

Epidemiology of Multiple Sclerosis in Iran: A Systematic Review

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Key Words

Multiple sclerosis · Iran · Epidemiology · Incidence · Prevalence

Abstract

Background: There is a wide variation in the prevalence of multiple sclerosis (MS) in different geographical regions and the epidemiology of MS in Iran has been a major topic of concern during the last decade. Several population-based studies have shown a sharp increase in the prevalence and incidence of MS in this region. In this study, for the first time, the aim was to provide a comprehensive review regarding the incidence and prevalence of MS across Iran. **Methods:** A comprehensive literature search was performed using PubMed, Embase, and Web of Science. We also did a manual search of reference lists from primary articles and relevant reviews. Databases of ongoing research and unpublished literature were also searched. **Results:** A total of 22 relevant studies were reviewed and 11 studies met the inclusion criteria. Incidence data were found in 5 studies and ranged from 0.68 to 9.1/100,000 per year in the Iranian population. Prevalence was reported in all studies and ranged from 5.3

to 74.28/100,000 with the higher prevalence among females (female/male ratio ranged from 1.8 to 3.6). The most prevalent subtype of MS was the relapsing-remitting form (65.8–87.8%). The sensory disturbance was the most initial presentation. **Conclusion:** The incidence and prevalence of MS in Iran has been increasing rapidly, especially in females. Future research should focus on determining the epidemiological features of MS in the neglected provinces with different ethnicities. Such an effort along with further research towards improvement of data on previously studied areas can enable a field to be opened up to identify the patterns of MS in varied genetic backgrounds and environments of Iran.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory and immune-mediated demyelinating disease with complex etiology and still unknown causes, which affects individuals in their productive years [1]. There is a wide variation in the prevalence of MS in different geographical regions. About 30 years ago, Kurtzke [2, 3] proposed that higher

latitude increases the prevalence of MS and classified geographical areas for three regions by prevalence: (1) high >30/100,000, (2) intermediate (5–25/100,000), and (3) low risk <5/100,000. Based on such expectations, Middle-Eastern countries had been generally classified as low-risk areas, but to date, several studies in this region report the higher risk [4].

Iran, a high desert plateau with high mountains, latitude 32°00' N longitude 53°00', is a Muslim Middle-Eastern country with 31 provinces. Several ethnic groups, including Persians, Turks, Arabs, and Balochs, are now unified by Iranian culture. The majority speaks Persian, the official language.

For the last decade, the epidemiology of MS in this country has been a major topic of concern [5] and several population-based studies have shown a sharp increase in the prevalence and incidence of MS in this region. Iran's population has increased dramatically, rising from 17 million in 1950 to about 75 million by 2000, surpassing France, UK, and Italy.

At present, more than half of Iran's population is less than 35 years of age, born since 1977. The largest age group is 20–24. MS mostly affects young adults 20–40 years old, so the public health system is facing an increasing disease burden [6]. Any additional causes for such an increase are not clear, even as we consider the radical changes in lifestyle, now highly urbanized, and with vastly improved health care, with more MS cases diagnosed and reported [7]. To marshal data to sustain research, we present the first systematic review on the epidemiology of MS in Iran.

Methods

Search Strategy

We used computer databases to find population-based studies with data on MS epidemiology in Iran: PubMed, Embase, and Web of Science. We searched for papers published before August 1, 2013, using the following search terms: 'multiple sclerosis and Iran', 'multiple sclerosis and population', 'multiple sclerosis and epidemiology', 'multiple sclerosis and prevalence', 'multiple sclerosis and incidence'. All searches were repeated with 'demyelinating disease' in place of 'multiple sclerosis'. We also did a manual search of reference lists from primary articles and relevant reviews. If the search of international literature was unproductive, reliable evidence reported in non-English scientific literature or from local small population surveys was also used. No world language was explicitly excluded. Databases of ongoing research and unpublished literature were also searched. Our search strategy used a combination of controlled vocabulary with PubMed, and was adapted for the other databases.

