BMC Neurology

RESEARCH Open Access

Lifetime exposure to smoking and substance abuse may be associated with late-onset multiple sclerosis: a population-based case-control study

Naghmeh Abbasi Kasbi[1], Sajjad Ghane Ezabadi[1], Kosar Kohandel[1], Faezeh Khodaie[1], Amir Hossein Sahraian[1], Sahar Nikkhah Bahrami[1,3], Mahsa Mohammadi[1], Amir Almasi-Hashiani[2], Sharareh Eskandarieh[1*] and Mohammad Ali Sahraian[1*]

Abstract

Background Late-onset multiple sclerosis (LOMS), defined as the development of MS after the age of 50, has shown a substantial surge in incidence rates and is associated with more rapid progression of disability. Besides, studies have linked tobacco smoking to a higher chance of MS progression. However, the role of smoking on the risk of developing LOMS remains unclear. This study aims to evaluate the possible association between lifetime exposure to cigarette and waterpipe smoking, drug abuse, and alcohol consumption and the risk of LOMS.

Methods This population-based case-control study involved LOMS cases and healthy sex and age-matched controls from the general population in Tehran, Iran. The primary data for confirmed LOMS cases were obtained from the nationwide MS registry of Iran (NMSRI), while supplementary data were collected through telephone and on-site interviews. Predesigned questionnaire for multinational case-control studies of MS environmental risk factors was used to evaluate the LOMS risk factors. The study employed Likelihood ratio chi-square test to compare qualitative variables between the two groups and utilized two independent sample t-test to compare quantitative data. Adjusted odds ratio (AOR) for age along with 95% confidence intervals (CI) were calculated using matched logistic regression analysis in SPSS 23.

Results Totally, 83 LOMS cases and 207 controls were included in the analysis. The female to male ratio in the cases was 1.5: 1. The mean ± SD age of 83 cases and 207 controls was 61.14 ± 5.38) and 61.51 ± 7.67 years, respectively. The mean ± SD expanded disability status scale (EDSS) score was 3.68 ± 2.1. Although the results of waterpipe exposure had no significant effect on LOMS development (P-value: 0.066), ever cigarette-smoked participants had a significantly higher risk of developing LOMS than those who never smoked (AOR: 2.57, 95% CI: 1.44–4.60). Furthermore, people with a history of smoking for more than 20 years had 3.45 times the odds of developing MS than non-smokers. Drug

*Correspondence:
Sharareh Eskandarieh
sh_eskandarieh@yahoo.com
Mohammad Ali Sahraian
sahraian1350@yahoo.com

Full list of author information is available at the end of the article

and alcohol abuse were both associated with LOMS in our study; of which opioids (AOR: 5.67, 95% CI: 2.05–15.7), wine (AOR: 3.30, 95% CI: 1.41–7.71), and beer (AOR: 3.12, 95% CI: 1.45–6.69) were found to pose the greatest risk of LOMS, respectively.

Conclusion For the first time, we identified smoking, drug, and alcohol use as potential risk factors for LOMS development. According to the global increase in cigarette smoking and alcohol use, these findings highlight the importance of conducting interventional approaches for prevention.

Keywords Late-onset multiple sclerosis, Risk factor, Cigarette smoking, Alcohol, Opium, Water pipe smoking

Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease that affects the central nervous system by infiltration of immune cells and inflammatory demyelination of white matter [1]. Considered the most common chronic demyelinating disorder, MS leads to disability and a significant decline in quality of life, especially in young individuals [2]. Although the exact etiology is still unclear, research has increasingly focused on identifying potential risk factors that may contribute to its development and progression. Factors such as previous EBV infection, vitamin D deficiency, obesity, and smoking have been proposed as potential risk factors for MS development [3].

