016) was 22.47 (22.01–22.93) for male, 75.65 (74.80–76.51) for female, and 48.87 (48.37–49.35) for total case

[b] Age-adjusted prevalence for the Iranian standard population (2016) was 25.90 (25.41–26.4) for male, 92.31 (91.37–93.26) for female, and 59.05 (58.52–59.59) for total case

[c] Age-adjusted prevalence for the Iranian standard population (2016) was 18.11 (17.70–18.53) for male, 53.59 (52.87–54.32) for female, and 35.6 (35.19–36.02) for total case

general, MS in Iran does not conform to the global patterns of MS. Also, according to a literature review [14], most studies have been conducted in the central regions of Iran and no attention has been paid to border areas, especially in the northeast, where large cities such as Mashhad, Sabzevar and Neishabour are located. As a result, the present study examined the epidemiology of the disease over a 30-year period in this region. Studies that fully investigate the prevalence and incidence of multiple sclerosis in all provinces of Iran are very limited. The prevalence range in these studies is reported to be between 7.2 and 89 per 100,000 for different provinces [14].

In studies conducted in other parts of the world, a regional variation based on sex has been observed. For example, Alonso and Hernán surveyed the global epidemiological data for MS between 1966 and 2007, and estimated that the annual incidence rate of MS equals to 3.6 in female and 2 in male per 100,000 populations. The highest rates were found in Finland

(6.2 and 10.3 per 100,000 male and female, respectively), while the lowest measures were reported for Australia. Also, in Europe, the overall incidence was reported to be between 3.5 and 5.5 per 100,000 [30, 31].

The results showed that the female-to-male (F/M) ratio of MS incidence in Khorasan Razavi province is more than 3, which is consistent with the results of many studies. For example, in Iran, F/M ratios of 3.11 and 3.37 are reported for Tehran and Isfahan, respectively. Similar results have been also reported in Poland and Brazil (2.4 and 3.13, respectively). In countries such as Canada, there were also significant differences in female to male ratios (7.7). Also, our results showed that in Khorasan Razavi province, the highest values of F/M ratio are in the 19- to 45-year-old age groups, possibly due to the highest prevalence of multiple sclerosis in this age group. Although the F/M ratio in the present study was not higher than the ratio reported from other parts of the world,

Table 2 Incidence of MS per 100,000 populations in Khorasan Razavi Province patients, January 1988 to September 2018