Inclusion and Exclusion Criteria

The following criteria were used to select papers for inclusion in this systematic review: (1) the population was Iranian, defined primarily geographically as those living in Iran; (2) MS was defined according to accepted international diagnostic criteria in use at the time of the study, the Poser [8] or McDonald criteria [9], and (3) prevalence of MS was reported. Studies that were based in a single institution, or did not involve a network of hospitals serving a well-defined general population, were excluded.

Data Extraction and Assessment of Study Quality

Two of the authors agreed on the data to be extracted. Data included: study period, details of study population, and diagnostic selection criteria. One of the reviewers (Z.N.) extracted data using a data extraction form, while a second reviewer (M.F.-E.) confirmed the data. In cases of non-consensus, a third independent review (S.-H.A.) was obtained. In cases of weak study methodology, authors were approached to determine a study's potential inclusion. Each study was evaluated on the following items: (1) type of study design; (2) description of study population, and (3) adequacy of case definition, based on validated criteria. Those studies in which the items were not reported or unclear were excluded. The following data were extracted into table 1: (a) source: authors and journal published; (b) population denominator; (c) timescale: incidence time frame and prevalence date; (d) case ascertainment method; (e) diagnostic method, and (f) outcome: prevalence per 100,000 of population.

Results

Existing Systematic Reviews

No existing systematic reviews of incidence and prevalence were identified.

Study Yield

22 studies were identified. Of these, the following were excluded: 5 that reported the prevalence of MS among Iranian immigrants, 4 case reports, and 2 without prevalence and clinical patterns. Hence, 11 studies were included, published from 2006 to 2013 [10–20].

Findings

Table 1 illustrates a summary of results identified in the study.

Tehran

Tehran, the capital and most populated region of Iran, on the north of the central plateau, is expanding with mass immigration of people from all over the nation, with many different ethnic groups. Sahraian et al. [10] in 2010 used data from the Iran MS Registry 10-year national survey: prevalence 51.9, female/male ratio 2.60, age at disease onset 27.2 ± 8.3 . MS was more prevalent in

Table 1. Summary of the results of studies regarding the epidemiology of MS among the Iranian population

Reference (first author)	Province	Design	Case ascertainment	Time scale	Diagnostic method	Population denominator	Number of patients		Female/male ratio	Prevalence per 100,000			
							total	female		total	male	female	
Etemadifar [13] (2006)	Isfahan	cross-sectional	6 neurological departments of the province	2004–2005	McDonald	3,923,255	308	1,083	3.6	35.5	15.3	56.7	
Saadatnia [14] (2007)	Isfahan	cross-sectional	Isfahan MS Society	2003–2006	McDonald	3,923,255	388	1,330	3.4	43.8	19.2	69.6	
Abedini [17] (2008)	Mazandaran	cross-sectional	MS Society of Mazandaran	2007	McDonald	2,893,087	161	421	2.6	20.1	11.1	29.1	
Ghandehari [16] (2010)	Razavi Northern Southern	population-based	Khorasan MS Registries	2009	McDonald	5,593,079	166	555	3.8	12.9	5.9	19.2	
						811,572	25	46	1.8	8.7	6.2	11.2	
						636,420	8	26	3.2	5.3	2.5	8.3	
Etemadifar [15] (2010)	Isfahan	cross-sectional	Isfahan MS Society	2003–2010	McDonald	4,804,458	806	2,716	3.37	71.6	33.5	111.9	
Sahraian [10] (2010)	Tehran	cross-sectional	Iranian MS Society	1999–2010	McDonald	13,422,366	8,146	2,258	5.888	51.9	–	–	
Elhami [11] (2011)	Tehran	population-based	Iranian MS Society	1989–2009	Poser (up to 2001) McDonald	14,103,853	7,896	2,008	5.588	50.57	25.54	77.24	
Hashemilar [18] (2011)	East Azerbaijan		Registry of the Committee for Diagnosis and Treatment of MS	2005–2009	McDonald	3,600,000	1,000	731	2.7	27.7	14.51	20.69	
Moghtaderi [19] (2012)	Sistan and Balouchestan	cross-sectional	University hospitals	1996–2006	McDonald	1,346,367	206	–	–	7.69	–	–	
Sharafaddinzadeh [20] (2012)	Khuzestan	cross-sectional	Ahwaz MS Society	2009	McDonald	4,200,000	696	169	527	3.11	16.28	7.73	25.21
Heydarpour [12] (2013)	Tehran	population-based	Iranian MS Society	1991–2011		14,103,853	–	–	–	74.28	37.41	113.49	