The onset of MS usually occurs during the third to fourth decade of life [4]. However, some patients may experience symptoms beyond the age of 50 [5]. Recent studies have indicated that late-onset multiple sclerosis (LOMS) is more prevalent than previously believed, with estimates ranging between 4% and 9.4%. These findings challenge the notion that LOMS is of rare occurrence [6, 7]. In light of existing literature, progressive patterns of MS are more common in LOMS patients [8, 9]. Moreover, the diagnosis of LOMS can be challenging for clinicians, as many diseases in the elderly may present with similar characteristics [10]. This highlights the importance of early diagnosis, understanding the disease characteristics, and identifying its associated risk factors.

In the past few years, emerging epidemiological research has suggested a possible link between smoking and MS. Cigarette smoking amplifies inflammatory responses, diminishes specific components of the immune system, and enhances the propensity for infection [11]. Previous studies have also hinted at a possible connection between smoking and MS through the presence of low serum vitamin D levels and inadequate dietary vitamin D intake among smokers [12]. The duration and intensity of smoking play significant roles in the dose-dependent risks associated with MS, and the adverse effects gradually decline upon smoking cessation [13, 14]. Waterpipe smoking has also been recognized as a risk factor for the development of MS [15]. Notably, the role of alcohol consumption in MS remains debated, with studies supporting both risk and protective viewpoints [12, 16]. Some recent studies have also mentioned substance use as a potential risk factor for MS, although specific details are not provided [15]. However, there is limited evidence regarding the risk factors associated with LOMS.

This study aims to explore the potential effect of tobacco smoking, alcohol consumption, and substance abuse as risk factors for LOMS.

Materials and methods

Study design

A population-based case-control study was carried out during 9 months from November 2022 to July 2023 in Tehran to investigate the potential risk factors of late-onset MS. The study employed a hybrid approach, combining both in-person and remote data collection methods.

Participants

The source population of our study was all residents aged 50 years and above residing in one of the 22 districts within the Tehran municipality for a minimum of two years. Cases were defined as confirmed LOMS patients according to the 2017 McDonald criteria, registered at our official MS registry, the nationwide MS registry of Iran (NMSRI) [17, 18]. Besides, controls were healthy individuals within the source population with no history of MS, selected randomly through an age-matched randomization method from various areas of Tehran. Overall, 97 registered cases and 230 matched controls were contacted for further investigations and interview. Individuals with cognitive impairment or a lack of willingness to participate in the interview were excluded. Controls who presented any form of other neurological disease were also excluded.

Data collection

Clinical characteristics of LOMS cases were extracted from NMSRI to complete a structured questionnaire, designed specifically for multinational case-control research on environmental risk factors associated with MS [19]. Telephone interviews were also performed by four well-trained interviewers to gather supplementary data on the cases. Moreover, two interviewers conducted

a face-to-face interview with the general population as the control group, using the same questionnaire.

Exposure assessment

Participants were asked to fill out the study questionnaire comprising demographic items such as age, sex, marital status, the highest level of education, and self-rated health status - scored from 1 (the lowest) to 5 (the highest)-, and their history of cigarette and waterpipe smoking, substance (opioids, cannabis, stimulants, hallucinogen) use, and alcohol (whisky/vodka, beer, and wine) consumption across the life course.

The history of cigarette smoking was considered positive if the participant smoked cigarettes for at least 6 months or more than 180 cigarettes in total. Substance use and alcohol consumption were positive if participants used them at least once per month for more than 6 months, while for waterpipe it was considered at least once per week for more than 6 months [13, 20].

Statistical analysis

Quantitative data was described using mean and standard deviation, whereas qualitative data was described using number and percentage. Likelihood ratio chi-square test was utilized to compare qualitative variables between two groups and two independent sample t-test was employed to compare quantitative data. Crude and adjusted odds ratio (OR) and 95% confidence interval (CI) were also used to check the effect size of independent variables on dependent variables. All analyses were performed using Stata software version 14 and at a significance level of 0.05.

