

## Systematic Review

### Updated Systematic Review on Epidemiology of Multiple Sclerosis in Iran: Central Accumulation and Possible Role for Industrial Pollution

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#### ABSTRACT

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**Background:** In spite of previous studies, recent epidemiological studies estimated most of the Iran's provinces as intermediate to high risk areas. In the present study, we aimed to update our previous research and marshal newly published works on epidemiology of MS disease in Iran during recent five years.

**Methods:** For literature search, a comprehensive electronic search was performed on PubMed, EBSCO and Web of Sciences and regional data bases. Our search process in electronic databases was performed using the following search items: 'multiple sclerosis and Iran', 'multiple sclerosis and population', 'multiple sclerosis and epidemiology', 'multiple sclerosis and prevalence', 'multiple sclerosis and incidence'.

**Results:** MS distribution across Iran has a range from 7.4 to 101.39 per 100,000. Twenty one provinces of Iran are classified in high risk of MS disease (>25/100,000); 9 provinces in intermediate risk (5-25/100,000) and one province in low risk (<5/100,000).

**Conclusion:** the reason for the pattern of the current MS distribution in Iran is not explainable by the traditional gradient theory. The disease is seemingly more prevalent in central parts of Iran; to date, accumulation of MS in central parts of Iran has not been clearly reported.

**Keywords:** Multiple sclerosis, Iran, prevalence, epidemiology.

#### Introduction

Multiple sclerosis is the most common demyelinating disorder of the central nervous

system and the second common cause of disability in young population after trauma (1). The definite etiology of MS is elusive, however, some

environmental factors such as vitamin D deficiency, smoking, hormonal factors and genetic factors such as alleles from major histocompatibility complex II gene especially DRB1-1501 have been suggested (2, 3).

The geographical distribution of disease varied vastly, however, in higher latitudes, more prevalence of disease have been reported (4). Prevalence of MS disease have been reported as low as 0.5 per 100,000 in Africa to as high as 80 per 100,000 in Europe and approximately 2.5 million people are suffering from MS disease in the world (5). About three decades ago, Krutzke suggest higher prevalence of disease in higher latitudes and categorized countries to three regions: (1) low risk <5/100,000; (2) intermediate risk 5-25/100,000 and (3) >25/100,000 (4). According to this theory, Middle-East countries was considered as low risk region for MS disease. Although, initial reports on incidence and prevalence of Iran described Iran as a low risk region (incidence: less than 5/100,000); later studies suggested that Iran has an intermediate to high risk for MS (4, 6, 7). In spite of previous studies, recent epidemiological studies estimated most of the Iran's provinces as intermediate to high risk areas (6, 7). In 2013, we published a reputed systematic review on epidemiology of MS in Iran (1) by European Neurology. In the present study, we aimed to update our previous research and marshal newly published works on epidemiology of MS disease in Iran during recent five years.

## Methods

For literature search, a comprehensive electronic search was performed on PubMed, EBSCO and Web of Sciences and regional data bases. Our search process in electronic databases was performed using the following search items: 'multiple sclerosis and Iran', 'multiple sclerosis and population', 'multiple sclerosis and epidemiology', 'multiple sclerosis and prevalence', 'multiple sclerosis and incidence'. Our inclusion criteria for articles were (1) population was Iranian and be resident in Iran at the time of study; (2) patients were diagnosed according to accepted international diagnostic criteria, McDonalds criteria (8) and Poser criteria (9); (3) prevalence of MS was reported. All of the review articles, and studies reporting prevalence of disease in special populations or did not involve a network of hospitals serving a well-defined general population, were excluded. In cases of weak study methodology, authors were approached to determine a study's potential inclusion. All of the articles published after 1st August 2013 to 15th February 2018 were assessed for possible inclusion in the

study. Figure 1 presents our search protocol with its results.

Data extraction was performed by two authors (H. J-A and S-H A). Process of data extraction was done by one of the authors (H. J-A) by using especial provided forms and extracted data was checked by another author (S-H A). The extracted data was presented in Table 1 as follows: (1) first author and year of publication, (2) province, (3) design, (4) case ascertainment, (5) time scale, (6) diagnostic method, (7) population denominator, (8) number of patients (including total, male and female patients), (9) female/ male ratio, (10) prevalence per 100,000 (including total, male and female prevalence) and (11) 95% confidence interval of total prevalence.