ages 20–39 years. The main presenting symptom was visual impairment. RRMS 84.9% was much greater than other types 15.1%. Of 8,146 patients, early-onset MS (age at onset <16) was 6.2%, female/male ratio 3.3, and late-onset disease (age >50) 0.5%, female/male ratio 0.83. Family history was positive 9.5%, 4.1% first-degree kinship.

Elhami et al. [11] in 2011 used 20 years of data in a well-defined and stable population, with age- and sex-adjusted incidence rates. The crude incidence rate increased from 0.68 in 1989 to 5.68 in 2005. The adjusted incidence rate increased from 0.68 in 1989 to 2.93 in 2008. The age-adjusted prevalence rate was 50.57, female/male ratio 3.11. Prevalence was highest in the age group 35–39 years in females and 40–44 years in males. The mean age at onset of the disease was 27.53 ± 8.25 years and at diagnosis 29.02 ± 8.60 .

More recently, Heydarpour et al. [12] in 2013 employed Joinpoint regression analysis to evaluate the trend of MS incidence, male/female ratio, mean age at disease onset, and the incidence of pediatric MS during two decades. The age-adjusted prevalence rates increased to 74.28 (113.49 in women and 37.41 in men). The age-adjusted incidence rate increased from 1.3/100,000 in 1991 to 6.6 in 2005. Overall, two incidence peaks were reported in this study; the annual percent increase for the first Joinpoint in 2004 was 12.8% in females and 12.5% for males. Sex ratio trend analysis among patients born between 1950 and 1995 has shown a significantly decreasing male/female ratio. Pediatric MS (age at disease onset <18) was 7.23%. The crude incidence in girls increased from 3.4 per million in 1991 to 33.2 in 2007. The second Joinpoint in 2008 was 12.3% in girls and 14% in boys.

Isfahan

Isfahan, in central Iran, is one of the largest and most populous provinces. Three epidemiological assessments on MS in Isfahan are reported in the literature. The first was carried out by Etemadifar et al. [13] for the year 2006, with an age-adjusted prevalence rate of 35.5 (54.5 in women, 14.9 in men) and a female/male ratio of 3.6. Ages 30–39 years had highest prevalence rates. The most common initial presentations were sensory and visual disturbances with 51.1 and 47.0% prevalence, respectively. 76.6% of patients were born in Isfahan province. A positive MS family history was 11.6%.

Saadatnia et al. [14] in the second study in 2007 reported an incidence of 3.64 in 2005, an overall prevalence of 43.8 (69.6 among women and 19.2 among men), a female/male ratio of 3.4, mean age at onset of 25.4 ± 8.6

years, RRMS 87.8%, SPMS 6.4%, and PPMS 5.7%. Initial presentation was sensory and visual disturbances in 51.7 and 47.5% patients, respectively. Early- and late-onset MS was 5 and 1.1% of patients, respectively, and MS family history 12.2%.

Etemadifar and Maghzi [15] in 2010 presented the most recent data for Isfahan: incidence 9.1 in 2009, standardized prevalence 71.6, and female/male ratio 3.37.

Northeast Iran

Khorasan is an area in northeast Iran, the largest province of the country, containing three subareas. Ghandehari et al. [16] in 2010 characterized three main trends for Razavi, northern and southern Khorasan provinces: total prevalence was 12.9, 8.7 and 5.3, respectively, and female/male ratio 3.8, 1.8 and 3.2, respectively.