Years	Male			Female			Total		
	Cases	Population	Incidence (95% CI)	Cases	Population	Incidence (95% CI)	Cases	Population	Incidence (95% CI)
Khorasan Razavi Province[a]									
1988–1993	9	2,299,590	0.39 (0.2–0.75)	15	2,196,750	0.68 (0.41–1.13)	24	4,496,339	0.53 (0.36–0.8)
1993–1998	22	2,430,115	0.91 (0.6–1.37)	59	2,415,899	2.44 (1.89–3.15)	81	4,846,014	1.67 (1.34–2.08)
1998–2003	40	2,560,551	1.56 (1.15–2.13)	111	2,537,103	4.38 (3.63–5.27)	151	5,097,653	2.96 (2.53–3.47)
2003–2008	127	2,727,882	4.66 (3.91–5.54)	373	2,723,647	13.69 (12.37–15.16)	500	5,451,529	9.17 (8.4–10.01)
2008–2013	184	2,868,241	6.42 (5.55–7.41)	645	2,792,416	23.1 (21.38–24.95)	829	5,660,656	14.64 (13.68–15.68)
2013–2018	303	3,020,443	10.03 (8.96–11.23)	1078	2,940,595	36.66 (34.54–38.91)	1381	5,961,039	23.17 (21.98–24.42)
Mashhad County[b]									
1988–1993	5	1,018,217	0.49 (0.2–1.18)	11	972,681	1.13 (0.63–2.04)	16	1,990,898	0.8 (0.49–1.31)
1993–1998	18	1,104,287	1.63 (1.03–2.59)	46	1,097,827	4.19 (3.14–5.59)	64	2,202,115	2.91 (2.27–3.71)
1998–2003	27	1,222,649	2.21 (1.51–3.22)	84	1,211,453	6.93 (5.6–8.59)	111	2,434,102	4.56 (3.79–5.49)
2003–2008	74	1,373,205	5.39 (4.29–6.77)	266	1,371,074	19.4 (17.2–21.88)	340	2,744,279	12.39 (11.14–13.78)
2008–2013	120	1,514,673	7.92 (6.62–9.47)	437	1,474,631	29.63 (26.98–32.55)	557	2,989,305	18.63 (17.15–20.25)
2013–2018	201	1,647,564	12.2 (10.62–14.01)	741	1,604,009	46.2 (42.99–49.64)	942	3,251,572	28.97 (27.18–30.88)
Other counties[c]									
1988–1993	4	1,281,373	0.31 (0.12–0.83)	4	1,224,068	0.33 (0.12–0.87)	8	2,505,441	0.32 (0.16–0.64)
1993–1998	4	1,325,828	0.3 (0.11–0.8)	13	1,318,072	0.99 (0.57–1.7)	17	2,643,899	0.64 (0.4–1.03)
1998–2003	13	1,337,901	0.97 (0.56–1.67)	27	1,325,650	2.04 (1.4–2.97)	40	2,663,551	1.5 (1.1–2.05)
2003–2008	53	1,354,676	3.91 (2.99–5.12)	107	1,352,573	7.91 (6.55–9.56)	160	2,707,250	5.91 (5.06–6.9)
2008–2013	64	1,353,567	4.73 (3.7–6.04)	208	1,317,784	15.78 (13.78–18.08)	272	2,671,352	10.18 (9.04–11.47)
2013–2018	102	1,372,880	7.43 (6.12–9.02)	337	1,336,586	25.21 (22.66–28.05)	439	2,709,466	16.2 (14.76–17.79)

[a] The mean period incidence, based on a 6-period of observation, was 3.99 (95%CI 3.39–4.74) per 100,000 in male, 13.49 (95%CI 12.37–14.76) per 100,000 among female, and 8.69 (95%CI 8.05–9.41) per 100,000 among total. The incidence rate for women was 3.4 times higher than that for men

[b] The mean period incidence, based on a 6-period of observation, was 4.97 (95%CI 4.02–6.21) per 100,000 in male, 17.91 (95%CI 16.09–20.05) per 100,000 among female, and 11.38 (95%CI 10.34–12.57) per 100,000 among total. The incidence rate for women was 5.42 times higher than that for men

[c] The mean period incidence, based on a 6-period of observation, was 2.94 (95%CI 2.27–3.91) per 100,000 in male, 8.71 (95%CI 5.51–10.21) per 100,000 among female, and 5.76 (95%CI 5.08–6.65) per 100,000 among total. The incidence rate for women was 2.96 times higher than that for men

previous studies have shown that Iranian women are at higher risk of MS than men. For the time being, Iranian women have less exposure to the sunlight and less physical activity than men which can lead to vitamin D deficiency and, consequently, increased risk of MS [32–34]. Also, studies conducted by Johns Hopkins University have shown that obesity can be a very important risk factor for developing MS [13]. Other reasons for this may be related epigenetic modification of DNA including environmental or hormonal factors that differ between male and female. For example, responses to environmental factors such as sun exposure and vitamin D are different in male and female groups [9, 35]. Another study suggested lifestyle factors such as dietary habits, increased smoking rate, the timing of childbearing years, and changing the role of women in the workplace may be involved [36].

Until recent years, Khorasan Razavi province was considered as a region with a moderate or low risk of MS [6]. Limited studies conducted in different cities of the province in recent years have shown a high prevalence of MS. For instance, during a study conducted in 2018, in the cities of Torbat Heydarieh, high prevalence was reported, indicating a change in the trend of MS in the province [26].

