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Investigating the Relationship between Environmental Factors and the Incidence of Multiple Sclerosis in Three Regions of Iran: A Case-control Study

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Abstract

Introduction: Multiple sclerosis is one of the most prevalent debilitating neurological diseases among young people. Multiple sclerosis is a multifactorial disease in which both environmental and genetic factors are involved. Despite numerous studies conducted in this field, it remains a challenging topic. Therefore the present study aimed to explore the environmental factors associated with multiple sclerosis.

Methods: This case-control study was conducted in 2020-21 in three geographical areas of Iran. A total number of 445 subjects were included in the study, among whom 172 belonged to the case group and 273 to the control group. The inclusion criteria for patients were the confirmation of the disease by a neurologist, the age range from 15 to 50 years, full consciousness, not having acute or critical conditions of MS disease. The inclusion criteria for healthy subjects were not having the MS, not having any neuro-inflammatory peripheral disease, not having a cancer. The patient participants were randomly selected from the medical records of the MS Association of each city. The control group was randomly selected from among the people visiting the medical centers of each city. The collected data were punched into SPSS 20. Descriptive and inferential statistics including mean, standard deviation, frequency and chi-square were used to describe the research variables. Mann-Whitney U-test was used to compare the mean of interval variables in two groups, and chi-square test was used to determine the relationship between qualitative variables in two groups. A logistic regression analysis was used to estimate the relationship between risk factors and the disease.

Results: There was a significant difference between the two groups in terms of the duration of sunbathing , OCP, gender , history of blood transfusion , family history of MS , history of crisis , physical activity before illness , history of accident , job, ethnicity, predominant type of cooking, consumption of liquids and tea, salt consumption, Infant nutrition, consumption of vegetables and chicken, consumption of canned food, dairy products, nuts and beans ($p<0.05$).Bivariate logistic regression analysis of factors associated with multiple sclerosis showed that the most influential factors in the disease were: positive family history, history of accidents and trauma, baby nursing, and a high-salt diet ($p <0.05$).

Conclusions: The successful control of this disease depends on the identification of the complex network of factors. Despite the many researches about the factors related to MS, it seems that this issue has many complications and detailed and advanced studies should be done in this field. By better understanding these factors, we can create preventative strategies to reduce the risk of developing MS, develop more effective treatments, and lessen the burden of the disease on affected individuals and society

INTRODUCTION

Multiple sclerosis is one of the most prevalent debilitating neurological diseases among young people [1]. MS is on an unprecedented rise on a global scale [2]. The number of patients afflicted with MS has increased from 350 thousand people in the United States and 2.5 million people worldwide [3]. In the past, Iran was marked by a low prevalence of MS, but recent research has shown that the prevalence of MS has increased significantly in Iran. The prevalence of the disease in Iran is taken as average. Yet the prevalence of the disease is still increasing rapidly. The highest prevalence rate is in Isfahan Province (80 per hundred thousand people) [4] and the lowest prevalence rate is in South Khorasan Province (5.3 per hundred thousand people) [3]. In a systematic review and meta-analysis, the prevalence of MS in Iran was estimated at 5.3-89 per 100,000) [5].

This disease imposes high costs on the society and the individual's family. The direct and indirect costs of the disease is estimated to be approximately 24,475 dollars for each patient [6]. The exact economic burden of MS disease on society and individuals is not estimated. Yet, most MS patients are between 25 and 40 years of age, and patients mostly refrain from doing their physical and professional activities. As an example, it has been reported that nearly 39% of men and 19% percent of women are forced to retire early or become disabled due to MS. Thus, the economic burden of this disease on the society is significant [7].

In western societies, MS is the second cause of neurological disability, only next to trauma, in early middle age. Clinical manifestations can vary from a benign disease to a rapidly progressive and debilitating disease that requires extensive adaptation in lifestyle [8]. The complications and problems limit patients' cooperation in health-related activities, and as a result, increase secondary complications and further limit their independent lives, and ultimately have a negative effect on their quality of life. The onset of MS disease often causes an initial or comprehensive decrease in the individual's physical, social and cognitive functions and has a destructive effect on his/her quality of life, the family and close friends [9].