Mazandaran

Mazandaran, one of the most densely populated cities of Iran, is in north Iran, south of the Caspian Sea. Data is only available in local scientific literature. In 2006 [17] a survey found a prevalence rate of 20.1, a female/male ratio of 2.6, and more common in third decade of life. The mean age at onset was 26.9 ± 8.3 . Optical and sensory symptoms were more common at onset, with RRMS 71%, SPMS 15.8%, and PPMS 13.2%.

East Azerbaijan

East Azerbaijan is a province in northwest Iran, bordering on the republics of Azerbaijan, Armenia and Nakhchivan. Iranians with Turkish ethnicity reside in Azerbaijan. We found only one study in 2011 by Hashemilar et al. [18] where the crude prevalence rate was 27.7, female/male ratio 2.7, mean age of patients 33.4 ± 8.9 , RRMS 67.7%, PPMS 2.8%, and SPMS 11.2%.

Sistan and Balouchestan

Sistan and Balouchestan, with Balouch ethnic background, is a large province in southeast Iran, bordering on Afghanistan and Pakistan. Moghtaderi et al. [19] in 2011 found an age-adjusted prevalence of 13.96 and an incidence of 2.67, female/male ratio 2.18, RRMS 65.8%, SPMS 20%, PPMS 6.7%, and for progressive relapsing types 2%, while 5.4% of patients had Devic's disease. MS was most common between 16 and 35 years of age. The EDSS score were 3.62 ± 2.3 for men and 2.70 ± 2.1 for women. Symptoms: numbness and other sensory disturbances (not visual), 39.8%, motor dysfunction 28.6%, optic neuritis 28.2%, with positive family history in their first-degree relatives 6.2%.

Khuzestan

Khuzestan is in southwestern Iran, bordering on Iraq and the Persian Gulf, with both Persian and Arabic ethnic backgrounds. In 2012, Sharafaddinzadeh et al. [20] found total prevalence and incidence rates of 16.28 and 2.20, respectively. The mean age was 31.4 ± 8.50 years and the mean age at disease onset was 26.85 ± 7.63 years, female/male ratio 3.11 and the mean EDSS score 2.89 ± 1.91 , with a higher score among the Arab population. RRMS 81.3%, SPMS 12.2%, PPMS 3.2%. The most common presenting symptom was sensory signs and optic nerve involvement (78.2%) followed by cerebellar symptoms (11.3%) and motor deficit (10.3%). 24.7% of the Arabian patients versus 15.9% of Persians experienced progressive patterns.

Discussion

Epidemiological Reports and Their Limitations

MS prevalence in Iran varies geographically, from 5.3 to 74.28/100,000. The origin of such diversity is still elusive. Although different methodology, underestimation of the real incidence, and referral bias may be factors, there are different ethnicities – Kurds, Turks, Arabs and Balochs, – as well as different cultures and climates. This means great variations in diet and environmental exposures to many factors, both ancient traditional and novel modern.

Only 5 studies reported an age-adjusted prevalence [11–13, 15, 19], thus, age- and sex-adjusted prevalence and incidence should be considered in future reports. Moreover, there is a lack of complete data on incidence, clinical pattern, early-onset MS, late-onset MS, family history and prevalence of neuromyelitis optica among majority of reports. The minimum MS prevalence pertained to three eastern provinces of Khorasan [16] with the prevalence of 5.3–12.9, which is the lowest rate compared to the rest of the reports. This might be due to sampling flaw in this study. They only included patients who need interferon medication, so those who receive other immunosuppressive therapy or no therapy at all could have been overlooked [15]. However, overall, there has been a substantial rise in MS prevalence in a few decades. Possible explanations for such an increase are as follows. (1) The diagnosis of MS has improved due to more availability of MRI and paraclinical tests revising of the McDonald criteria, increasing numbers of neurologists and accidental diagnosis by physicians [14, 15]. (2) The lack of early childhood exposure to common viral agents like

Epstein-Barr virus due to hygiene promotion after the 1981 Iran revolution, in line with the hygiene hypothesis [21].