However, the results of the present study show that the prevalence of MS is 47 per 100,000 (21.54 for men and 72.92 for women). The high incidence of MS in the last two decades has made this province a high-risk area (prevalence of more than 30 per 100,000). In addition, the prevalence in the metropolitan area of Mashhad was 58.51 per 100,000 (25.54 for men and 91.76 for women). A total of 2966 MS patients were identified in the whole province, of which 2030 and 936 were residents of Mashhad and other counties of Khorasan Razavi province, respectively. The high prevalence of MS in Mashhad can be attributed to the factors such as better access to modern diagnostic facilities, the presence of neurologists, disease registration and patient support systems, introduction of routine MRI tests, improvement of accurate diagnostic methods such as McDonald tests, different lifestyles, and urbanization and modernity effects including air pollution. In

Dehghani et al.'s study, factors such as better social and economic situation along with greater access to diagnostic facilities and higher number of specialists in a region were considered among the possible factors influencing the variety of prevalence in different regions [26]. Furthermore, higher incidence and accumulation of disease cases can be another factor for the different prevalence ratios among regions [37–39].

The 5-year raw incidence rates of MS have risen in recent years, from 0.53 per 100,000 in 1988–1993 to 23.17 per 100,000 in 2013–2018. For Khorasan Razavi province, the average of incidence in all the six time periods was calculated to be 8.7 per 100,000 (Table 2). There is also a significant difference between the incidence in the Mashhad County and the other counties. Although this difference between men is not significant, but in the group of women, a distinct difference was observed, indicating the difference in risk of disease between residents of Mashhad and other areas, especially for the female population. Several factors can be involved. For example, vitamin D deficiency can be observed among Iranian women, especially those living in large cities, possibly due to their special lifestyle, insufficient physical activity, and the use of sunscreen and cosmetic products. In particular, Iranian women suffer from vitamin D deficiency during adolescence and youth [40, 41].

Also, some studies have considered high obesity rate in a region as a risk factor of MS [42]. As a matter of fact, a high percentage of the Iranian population, especially urban women, suffer from obesity [43]. In addition, factors such as air pollution, stress, and differences in dietary patterns and access to diagnostic facilities can be a factor in the high incidence of MS in large cities' populations [26].

The average age of the patients in the year of prevalence calculation and in the year of disease onset did not show a significant difference between the Khorasan Razavi province, Mashhad County, and other counties (Appendix Table 4). On the other hand, the average age of onset of the disease has decreased during the study period until 2018, probably due to the improvement and advancement of medical diagnostic equipment and facilities, as well as increasing the general literacy level of community about the disease. For example, one of the effective factors in the diagnosis of neurological diseases is the increase in per capita neurologist in Iran [26].

One of the limitations of this study is the inability to determine the patients with a long history of MS that can underestimate the parameters. There are also issues with people's access to health care, which is one of the limitations of epidemiological studies. On the other hand, it is possible that some patients especially the young ones may not have referred to health care centers due to the mild conditions of the disease. In addition, because of the fact that MS registration system has improved in recent years, some cases may not have been recorded over time, or due to changes in diagnostic tests, similar process may not be performed for everyone. However, this study can be considered as a map for the distribution of MS in northeast of Iran, and be a model for other provinces of Iran and other countries. Long-term study of chronic diseases such as MS is one of the most important advantages of these studies.

Conclusion

The results of this study showed that contrary to what was previously thought, the northeastern region of Iran, and especially the city of Mashhad, has become a high-risk area for MS over the past three decades. It was also found that the prevalence ratio and incidence rate of MS can considerably vary in different parts of a province. In addition, noteworthy is the significant increase in the prevalence ratio of women to men. According to the results, as can be seen in other parts of Iran, MS incidence and prevalence rates in large cities are much higher than those in rural areas and smaller cities.