## Results

25 articles were evaluated. 10 out of them were excluded; 6 papers did not report prevalence of MS disease and 4 of them were review articles. Table 1 illustrates search results. Description of the updates on the epidemiology of MS in Iran is presented as follows.

### General prevalence of MS disease in the rest of country

Etemadifar had reported that prevalence of MS in Iran was 24.26 per 100,000 in 2006 and it has significant steep rise during last decade (6). Izadi et al. (10) estimated prevalence of MS to be 45 per 100,000 in Iran. Etemadifar et al. (6) reported prevalence and incidence rates of MS disease 54.51 (95%CI: 50.0-51.0) and 5.87 per 100,000 individuals, respectively with 3.48 female to male ratio.

### Central Iran

#### Tehran

Tehran, the capital of Iran, has the increasing rate of MS prevalence during recent decade. In 2008, prevalence of MS was estimated 51.9 per 100,000 (11). Recent studies suggest higher rate of MS prevalence in Tehran city. Etemadifar et al. estimated prevalence of MS disease to be 88 per 100,000 (6). In another study, annual incidence of MS disease varied between 11.1 to 2.65 in different metropolitan zones of Tehran and significant higher rate of incidence in northern than southern zones (12). In the most recent study, it was suggested that point prevalence of MS disease is 101.39 (95%CI: 99.5-103.3) per 100,000 and the incidence rate was estimated 6.02 per 100,000. Most of the new cases aged between 25-29 years with 3.18 female to male ratio (13).

**Table 1.** Summary of the results of studies regarding the epidemiology of Multiple Sclerosis among Iranian population.

Source condition	Province	Design	Case ascertainment	Time scale	Diagnostic method	Population denominator	Number of patients			Female:Male ratio		Prevalence per 100000			95% CI of total prevalence
							total	Male	Female	total	male	female			
<a href="#">Kerzali et al. (17)</a>	Qom	Cross-section	Iranian MS Society and MS Society of Qom	Feb to Aug (2011)	McDonald or Poser	1,151,672	581	132	449	3.4	50.4	NA	NA	[46.4-54.6]	
<a href="#">Ebrahimi and Sedighi (20)</a>	Kerman	Population-based	Kerman MS Society, MS society of Kerman and Rafsanjan medical universities and neurology at Shahid medical center	Six months of 2011	McDonald	3,000,000	932	NA	NA	3	31.5	25.5	NA	[29.5-33.52]	
<a href="#">Esmailifar et al. (14)</a>	Isfahan	Cross-section	Isfahan MS Society	2003-2013	McDonald	4,555,940	4,503	1028	3508	3.41	85.8	39.2	133	[83.3-88.4]	
<a href="#">Esmailifar et al. (15)</a>	Isfahan	Cross-section	Isfahan MS Society	2003-2014	McDonald	2,930,380	2,974	NA	NA	4.3	99.2	NA	NA	[96.2-103.4]	
<a href="#">Radoojin et al. (33)</a>	Kinzaestan	Cross-section	MS Society of Ahvaz and Dezful neurology departments of general hospitals and neurology clinics	April to Aug (2012)	NA	957,133	142	46	96	2.08	15	NA	NA	[12.4-17.3]	
<a href="#">Izadi et al. (34)</a>	Fars	Cross-section	Fars MS Society	Up to 2013	McDonald	4,651,718	3354	665	2689	4.04	72.1	28.3	116.5	[69.6-74.5]	
<a href="#">Esmailifar et al. (16)</a>	Isfahan	Cross-section	Isfahan MS Society and Karhan MS Society	Up to 2014	McDonald	4,879,312	5195	4084	1111	3.67	106.5	44.9	169.9	[103.6-109.4]	
<a href="#">Eshardubak et al. (13)</a>	Tehran	Cross-section	Iranian MS Society	1991-2014	McDonald or Poser	12,559,000	15,672	NA	NA	3.18	101.4	42.5	134	[99.5-103.3]	
<a href="#">Mansourizadeh et al. (21)</a>	Kohgiluyeh and Boyer-Ahmad	Cross-section	MS surveillance registry system	1990-2015	NA	700,000	421	98	323	3.3	60.1	NA	NA	[54.4-65.9]	