Mental health suffers in MS patients too due to the extensive damage to the white matter in the subcortical and central areas, leading to anxiety and stress, which are very common [10]. MS significantly affects the patients' and their families' quality of life [7]. The existing research shows that a combination of genetic and environmental factors can be involved in the occurrence of multiple sclerosis. These can include smoking, occupational exposure to toxins, stress, some viral infections and bacterial infections [5, 11-14].

The cultural diversity and the co-existence of different ethnic groups with different cultures is quite evident in Iran. These differences have caused changes to people's lifestyle [5]. Therefore, these factors can influence the rate of MS disease. Since some environmental factors are associated with the prevalence of MS and many of these factors can be manipulated, the present study investigated the factors related to MS in three different geographical regions of Iran.

Extending our knowledge of these factors can generate new and more effective approaches to patient counseling and possibly disease prevention and management. Considering the above-mentioned conditions, the high prevalence of MS and the severe adverse effects of this disease on the individual, family and society, it seems essential to investigate the factors associated with this disease. Concerning the factors affecting the incidence of MS, there have been studies that looked into some of these factors. Therefore, conducting the present study with the aim of determining the environmental factors related to MS disease seemed necessary as an effective measure taken for future policy making and planning both for public education and educating MS patients.

METHODS

In this case-control analytical study, 445 people from three cities of Iran in different geographical areas (Mashhad, Kermanshah and Gorgan) in 2020-21 were included in the study.

Participant

The research population consisted of all people afflicted with multiple sclerosis visiting the MS Association. Healthy people were also included as the control group. The sample size was estimated using the G-Power3.1.9.2 software, the z-test family and the proportion test. The difference between two independent proportions was p2=0.2, p1=0.01, α=0.05, 1-β=0.95). p1 and p2 were adopted from the study by Sahebalzamani for the accident and trauma history variable(16). Thus, 162 subjects were assigned to each research group. With an attrition rate of 10%, 173 subjects were assigned to each group. Thus, a total number of 346 patients were included. This number was multiplied by 2 for the control group. To achieve the best statistical power and reduce the error, a superiority ratio equal to 3 was used. After, the data were collected, 73 questionnaires were excluded from the control group because of incompleteness. In total, 158 subjects from Mashhad, 131 from Kermanshah and 156 people from Golestan Province (city of Gorgan) were included in the study. Sampling for the case group was done in a simple randomized way from the MS Association of each city. The available list of patients in the association was used to this aim. The control group was randomly selected from among the people visiting the medical centers of

each city. To this aim, after approving the research plan and obtaining a written permission from the Gonabad University of Medical Sciences (proposal's code 636/T/P and code of ethics IR.GMU.RES.1397.050), the researchers visited the MS Associations of Mashhad, Gorgan and Kermanshah and after handing the permission letter to those in charge in the associations, they elaborated on the objectives of the research. After that, the researchers randomly selected people from among the medical records based on the sample size and contacted them. After introducing themselves and stating the objective of research, the researchers invited the patients who were willing to participate in the study and met the inclusion criteria. In order to select the healthy participants, individuals were selected who had no symptoms of the disease and were healthy as self-reported using the definitive diagnosis criteria of MS (McDonald). The inclusion criteria for patients were the confirmation of the disease by a neurologist, the age range from 15 to 50 years, full consciousness, not having acute or critical conditions of MS disease. The inclusion criteria for healthy subjects were not having the MS, not having any neuro-inflammatory peripheral disease, not having a cancer. The two groups were matched for age through frequency matching. The data collection instrument was a researcher-made questionnaire containing demographic information and environmental factors. This questionnaire was developed based on a review of academic publications. The validity of this questionnaire was substantiated through face and content validation methods, and its reliability (On 20 people from research units) was estimated using Cronbach's alpha (α=0.88). The collected data were punched into SPSS 20. Descriptive and inferential statistics including mean, standard deviation, frequency and chi-square were used to describe the research variables. Kolmogorov-Smirnov test showed that all the variables of the study did not have a normal distribution (p<0.05). Mann-Whitney U-test was used to compare the mean of interval variables in two groups, and chi-square test was used to determine the relationship between qualitative variables in two groups. A logistic regression analysis was used to estimate the relationship between risk factors and the disease.