Table 1 Demographic characteristics of LOMS cases and general population controls

Variables		LOMS	Control	*P*-value
Sex, N (%)	Male	33 (39.8%)	84 (40.6%)	0.897
	Female	50 (60.2%)	123 (59.4%)	
Age, mean (SD)		61.14 (5.38)	61.51 (7.67)	0.690
Age at onset, mean (SD)		53.58 (4.09)	-	-
Age at diagnosis, mean (SD)		55.20 (4.39)	-	-
Marital status, N (%)	Single	2 (2.41%)	9 (4.43%)	0.444
	Married	74 (89.16%)	169 (83.25%)	
	Widow	4 (4.82%)	19 (9.36%)	
	Divorced	3 (3.61%)	6 (2.96%)	
Education, N (%)	Illiterate or primary school	18 (21.68%)	25 (12.13%)	**0.030**
	Guidance school	9 (10.84%)	15 (7.28%)	
	High school	32 (38.55%)	67 (32.52%)	
	Associate's or bachelor's degree	21 (25.3%)	75 (36.41%)	
	Master's degree and higher	3 (3.61%)	24 (11.65%)	
Self-rated health status[†]; mean (SD)		3.0 (1.06)	3.7 (0.87)	**0.001**

SD: standard deviation, LOMS: late-onset multiple sclerosis, [†]The score for self-rated health status ranged from 1–5

Ethical considerations

Each participant was thoroughly informed about his/her role in the study as well as the purpose of the research, and their probable questions about the study were answered. All participants were required to give verbal consent to be informed that their personal information is kept secure. Those who were unwilling to take part in our study were excluded. The ethics committee at Tehran University of Medical Sciences approved the current study by the code: IR.TUMS.NI.REC.1402.028. Furthermore, all the steps taken in this study adhere to the principles outlined in the Declaration of Helsinki.

Results

Overall, 83 cases with LOMS and 207 controls were included. The demographic variables are compared between the two groups in Table 1. The mean ± SD expanded disability status scale (EDSS) score was 3.68 ± 2.1 in cases. The results indicate that there was no significant difference between the two groups concerning marital status ($p=0.444$). Compared to the controls, the cases had less education ($p=0.030$) and a lower mean self-rated health score ($p=0.001$).

The frequency distribution of cigarette and waterpipe smoking is shown in Table 2. There was no significant difference in the frequency of waterpipe use between the two groups (6.0% vs. 4.3%). The frequency of ever cigarette smoking in the case group was significantly higher than in the control group (36.1% vs. 18.8%), and after adjusting for age, the odds of MS in smokers were 2.57 (95% CI: 1.44–4.60, $p=0.001$) times that of non-smokers. In addition, the odds of developing MS in current smokers were 4.33 (95% CI: 2.06–9.09, $p=0.001$) times that of non-smokers, while those who quit smoking had no higher odds of developing MS compared to non-smokers (OR = 1.40, 95% CI: 0.62–3.17, $p=0.417$). Subjects who had a history of smoking for more than 20 years had 3.45 times higher odds of developing MS than non-smokers (95% CI: 1.82–6.90, $p=0.001$). Passive smoking and its duration showed no significant difference between the two groups.

Table 3 depicts the association between substance and alcohol use and LOMS development. The prevalence of opium use in patients with LOMS was significantly higher than in the control group (14.5% vs. 2.9%), and after adjusting for age, the odds of developing MS in people with a history of opium use was 5.67 (95% CI: 2.05–15.7, $p=0.001$) times higher than those without a history. On the other hand, the prevalence of cannabis use in patients with LOMS were significantly lower (p-value = 0.025). There were no reports by any