The 20-year incidence trend of MS in Tehran, Iran, showed a huge increase over the past 18 years, from 0.68 in 1989 to 5.68/100,000 in 2006, an 8.3-fold rise with generally higher prevalence rates among women [11].

A similar trend between 2007 and 2010 is reported from Isfahan province at the center of Iran, by which a dramatic increase in the prevalence and incidence of MS has been observed. Isfahan is a well-studied area, now globally known for its high and increasing incidence and prevalence of MS during the last decade, probably caused in part by changes in lifestyle and vitamin D deficiency [15, 22]. Further features found among Isfahan MS patients include: (1) increasing female preponderance over the recent decade [23]; (2) highest rates among the 30- to 39-year age group, decreasing with increasing age; (3) high percentage in early-onset MS, and (4) the lower frequency of oligoclonal IgG bands in CSF of Isfahan MS patients than in the West [14]. Similar reports from Japan and Jordan may be evidence that oligoclonal IgG bands are less frequent in the CSF of Asian MS patients than MS patients in the West; however, more accurate studies are required to support this hypothesis [14, 24, 25].

Sistan and Baloochestan, a southeastern province, reported a relatively low prevalence of 13.96 [19]. Although their results are inconsistent with reports from Isfahan and Tehran, it is not surprising because the people who live in this area have different ethnicity and lifestyle compared to people in Isfahan and Tehran. The majority of people in Sistan and Baloochestan are from the Baloch ethnic group, which closely resembles the population residing in Pakistan, where MS is reported to be rare [26–28]. Furthermore, nearly half of the population still lives in rural areas, while only 17 and 9% of the population of Isfahan and Tehran, respectively, live in rural areas. This factor alone plays an important role to show the major lifestyle differences between these regions. As mentioned, hypovitaminosis D has been shown to be associated with urban life.

The prevalence of 27.7 in east Azerbaijan, the northwest province was higher than its neighbor with the same population, Armenia, where MS has been reported to be 11.8/100,000 individuals [29]. These results show that the prevalence of MS in Iran is more than its neighbors and indicates the role of genetics and environment in susceptibility to MS among the Iranian population.

Khuzestan, a southwest province, reported a prevalence of 18.50 among Persians versus 10.58 among Arabs.

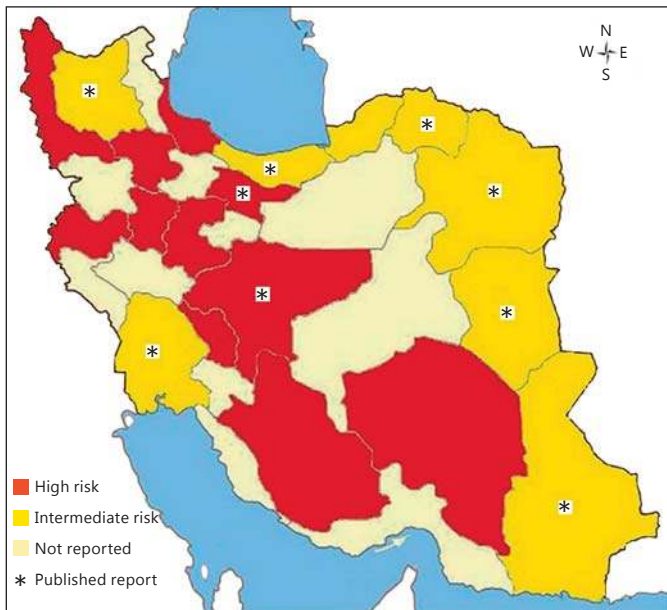


Fig. 1. Distribution of MS in Iran according to geographical classification. High risk: $>30/100,000$; intermediate risk: $5-25/100,000$; low risk $<5/100,000$.