RESULTS

The preliminary analysis showed that 67.9% of the subjects were female, 63.6% had a Persian ethnicity and 59.6% were married. Most of the subjects (i.e., 13.9%) were born in September. Also, most of the subjects (25.8 percent) were the second child in the family. Moreover, 46.7% of the subjects held a diploma degree. 33.2% were unemployed. The blood group of 39.2% was O, and 78% were Rh-positive. Also, 93.9% of the participants were urban residents, and 86.7% used to live in cities. In other words, 7.2% of the participants migrated from the village to the city. 58% owned their own house or apartment. The average age of the participants was 33.67±10.58 years and their average weight was 69.34±13.25 kilos. Kolmogorov-Smirnov's test showed that none of the variables in the study had a normal distribution. Mann-Whitney U-test showed that age, height, weight and monthly income, amount of sleep, duration of contact with birds and pets, age of first menstruation, duration and amount of smoking were not significantly different between the two research groups (p>0.05). There was a significant difference between the two groups in terms of the duration of sunbathing and duration of taking OCP (p<0.05) (Table 1). The chi-square test showed no significant difference between the two groups in terms of the month of birth, education, blood type, age, current and previous place of residence, accommodation type, use of sunscreen, type and frequency of meat consumption, type of vegetables consumed, coffee consumption, tobacco and alcohol, type of oil consumed, chocolate, contact with birds and pets, history of chronic and autoimmune disease, history of surgery, consumption of fast food, consumption of fruit, sweets (p>0.05)(table2). According to the Fisher's exact test, there was no significant difference between the two groups in terms of marital status (p=0.093), but the differences were significant in terms of gender (p=0.037) history of blood transfusion (p=0.013), family history of MS (p=0.004), history of crisis (p=0.001), physical activity before illness (p=0.001), history of accident and trauma (p=0.007).

Table1. Comparison of the mean scores of interval variables in the two groups

Variable	Case group	Control group	Mann-Whitney U test
Height	164.77±12.20	166.60±11.31	Mann U=21385.5; P-value=0.112
Weight	68.41±12.46	69.92±13.72	Mann U=21959.0; P-value=0.250
Duration of sun exposure	37.70±70.27	70.53±85.06	Mann U=23724.0; P-value=0.0001
Income	1054.65±1176.43	1229.57±1765.43	Mann U=23242; P-value=0.856
Sleep duration	7.85±2.11	7.94±1.82	Mann U=22842; P-value=0.662
Duration of contact with birds	0.65±2.17	0.72±2.74	Mann U=23472; P-value=0.994
Duration of contact with pets	0.20±0.92	0.31±2.0	Mann U=23192; P-value=0.587
Age of first menstruation	13.11±1.66	13.23±1.48	Mann U=10607/50; P-value=0.491
Smoking duration	1.34±4.42	0.82±3.18	Mann U=22836; P-value=0.353
Number of cigarette butts	1.42±4.79	0.98±4.08	Mann U=22495; P-value=0.167
Duration of OCP consumption	0.96±2.42	0.53±1.77	Mann U=20884; P-value=0.006