Appendix

Table 3 Age-specific female-to-male (F/M) prevalence ratio for MS

Age category	Khorasan Razavi province	Mashhad county	Other counties
<18	2.444	3.2	1.5
19–30	3.935	3.814	4.275
31–45	3.482	3.84	2.803
46–60	2.519	2.567	2.455
>61	2.5	3.333	1.875
Total	3.33	3.562	2.9

Table 4 Mean age of patients in prevalence year and the age at onset in MS

Year	Age at disease onset for total case		Age at prevalence day (y) for total case	
	Mean	95% CI	Mean	95% CI
Khorasan Razavi Province				
1988–1993	32.87	32.39–33.34	49.16	47.15–51.17
1993–1998	30.49	29.94–31.04	48.42	45.01–51.82
1998–2003	30.82	30.06–31.59	43.58	42.06–45.10
2003–2008	29.61	28.17–31.06	40.81	40.00–41.61
2008–2013	30.84	29.08–32.61	36.67	36.10–37.24
2013–2018	24.82	22.45–27.2	34.33	33.84–34.81
Mashhad County				
1988–1993	31.92	31.38–32.47	49.56	47.29–51.83
1993–1998	29.74	29.1–30.37	48.94	44.56–53.32
1998–2003	30.40	29.5–31.31	42.41	40.66–44.15
2003–2008	28.69	27.02–30.36	40.35	39.4–41.3
2008–2013	31.15	29.17–33.12	36.03	35.37–36.68
2013–2018	25.09	21.9–28.28	33.35	32.79–33.91
Other counties				
1988–1993	34.90	33.99–35.81	48.38	40.53–54.22
1993–1998	32.06	31.01–33.11	47.65	42.93–52.37
1998–2003	31.69	30.27–33.11	46.83	43.86–49.79
2003–2008	31.95	29.1–34.79	41.77	40.26–43.27
2008–2013	29.64	25.25–34.03	37.99	36.88–39.1
2013–2018	24.33	19.34–29.33	36.43	35.49–37.37

Declarations

References

1. Stadelmann C, Wegner C, Brück W (2011) *Inflammation, demyelination, and degeneration—recent insights from MS pathology.* Biochim Biophys Acta (BBA)-Molec Basis Dis 1812(2):275–282
2. Ysrraelit MC, Correale J (2019) *Impact of sex hormones on immune function and multiple sclerosis development.* Immunology 156(1): 9–22
3. Bergamaschi R, Monti MC, Trivelli L, Introcaso VP, Mallucci G, Borrelli P, Gerosa L, Montomoli C (2020) *Increased prevalence of multiple sclerosis and clusters of different disease risk in Northern Italy.* Neurol Sci 41(5):1089–1095
4. Branco M, Ruano L, Portaccio E, Goretti B, Niccolai C, Patti F, Chisari C, Gallo P, Grossi P, Ghezzi A, Roscio M, Mattioli F, Bellomi F, Simone M, Viterbo RG, Amato MP (2019) *Aging with multiple sclerosis: prevalence and profile of cognitive impairment.* Neurol Sci 40(8):1651–1657
5. Bagur MJ, Murcia MA, Jiménez-Monreal AM, Tur JA, Bibiloni MM, Alonso GL, Martínez-Tomé M (2017) *Influence of diet in multiple sclerosis: a systematic review.* Adv Nutr 8(3):463–472
6. Dehghani R, Yunesian M, Sahraian MA, Gilasi HR, Kazemi Moghaddam V (2015) *The evaluation of multiple sclerosis dispersal in Iran and its association with urbanization, life style and industry.* Iran J Public Health 44(6):830–838
7. Killin LO et al (2016) *Environmental risk factors for dementia: a systematic review.* BMC Geriatr 16(1):1–28
8. Kazemi Moghadam V, Dickerson AS, Shahedi F, Bazrafshan E, Seyedhasani SN, Sarmadi M (2021) *Association of the global distribution of multiple sclerosis with ultraviolet radiation and air pollution: an ecological study based on GBD data.* Environ Sci Pollut Res Int 28(14):17802–17811
9. Harbo HF, Gold R, Tintoré M (2013) *Sex and gender issues in multiple sclerosis.* Ther Adv Neurol Disord 6(4):237–248
10. Degelman ML, Herman KM (2017) *Smoking and multiple sclerosis: a systematic review and meta-analysis using the Bradford Hill criteria for causation.* Multiple Sclerosis Relat Disord 17:207–216
11. Ascherio A, Munger KL, Simon KC (2010) *Vitamin D and multiple sclerosis.* Lancet Neurol 9(6):599–612
12. Jasper EA, Nidey NL, Schweizer ML, Ryckman KK (2020) *Gestational vitamin D and offspring risk of multiple sclerosis: a systematic review and meta-analysis.* Ann Epidemiol 43:11–17