They attributed the origin of such differences to ethnic distinction of the aforementioned two groups residing in the same region. However, according to an anthropological study [30] there is no close genetic relationship between Iranian Arabs and Middle-Eastern Arabs, as Iranians who talk in Arabic have a genetic affinity to the rest of the Iranian ethnic groups. As we recently postulated [31], although the authors have shown that motor deficits and cerebellar findings are more frequent among Arabs than Persians, the overall patterns of MS presentation in both populations are the same with the predominance of optic nerve involvement, followed by sensory problems (28.6%) and motor deficits – a pattern that resembles other reports from the rest of Iranian provinces. Engagingly, such a pattern is in obvious contrast with the clinical presentation of MS in other Middle-Eastern Arab countries neighboring Khuzestan, e.g. Iraq and Saudi Arabia, where motor deficits were the most common mode of presentation.

Prevalence of MS across Iran and Geographical Distribution Hypothesis

According to the north-south latitude hypothesis, Iran should be a low-risk area with a less than $5/100,000$ MS prevalence. Of note, to date, the published epidemiology data of MS are insufficient for determining the geograph-

Table 2. Estimations of Iranian local MS registries about the number of their definitely diagnosed subjects

Province	Population denominator	Total patients	Female patients	Male patients	Prevalence per 100,000
West					
Azerbaijan	3,080,576	1,401	1,008	393	45.47
Isfahan	4,879,312	4,541	3,527	1,014	93.06
Kerman	2,938,988	1,029	811	218	35.01
Kermanshah	1,945,227	850	–	–	43.69
Charmahal	895,263	830	780	50	92.71
Hamadan	1,758,268	1,100	850	250	62.56
Markazi	1,413,959	1,043	806	237	73.76
Zanjan	1,015,734	338	220	118	33.27
Fars	4,596,685	3,573	2,843	730	77.72
Gilan	2,480,874	890	630	260	35.87
Golestan	1,777,014	320	250	70	18.00

Data gathered by Isfahan MS Society using a national query from the rest of Iranian MS societies and registries.

ical distribution of MS in Iran. Nevertheless, in order to show the overall pattern of MS in Iran, we also investigated unpublished data on the prevalence of MS from local MS registries across the country and presented them in line with previously reported data. Figure 1 indicates that Iran is an intermediate- to high-risk region and the bulk of studies in different provinces have rejected the geographical distribution hypothesis [2, 32].

Role of Vitamin D Deficiency in Epidemiology of MS in Iran

Available literature now supports the crucial role of vitamin D deficiency in MS. The high prevalence of vitamin D deficiency among women, youngsters and high school students, especially girls, has been found by recent studies in Isfahan and Tehran [33–35]. Although it has been found that veiled women have a low vitamin D status [36], a major changing lifestyle trend during the past decades, there is spread of urbanization, indoor living, air pollution, changes in diet, widespread use of sun screens, avoiding sun exposure for fear of skin cancer and concern about skin beauty, all of which are thought to cause vitamin D deficiency, with the latter two being more prevalent among females. Moreover, Iranian women spend less time in the sun, compared to men, which could also lead to vitamin D deficiency, but is independent of wearing a

hijab or veil and therefore is mostly due to culture and lifestyle. These factors might have caused the gender difference in vitamin D deficiency in Iran [7, 37].

Conclusion

In conclusion, the incidence and prevalence of MS in Iran has been increasing rapidly, steadily, hugely, and mysteriously, especially in females. The overall epidemiologic picture is still unclear in a number of provinces, although at present unpublished estimations made by local MS registries are available (table 2). Future research should focus on determining the epidemiological features

of MS in the overlooked provinces with different ethnicities, especially Yazd, Kurdistan, West Azerbaijan, Orumieh, and the northern areas of the country. Such an effort along with further research towards improvement of data on previously studied areas can enable a field to be opened up to identify the patterns of MS in varied genetic backgrounds and environments of Iran.

Acknowledgment

The authors are very grateful to Mr. Richard T. Murray (Medical Researcher) for revising and commenting on the manuscript.

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