## Isfahan

Isfahan province is located in the central Iran. Prevalence of MS disease is increasing in this province during last decade. In the first study regarding MS epidemiology in Isfahan province, prevalence of MS disease estimated 35.5 per 100,000 (7). In a study by Etemadifar et al. in 2014 (14), overall age-adjusted prevalence rate per 100,000 has been estimated as 85.8 with 3.41 female to male ratio and three-year cumulated incidence of MS was accounted as 26.03 per 100,000. In 2014, another study on Iran's Ministry of Health and Medical Education reports, estimated prevalence of MS to be 89 per 100,000 in Isfahan .(6)

In 2015, it has been shown that MS disease has distinct prevalence between Armaninans and Persians of Isfahan. Prevalence of MS disease was 559.04 (95%CI: 309.92–870.9) per 100,000 among Armaninans while it was 99.2 (95%CI: 96.2-103.4) per 100,00 in Persians .(15)

In the most recent study by Etemadifar and associates, it has been showed that MS prevalence ranges from 5.26 to 156.65 and incidence ranges from 0.07 to 0.67 per 1,000 in different regions of Isfahan province. In this study, it was shown that more than 96% of MS patients were living in urban areas with female to male ratio 3.24 and most of the patients aged 22-32 years.(16)

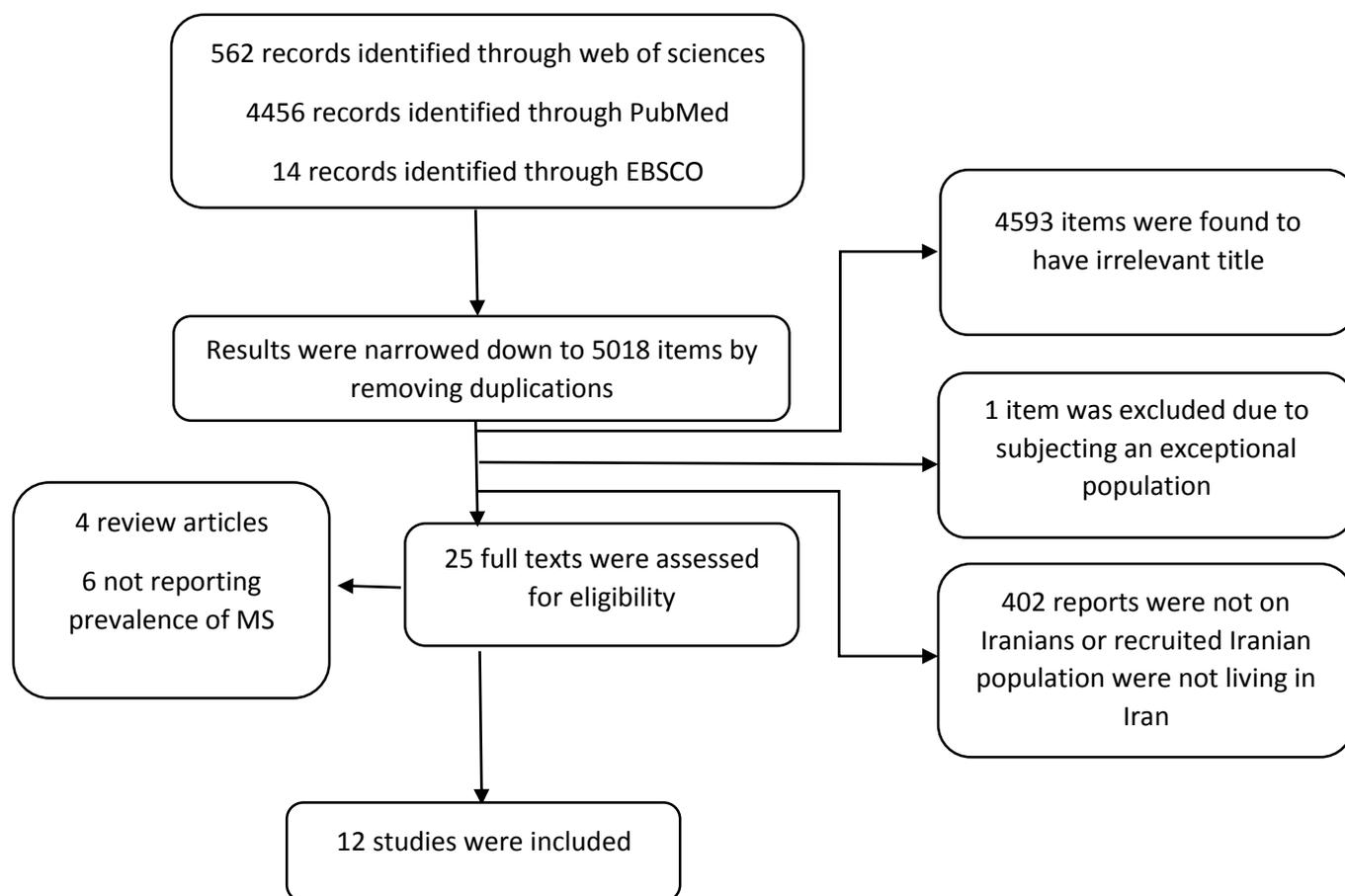


Figure 1. Flowchart of search protocol.

## Qom

Qom province is located in central Iran. Rezaali and associates conducted a study in 2011 (published in late 2013) by Iranian MS society and Qom MS society reports (17). The rate of MS prevalence was 50.4 (95%CI: 46.4-54.6) per 100,000; female to male ratio was 3.4; and mean age was  $34.25 \pm 9.01$  years.

## Southern Iran

## Khuzestan

Khuzestan province located in southwest of Iran has both Persian and Arabic ethnicities. In 2012, some researchers estimated prevalence and incidence of MS to be 16.28 and 2.20 per 100,000 respectively (18). In another study, prevalence of MS in Khuzestan was 40 per 100,000; with mean age at onset of 29.26 years; female to male ratio of 3.02 (19). Recently, in a study by Radmehr and colleagues, prevalence of MS in northern cities of