13. Mowry EM, Azevedo CJ, McCulloch CE, Okuda DT, Lincoln RR, Waubant E, Hauser SL, Pelletier D (2018) *Body mass index, but not vitamin D status, is associated with brain volume change in MS.* Neurology 91(24):e2256–e2264

14. Azami M et al (2019) *Epidemiology of multiple sclerosis in Iran: a systematic review and meta-analysis.* PLoS One 14(4):e0214738

15. Eskandarieh S, Allahabadi NS, Sadeghi M, Sahraian MA (2018) *Increasing prevalence of familial recurrence of multiple sclerosis in Iran: a population based study of Tehran registry 1999–2015.* BMC Neurol 18(1):15

16. Almasi-Hashiani A, Sahraian MA, Eskandarieh S (2020) *Evidence of an increased prevalence of multiple sclerosis: a population-based study of Tehran registry during 1999–2018.* BMC Neurol 20(1):169

17. Etemadifar M, Maghzi A-H (2011) *Sharp increase in the incidence and prevalence of multiple sclerosis in Isfahan, Iran.* Multiple Sclerosis J 17(8):1022–1027

18. Pakdel M, Hedström A, Bidkhori M, Hadei M, Kazemi Moghaddam V, Sarmadi M, Zohdi S, Marufi N (2019) *Do socio-economic factors affect the prevalence of multiple sclerosis in Iran?* Acta Neurol Scand 140(5):328–335

19. Hosseinzadeh A, Baneshi MR, Sedighi B, Kermanchi J, Haghdoost AA (2019) *Incidence of multiple sclerosis in Iran: a nationwide, population-based study.* Public Health 175:138–144

20. Ashtari F, Esmaeil N, Mansourian M, Poursafa P, Mirmosayyeb O, Barzegar M, Pourgheisari H (2018) *An 8-year study of people with multiple sclerosis in Isfahan, Iran: Association between environmental air pollutants and severity of disease.* J Neuroimmunol 319:106–111

21. Molazadeh N, Mohebi F, Altafi D, Sahraian MA (2021) *Prevalence and incidence of multiple sclerosis in Ardabil, Northwest of Iran.* Multiple Sclerosis Relat Disord 47:102605

22. Moghaddam VK, Dickerson AS, Bazrafshan E, Seyedhasani SN, Najafi F, Hadei M, Momeni J, Moradi G, Sarmadi M (2021) *Socioeconomic determinants of global distribution of multiple sclerosis: an ecological investigation based on Global Burden of Disease data.* BMC Neurol 21(1):145

23. Von Elm E et al (2007) *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.* Ann Intern Med 147(8):573–577

24. Statistical Center of Iran. *Population.* 2019 [cited 2020; Available from: https://www.amar.org.ir/english/Statistics-by-Topic/Population#288290-statistical-survey. Accessed 30 May 2019

25. Etemadifar M, Izadi S, Nikseresht A, Sharifian M, Sahraian MA, Nasr Z (2014) *Estimated prevalence and incidence of multiple sclerosis in Iran.* Eur Neurol 72(5-6):370–374

26. Moghaddam VK, Sarmadi M, Tatari M, Najafi F, Esmaeili A, Hadei M (2018) *Epidemiology of multiple Sclerosis in Torbat-e Heydarieh (Northeast of Iran) during 1982-2016.* Multiple Sclerosis Relat Disord 24:184–189

27. Etemadifar M, Nikanpour Y, Neshatfar A, Mansourian M, Fitzgerald S (2020) *Incidence and prevalence of multiple sclerosis in persian gulf area: a systematic review and meta-analysis.* Multiple Sclerosis Relat Disord 40:101959