Table 2. Comparison of the frequency of non-interval variables in the two groups

Variable	Case group	Control group	
Gender			Fisher 's p=0.037
Female	127	175	
Male	45	98	
Marital status			Fisher 's p=0.093
Married	111	154	
Single	61	119	
Job			X2=34.949; Df=3; P=0.0001
Office work (governmental)	40	78	
Freelance	38	102	
Retired	9	30	
Unemployed	85	63	
Ethnicity			X2=41.047; Df=4; P=0.0001
Persian	126	157	
Turkish	7	10	
Kurd	6	57	
Lur	12	38	
Arab	21	11	
Family history of M.S			Fisher 's p=0.037
Yes	16	8	
No	156	265	
History of accidents			Fisher 's p=0.037
Yes	32	27	
No	140	246	
Infant nutrition			X2=21.883; Df=3; P=0.0001
Breast feeding	128	222	
Formula milk	21	32	
Cow milk	4	15	
Mixed	19	4	
Salt consumption			X2=15.718; Df=2; P=0.001
Low	69	63	
Moderate	98	193	
High	5	17	
Liquids and tea consumption			X2=10.144; Df=3; P=0.017
>4 cups	59	63	
4-6 cups	74	122	
7-8 cups	20	57	
>8 cups	19	31	
Consumption of white meat and chicken			X2=10.821; Df=4; P=0.029
0	8	8	
Once a week	41	35	
2/week	47	83	
3/week	45	83	
4 >/week	31	64	
Dairy consumption			X2=15.890; Df=6; P=0.014
0	12	3	
Once a week	21	19	
2/week	19	30	
3/week	26	45	
4 /week	12	21	
5/week	12	23	
6 , >/week	70	132	
History psychological tension			Fisher's p= 0.001
Yes	73	76	
No	99	197	
Dominant type of cooking			X2=14.253; Df=4; P=0.007
Boiled food	57	49	
Steamed food	7	16	
Grilled	3	10	
Fried	67	127	
Smoked	38	71	
Physical activity			Fisher p:0.001
Yes	117	224	
no	55	49	
Chronic disease history			X2=6.531; Df= 5; P=0.303
No	135	204	
Cardiovascular	11	29	
Diabetes	10	14	
Livery disease	2	10	
Renal disease	3	5	
other	11	11	

Table 3. Results of binary logistic regression of MS related factors

Variable	β	S.E	Wald	EXP(β)	C.I(MIN)	C.I(MAX)	P
Family history of MS	-1.316	0.516	6.512	0.268	0.098	0.737	0.011
History of accidents	-0.941	0.313	9.053	0.390	0.212	0.720	0.003
Infant nutrition	0.416	0.139	8.966	1.516	1.154	1.989	0.003
Salt consumption	-0.856	0.212	16.430	0.425	0.281	0.643	0.0001
Liquids and tea consumption	-0.206	0.072	8.237	0.814	0.707	0.937	0.004
Consumption of white meat and chicken	-0.234	0.100	5.462	0.791	0.650	0.963	0.019
Dairy consumption	-0.186	0.057	10.791	0.830	0.743	0.928	0.001
Job	0.448	0.902	23.536	1.565	1.306	1.876	0.0001

Chi-square test showed a significant between-group difference in terms of job, ethnicity, predominant type of cooking, consumption of liquids and tea, salt consumption, Infant nutrition, consumption of vegetables and chicken, consumption of canned food, dairy products, nuts and beans ($p<0.05$). Finally, the variables of gender, marriage, job, ethnicity, duration of sunbathing, duration of OCP consumption, consumption of legumes, consumption of canned foods, brains, dairy products, chicken, vegetables, blood transfusion history, accident history, Infant nutrition, trauma history, family history of MS , the consumption of salt, tea and liquids, the type of food cooking were included in the logistic regression. A binary logistic regression analysis was used for factors related to MS. The Hosmer and Lemeshow Test confirmed the usefulness of our model ($p=0.210$). The values of Cox & Snell R Square and Nagelkerke R Square were 0.180, 0.245, respectively. Therefore, the explained variation in the dependent variable based on our model ranges from 18.0% to 24.0% depending on the Cox & Snell R2 or Nagelkerke R2 methods, respectively.