Khuzestan was estimated as 15 (95%CI: 12.4-17.3) per 100,000 with 2.08 female to male ratio. Mean age of patients were  $33.4 \pm 9.4$  years; mean age at onset of  $25 \pm 8$  years. In another study, prevalence of MS in north and south of Khuzestan has been estimated to be 18 and 16 per 100,000, respectively (6).

## *Fars*

Fars province located in southwest of Iran and has 122,608 km<sup>2</sup> area. Prevalence of MS disease in October 2013 was 72.1 (95%CI: 69.6-74.5) per 100,000; female to male ratio was 4.04 with 5.2 per 100,000 annual incidence rate. Etemadifar et al. (in December 2014) in another study estimated prevalence of MS in Fars to be 78 per 100,000.(6)

## *Kerman*

Kerman province, one the largest provinces of Iran, is located in southeast. The crude prevalence of disease was 31.5 (95%CI: 29.5-33.52) in 100,000; 57.3 in Kerman city, as the highest rate of prevalence, and 1.9 in Kahnoj, as the lowest rate; mean age of patients were 28.35 years with female to male ratio of 3 (20). In another study, Etemadifar et al. estimated the crude prevalence of MS in Kerman to 37 in 100,000.(6)

## *Kohgiluyeh and Booyer Ahmad*

Kohgiluyeh and Booyer Ahmad, is one of the provinces of Iran, located at southwest. This province is nearby Zagros Mountains and ethnicity of most residents is Lor. Previously, Etemadifar and associates estimated MS prevalence in this province to 40.5 (6). More recently, Mousavizadeh and colleagues reported cumulative prevalence of disease to 60.14 (95%CI: 54.4-65.9), with 3.3 male to female ratio and  $29.78 \pm 8.5$  years mean age of patients at the time of diagnosis.(21)

## *Sistan and Baluchestan*

Sistan and Baluchestan is a southeastern province, bordering Pakistan and Afghanistan. It has an age-adjusted prevalence rate of 13.96 (95%CI: 11.9-15.9) per 100,000 and another recent research reported its prevalence to be 7.4 per 100,000 .(22 ,6)

## *Northern Iran*

### *Mazandaran*

Evidences on epidemiology of MS in Mazandaran province, a northern province, suggested a prevalence of MS 20.1 per 100,000 (23). However, in a recent research, MS prevalence in Mazandaran was estimated as 39 per 100,000 .(6)