28. Hosseinzadeh A et al (2021) *Is the sharp increasing trend of multiple sclerosis incidence real in Iran?* BMC Neurol 21(1):1–5

29. Nasiri M, Maroufi H, Sahraian MA, Eskandarieh S (2021) *Prevalence of multiple sclerosis and its risks in Tehran, Iran, in 2019.* Neurol Sci

30. Alonso A, Hernán MA (2008) *Temporal trends in the incidence of multiple sclerosis: a systematic review.* Neurology 71(2):129–135

31. Pugliatti M, Sotgiu S, Solinas G, Castiglia P, Rosati G (2001) *Multiple sclerosis prevalence among Sardinians: further evidence against the latitude gradient theory.* Neurol Sci 22(2):163–165

32. Rhead B, Bäärnhielm M, Gianfrancesco M, Mok A, Shao X, Quach H, Shen L, Schaefer C, Link J, Gyllenberg A, Hedström AK, Olsson T, Hillert J, Kockum I, Glymour MM, Alfredsson L, Barcellos LF (2016) *Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk.* Neurol Genet 2(5):e97

33. Maghzi AH, Ghazavi H, Ahsan M, Etemadifar M, Mousavi SA, Khorvash F, Minagar A (2010) *Increasing female preponderance of multiple sclerosis in Isfahan, Iran: a population-based study.* Mult Scler 16(3):359–361

34. Guzel R, Kozanoglu E, Guler-Uysal F, Soyupak S, Sarpel T (2001) *Vitamin D status and bone mineral density of veiled and unveiled Turkish women.* J Womens Health Gend Based Med 10(8):765–770

35. Kragt J, van Amerongen B, Killestein J, Dijkstra CD, Uitdehaag BMJ, Polman CH, Lips P (2009) *Higher levels of 25-hydroxyvitamin D are associated with a lower incidence of multiple sclerosis only in women.* Mult Scler J 15(1):9–15

36. Kramer MA, van der Maas NAT, van Soest EM, Kemmeren JM, de Melker HE, Sturkenboom MCJM (2012) *Incidence of multiple sclerosis in the general population in the Netherlands, 1996–2008.* Neuroepidemiology 39(2):96–102

37. Benjaminsen E, Olavsen J, Karlberg M, Alstadhaug KB (2014) *Multiple sclerosis in the far north-incidence and prevalence in Nordland County, Norway, 1970–2010.* BMC Neurol 14(1):226

38. Wallin MT, Culpepper WJ, Campbell JD, Nelson LM, Langer-Gould A, Marrie RA, Cutter GR, Kaye WE, Wagner L, Tremlett H, Buka SL, Dilokthornsakul P, Topol B, Chen LH, LaRocca N, US Multiple Sclerosis Prevalence Workgroup (2019) *The prevalence of MS in the United States.* Neurology 92(10):e1029–e1040

39. Kurtzke JF (2015) *On the epidemiology of multiple sclerosis in the Middle East and North Africa.* Neuroepidemiology 44(4):245–248

40. Esmaeili SA, Mohammadian S, Radbakhsh S, Momtazi-Borojeni AA, Kheirmand Parizi P, Atabati H, Mardani F, Saburi E, Moghaddam AS (2019) *Evaluation of vitamin D3 deficiency: a population-based study in northeastern Iran.* J Cell Biochem 120(6):10337–10341

41. Moussavi M, Heidarpour R, Aminorroaya A, Pournaghshband Z, Amini M (2005) *Prevalence of vitamin D deficiency in Isfahani high school students in 2004.* Hormone Res Paediatr 64(3):144–148

42. Manouchehrinia A, Hedström AK, Alfredsson L, Olsson T, Hillert J, Ramanujam R (2018) *Association of pre-disease body mass index with multiple sclerosis prognosis.* Front Neurol 9:232

43. Emamian MH, Fateh M, Hosseinpoor AR, Alami A, Fotouhi A (2017) *Obesity and its socioeconomic determinants in Iran.* Econ Hum Biol 26:144–150