A value of β = -1.316, in those without a family history of MS shows that they had a lower chance of developing MS.in other words an odds ratio less than 1 indicates a protective association. A value of β = -0.941indicates that, those with no history of accidents and trauma had a lower chance of affliction with MS. Similarly, a value of β = 0.416 shows those who consumed different types of milk during infancy had a higher chance of affliction with the disease. The results also showed that those who followed a low-salt diet had little chance of developing MS compared to others (β = -0.856). Also, those who consumed more dairy products and white meat (chicken) had a lower chance of affliction with MS as a value of β = -0.186 and -0.234 show. Also, a value of β = 0.448 shows that one's job can be a significant factor affecting the affliction with MS disease. The unemployed had a higher chance of affliction with MS than office workers (Table 3).

DISCUSSION

The results of the present study showed that the height, weight, monthly income, and the amount of sleep in the two groups did not have a significant difference. This finding is consistent with the study conducted by Behrouz et al. They found no significant difference in weight and body mass index of the two groups [15]. The results of the present study showed that the age of first menstruation (in women) was not significantly different in the two research groups. This finding is contrary to the study conducted by Sahebalzamani, who observed that the age of first menstruation was higher in the control group [16] but it is confirm with the study of Zarabadi [17]. In Zarabadi study, it was shown that the age of the first menstruation may be effective in the occurrence of menstrual disorders, but the relationship between the age of the first menstruation and the occurrence of MS was not investigated [17]. Manouchehri et al. showed that there was no significant relationship between the duration of MS disease and the duration of menstruation, the amount of menstrual bleeding, menstrual interval and dysmenorrhea [18].

There was a significant statistical difference between the two groups in terms of the duration of sunbathing. The duration of sunbathing in the case group was significantly lower than in the control. This finding is confirm with other studies [16, 19-28]. Deseilligny and Souberbielle also showed that hypovitaminosis D has a significant correlation with the MS disease [29]. There was a significant difference between the two groups in the duration of OCP consumption. The average duration of OCP consumption was higher in the patient group. This finding is contrary to the findings reported by Sahebalzamani [16].

In this study, the two groups did not have a significant difference in marital status. In Mehri's study, the married status was significantly correlated with the MS disease [30]. Samannejad showed that 68.1% of patients were married [31]. In Sahebalzamani's study 63.8% were married in the case group and 81.2% were married in the control group. But in these two studies, no between-group comparison was made in terms of the marital status [16]. In Abedini's study, the prevalence of the disease was higher in the married persons [32]. In Silva's study, the disease was more common in single persons [33].

In the present study, there was a significant difference between the two groups in terms of gender. There were more women in the patient group. Abedini's and Azami study also confirmed this finding [5, 32]. In Raisi's study, women with MS in Kerman were almost three and a half times as many as men, and 77.8% of the patient population were women [19]. Koriem in England showed that the number of women with MS

was almost twice that of men [34]. Also, in Maleki study, the rate of disease in female was 71.4% [4]. In Sai study 99.75% of all MS patients were women [35]. In their review, Dehghani and Kazemimoghadam concluded that 72.3% of patients are women and their average age was 27.24 years [21]. According to Sreeram's and Samannejad findings, the incidence of the disease among women was more than men [31, 36]. Perhaps one of the reasons why more women suffer from MS is their less exposure to the sun than men and the lack of vitamin D, and perhaps the type of clothing and hijab of Iranian women is related to the lack of vitamin D and the consequent MS, which needs to be investigated further.

In the present study, blood transfusion history, physical activity before the disease, history of accident and trauma showed significant differences between the two groups. In SahebalZamani's study, the two groups had a significant difference in the history of trauma [16]. In their study, Behrouz et al. showed that there was no significant relationship between physical activity and the MS disease [15]. No similar study was found in the inquiry about blood transfusion.

In the present study, the family history of MS was 9.3% and there was a significant difference between the two groups in the positive family history of the disease. This finding is confirm with study of Sahebalzamani [16], Zorzon [37] and Nielsen [38]. In Samannejad's study, there was a 1.2% history of MS disease in close relatives and 2.1% history of MS disease in distant relatives [31]. In Ashtari's study in Isfahan, the history of disease in close relatives was 20.1%. No cross-comparison was made in this study [39].