### *Khorasan*

Khorasan, in the northeastern of Iran, bordering with Afghanistan and Turkmenistan includes Razavi, northern and southern Khorasan provinces with previously reported prevalence of MS of 12.9 (95%CI= 11.95-13.83), 8.7 (95%CI= 6.7-10.7) and 5.3 (95%CI= 3.5-7.1) per 100,000 and female to male ratio of 3.8, 1.8, and 3.2, respectively (24). A more recent study proposed that this epidemiologic picture might had been an underestimation; and, estimated the prevalence of MS in Razavi, northern and southern Khorasan provinces must be as high as 36, 18, 16 per 100,000 respectively.(6)

### *Azerbaijan*

MS prevalence in the East Azerbaijan, a northwestern province bordering Armenia and Republic of Azerbaijan was 27.7 with female/male ratio 2.7 (25). In a study by Etemadifar et al. it has been shown that its prevalence is 59 per 100,000 (6). In the most recent study by Yousefi et al. in 2017, it was demonstrated that MS prevalence in east Azerbaijan is 73.26 (95% CI= 70.5-75.9) per 100,000 with female to male ratio of 2.76 and  $38 \pm 9$  years, mean age for males and  $37.09 \pm 9$  years for females (26).

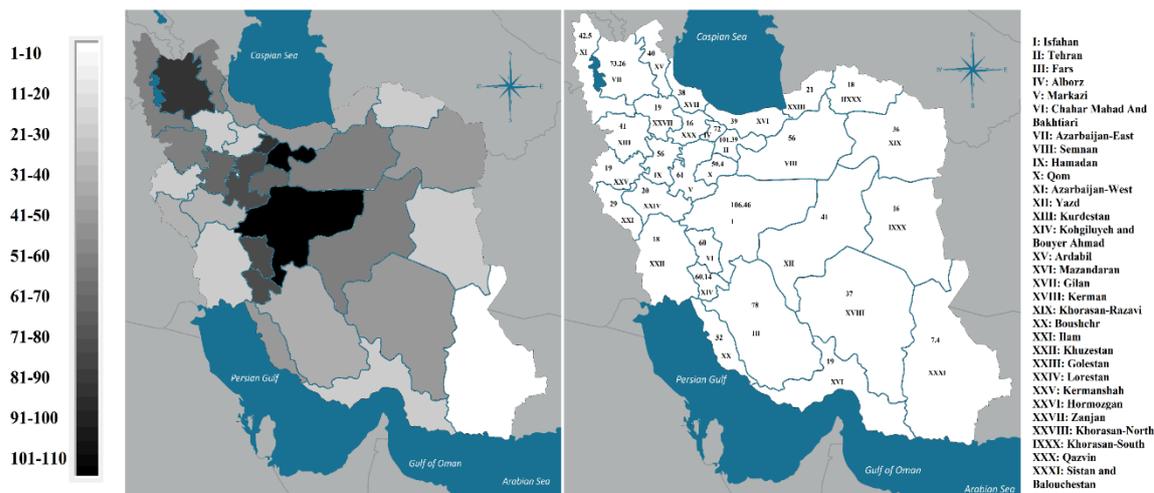
## **Discussion**

### *Map of MS distribution: Central Accumulation versus the old theory of gradient distribution*

For the first time in 2013, we had depicted a color map to depict prevalence rate of MS in different provinces of Iran. Unfortunately, that map lacked the actual data of many areas and some of its data were unreliable. In the current report, we complete our puzzle with all the available data as well as a new gradient grayscale (Figure 2) for better understanding of the MS distribution across Iran; the map depicts the geographical distribution with a range from 7.4 to 101.39 per 100,000 .

As figure 2 depicts, recent researches show higher prevalence picture of MS in rest of Iran than before; 21 provinces of Iran are classified in high risk of MS disease ( $>25/100,000$ ); 9 provinces in intermediate risk ( $5-25/100,000$ ) and one province in low risk ( $<5/100,000$ ). In the previous systematic review, 11 provinces were classified as high risk; 8 provinces as intermediate risk for MS disease. In that report, there was no report on epidemiology of MS in the remaining 11 provinces .(1)

As it is obvious from the figure 2, the reason for the pattern of the current MS distribution in Iran is not explainable by the traditional gradient theory. The



**Figure 2.** Prevalence rate of MS in various provinces of Iran. Left: Gray-scale gradient map corresponding to the actual number of the prevalence rate in each province. Rates are presented as cases per 100,000. Right: Actual prevalence of MS per 100,000 presented by Arabic numerals for each province. The roman numerals are for the names of provinces adjacent to the figure.

disease is seemingly more prevalent in central parts of Iran; to date, accumulation of MS in central parts of Iran has not been clearly reported.