In the present study, the history of psychological stress accounted for a significant difference between the two groups. Samannejad et al. also concluded that stress and anxiety increased the symptoms of MS and decreased the response to treatment [31].

In the present study, there was no significant difference between the two groups in terms of current and previous place of residence. Behrouz et al. also confirmed this finding [15]. In another study, Samannejad et al. concluded that 79.5% of patients were born in the city and suggested urban and industrial life as a risk factor for the MS disease [31]. In a body of research by Raisi [11], Raisi [19], Golmohammadi [40] and Abedini [32], urban residence had a higher prevalence than rural residence. Perhaps the reason for the difference is that most of the members of the MS Association live in cities.

Moreover, there was no significant difference between the two groups in the history of chronic and autoimmune diseases. This finding consist with Behrooz's study [15]. Yet, this finding is contrary to the findings reported by Khadilkar [41], Sahebalzamani [16], Olsson et al. and Zorzon [22, 37]. In the case group, the history of autoimmune disease was 11.2% compared to the 2.5%. in the control group. The case group in which one of their family members had a rheumatic fever was 3.3 times more at risk of developing MS than the control group [16]. In Samannejad's study, 12.3% had a history of another chronic disease [31]. In their review, Mir et al. concluded that some infectious agents can affect the nervous system by stimulating the body's immune response and play a role in the occurrence of MS [42], which was not significant [43]. Ascherio and Munger and showed that among the infectious agents proposed to be associated with MS, only EBV (Epstein-Barr virus) stands out as a consistent and strong risk factor [44].

Moreover, the analysis of the findings showed there was no significant difference between the two groups in the education level. In Sahebalzamani's and Mehri's study the level of education and job was not significant between the two groups [16, 33]. However, in Abedini's study, the incidence of the disease was higher in educated people [32].

Furthermore, the findings revealed no difference between the two groups in food consumption, the type and frequency of consuming meat, the type of vegetables, oil, chocolate, fast food, fruit, sweets, and coffee consumed. In the present study, there was a significant difference between the two groups in terms of job, ethnicity, predominant type of cooking, consumption of liquids and tea, consumption of salt, consumption of vegetables and chicken, consumption of canned food, dairy products, and legumes. In the study of Sahbalzamani [16] and Khadilkar [41], there was a significant difference between the two groups in dairy consumption. In Behrouz et al.'s study, after adjusting the effect of the confounding variables, people in the highest tertile of consuming fruits, tomatoes, other vegetables and liquid oils had a significantly lower chance of developing MS. On the other hand, people who were in the highest tertile of consuming solid oil and soft drinks had a significantly higher chance of developing MS [15]. In their study, Dehghani and Kazemimoghadam showed that obesity, food quality, alcohol consumption, smoking, air pollution, and some chemicals can play a role in MS [21]. Hosseini et al. also showed that there is a significant negative association between vegetable consumption and MS disease [45].

In the present study, people who were fed with different milks during infancy had a higher chance of affliction with the disease. The works of research by of Sahebalzamani [16] also confirm this finding. Behrouz et al. showed there was no significant relationship between cow's milk consumption in childhood and the MS disease [15]. The potential reason for this difference was the duration of consuming milk. In the present study, the emphasis was on nutrition in the first 2 years of life. Also, there was no significant difference between the two groups in terms of tobacco and alcohol consumption. This finding is consistent with the results

reported by Behrouz et al. [15]. Yet, this finding is contrary to the study by Sahebalzamani [16]. Also, in the study of Mehri [30] and Olsson et al. [22], it was shown that MS was related to smoking. In their study, Dehghani and Yunsian et al. showed in areas where smoking is more common, the rate of disease was also increased [46].

Also, the results of the present study showed no significant difference between the two groups in the month of birth. The results of Staples et al.'s study also confirmed this finding [47]. However, this result is not consistent with the studies by Disanto et al. [23] and Nourbakhsh and Mowry [24] and the study conducted by Gorman et al. [25] and Milo and Kahana [27]. In these works of research, it was shown that vitamin D deficiency, the season of birth, Epstein-Barr virus infection, and smoking behavior are significantly involved and can influence the genetic predisposition to MS. Also, in their study, Behrouz et al. reported a significant correlation between the birth season and disease [15].

The present study revealed no significant difference between the two groups in terms of surgical history and monthly income. In his study, Dehghani contends that for people with a better economic status during childhood, the adaptation of the immune system to external factors is lower, which can be a risk factor for MS in adulthood [21].

CONCLUSION

MS is one of the most common neurological disorders in the world, and affects mostly young populations. Moreover, the highest rate of occupational activity and productivity belongs to the young age. When people at young age are more prone to the disease their personal and social lives can be adversely affected. Thus, it is necessary to pay attention to the risk factors of the disease and consider the ways to prevent the controllable factors. The present study, in line with recent studies in MS research, showed that MS is induced by a combination of genetic factors and environmental exposure from pregnancy to early adulthood. It seems that many environmental and genetic factors are interactively involved in the occurrence of the disease. Evidence suggests that a large proportion of MS is preventable, and understanding how and when risk factors operate throughout life can ultimately help develop preventive strategies. Considering the many problems that this disease imposes on families, it is expected that the percentage of family disorders in patients will increase, which of course needs further investigation. Therefore, a fundamental step should be taken in order to prevent and adjust the controllable factors. There is a need for more in-depth investigations of lifestyle, nutrition, activity and exercise, the importance of infant nutrition, being in touch with animals and birds and its relationship with disease. Awareness-raising should be done in mass media especially the television. It is also possible to identify at-risk families and hold training courses for them. A low-salt diet, adequate fluid intake throughout the day, consumption of white meat, chicken and fish, consumption of vitamin D and exposure to sunlight should be taken into account too. As a history of accidents and trauma is a risk factor in this disease, public awareness needs to be raised of this important factor too. New instructions are needed to change people's styles of driving, preventing accidents, using helmets for motorcycle riders, and observing the correct principles of driving in society, especially among the young people.

It is noteworthy that the intertwined genetic and environmental factors and the different research findings in different regions show the complexity of the issue and the possibility of some other factors related to MS. These need to be further investigated. Besides, it seems that the outcome, simultaneity and interaction of risk factors play a major role in the occurrence of the disease. These factors may act synergistically to increase the risk of developing MS in people who are exposed to more than one factor. Also, the role of internal and personal factors to an individual in the occurrence of the disease and its relationship with other risk factors needs further investigation. Therefore, due to the increase of MS patients in Iran, wider and comprehensive studies should be conducted in different regions of the country. MS seems to be related to a complex network of factors. The successful control of this disease depends on the identification of these factors. Despite the many researches about the factors related to MS, it seems that this issue has many complications and detailed and advanced studies should be done in this field. The relationship between MS and blood transfusion and anemia, OCP, occupation, culture, type of food consumed, etc., each requires a separate investigation and research. One limitation of the present study was that some participants did not know or remember things about their childhood, such as vaccination or diseases during childhood.

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AUTHOR'S CONTRIBUTIONS

Sajjad Rezaei: Ideation, proposal writing, data gathering. Maryam Moradi: Proposal writing, data analysis, Interpretation of findings. Zahra Gharedashi, Fatemeh Khosravi, Fatemeh Hosseini-Moghaddam: data gathering. Mehrsa Basiri Moghaddam: Ideation, proposal writing, data analysis, Interpretation of findings, article writing and editing

ETHICAL CONSIDERATION

Ethical committee approval was received from the Ethics Committee of the Gonabad University of Medical Sciences (proposal's code 636/T/P and code of ethics IR.GMU.RES.1397.050)

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CONFLICTS OF INTEREST

None to declare.

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