Herein comes the question of whether there is a reason behind such an epidemiologic phenomenon. We know that explanation of increase of a disorder like MS that has both genetic and environmental components is too much complex to be simply proven or rejected by a theory or an example; instead, to explain, one needs a comprehensive modeling of all possible epidemiologic data. Unfortunately, at present, the literature lacks accurate data on the risk factors of MS in our country. Hence, at the current level of evidence, we would like to justifying the condition by the most rational reasons .

Firstly, we would like note that any postulation in this regard should rely on factors that have been emerged during the last four decades; since, average age of MS patients throughout the country is 30-40 years. This means that majority of the cases have been exposed to hazardous factors present since the last four decades. Thus, we postulate that steady risk factors like ethnicity, sun light exposure, and, level of vitamin D are less likely able to explain MS increase and especially, its central accumulation in our country .

In the literature, various risk factors have been suggested to explain increase of MS in Iran during the last decades; neither have any of them pointed toward the central accumulation nor have none of

them been proven. Here, we concisely criticize these issues .

Regarding ethnicity of the population, it is well-known that migration to central industrialized provinces such as Isfahan and Tehran has been occurred vastly during the last four decades; hence, these provinces presently have a mixed ethnicity. Recently, it has been reported that individuals with Lur ethnicity who live in Tehran have higher risk of MS development compared others (27). Yet, in another study on Lorestan province (a majorly Lur constituted province) (Figure 2) has an intermediate risk of MS and this highlight the importance of environmental risk factors rather than the genetic background.

Previously, some researchers attributed recent increase of MS incidence to Islamic Hijab (a special veil) that became obligatory after Islamic revolution of Iran that occurred 40 years ago. They postulated that women with such clothes may be deprived of sufficient sun exposure and consequently develop vitamin D deficiency, (28). Even if we assume some role for this factor, this explanation again may not explain the reason why the most religious provinces of Iran like Yazd, Qom and Khorasan Razavi provinces are not among the hot points of MS incidence or prevalence (see figure 2) .

Moreover, urbanization, living in room and using sun screens have also been supposed to cause hypovitaminosis D. Vitamin D deficiency is a well known risk factor for MS development, but this

factor again cannot justify the central accumulation of MS in Iran. Some studies have directly evaluated vitamin D levels in Iran. For example, Kermanshah province has been documented to have high prevalence of vitamin D deficiency though it has intermediate risk of MS. (29-31). Thus, it is obvious that none of these factors can justify the central accumulation of MS in Iran.

Other suggested risk factors like smoking and Epstein Barr Virus infection are not supposed to be increased among Iranian population during recent years, though, there are scanty data in this regard. Nevertheless, if we assume that such factors have been pronounced, they have not preferentially been increased in central parts of the country (5, 6, 32).

Other previously suggested explanations, like increase in availability of medical/imaging services that could enhance the disease diagnosis may be able to justify increase of MS new cases. However, these factors may not again justify the central accumulation. For example, Khorasan Razavi province (see figure 2) is among the very well equipped parts that have intermediate MS prevalence. Although the minimum prevalence of MS in rest of Iran was estimated 45 per 100,000; it seems that such underestimation could be due to sampling flaw as the researchers included only patients who received  $\beta$  interferon for treatment (10). Therefore, those patients who received other therapeutic agents could be ignored .

Furthermore, most of the epidemiological studies of MS from Iran are not age-adjusted. Iran is young population in comparing with other countries (i.e. European countries) and age-adjusted prevalence reports permit the researchers to compare MS prevalence of Iran with other countries as well as comparing MS prevalence among Iran's provinces.

Yazd province had not prevalence of MS disease as high as old industrialized provinces. Therefore it can be proposed that 10 to 20 years later higher prevalence of MS disease could be expected in new industrialized provinces such as Yazd province.

## Conflict of interest

All of the authors declare that there is no conflict of interest.

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