Table 2 Association between smoking and waterpipe with LOMS

Variables		LOMS *N* (%)	Control *N* (%)	Unadjusted OR (95% CI)	*P*-value	Adjusted OR* (95% CI)	*P*-value
Waterpipe smoking	Never	78 (94.0%)	198 (95.7%)	1	-	1	-
	Ever	5 (6.0%)	9 (4.3%)	1.41 (0.45–4.34)	0.549	1.42 (0.46–4.39)	0.537
Cigarette smoking	Never	53 (63.9%)	168 (81.2%)	1		1	
	Ever	30 (36.1%)	39 (18.8%)	**2.43 (1.38–4.30)**	**0.002**	**2.57 (1.44–4.60)**	**0.001**
Cigarette smoking	Never	53 (63.9%)	168 (81.2%)	1	-	1	-
	Current	20 (24.1%)	15 (2.2%)	**4.22 (2.02–8.83)**	**0.001**	**4.33 (2.06–9.09)**	**0.001**
	Ex-smoker	10 (12.0%)	24 (11.6%)	1.32 (0.59–2.93)	0.495	1.40 (0.62–3.17)	0.417
Cigarette smoking duration (years)	Never	53 (63.9%)	168 (81.5%)	1	-	1	-
	⩽20	6 (7.2%)	15 (7.3%)	1.26 (0.46–3.43)	0.640	1.33 (0.49–3.64)	0.569
	> 20	24 (28.9%)	23 (11.2%)	**3.30 (1.72–6.33)**	**0.001**	**3.54 (1.82–6.90)**	**0.001**
Passive smoking	Never	46 (55.4%)	111 (53.6%)	1	-	1	-
	Ever	37 (44.6%)	96 (46.4%)	1.43 (0.86–2.39)	0.165	1.46 (0.86–2.46)	0.145
Passive smoking duration (years)	Never	38 (45.8%)	122 (58.9%)	1	-	1	-
	⩽20	21 (25.3%)	41 (19.8%)	1.64 (0.86–3.11)	0.128	1.65 (0.87–3.14)	0.122
	> 20	24 (28.9%)	44 (21.3%)	1.75 (0.94–3.24)	0.075	1.79 (0.96–3.33)	0.066

LOMS: late-onset multiple sclerosis, CI: confidence interval, OR: odds ratio, *Adjusted for age

Table 3 Association between substance use and alcohol consumption with LOMS

Variables		LOMS *N* (%)	Control *N* (%)	Unadjusted OR (95%CI)	*P*-value	Adjusted OR* (95%CI)	*P*-value
Drug use	No	70 (84.3%)	201 (97.1%)	1	-	1	**< 0.001**
	Yes	13 (15.7%)	6 (2.9%)	**6.22 (2.27–16.99)**	**< 0.001**	**6.28 (2.29–17.20)**	
Opium use	No	71 (85.5%)	201 (97.1%)	1	-	1	**0.001**
	Yes	l2 (14.5%)	6 (2.9%)	**5.66 (2.04–15.6)**	**0.001**	**5.67 (2.05–15.7)**	
Cannabis	No	207 (100)	81 (97.6)		**0.025**		**0.025**
	Yes	0 (0)	2 (2.4)				
Alcohol consumption	No	63 (75.9%)	183 (88.4%)	1	-	1	
	Yes	20 (24.1%)	24 (11.6%)	**2.42 (1.25–4.67)**	**0.009**	**2.45 (1.26–4.76)**	**0.008**
Wine consumption	No	196 (94.7%)	70 (84.3%)	1	-	1	-
	Yes	11 (5.3%)	13 (15.7%)	**3.30 (1.41–7.72)**	**0.006**	**3.30 (1.41–7.71)**	**0.006**
Whisky/Vodka consumption	No	193 (93.2%)	73 (87.9%)	1	-	1	-
	Yes	14 (6.8%)	10 (12.1%)	1.88 (0.80–4.44)	0.145	1.91 (0.81–4.50)	0.138
Beer consumption	No	67 (80.7%)	192 (92.7%)	1	-	1	-
	Yes	16 (19.3%)	15 (7.3%)	3.05 (1.43–6.51)	0.004	**3.12 (1.45–6.69)**	**0.003**

LOMS: late-onset multiple sclerosis, CI: confidence interval, OR: odds ratio, *Adjusted for age

Table 4 Clinical characteristics of LOMS cases and general population controls

MS type	Frequency *N* (%)
Progressive forms	53 (63.8%)
Relapsing forms	30 (36.14%)
	Mean (years)
Age at MS diagnosis	55.2 ± 4.39
Age at first symptoms	53.5 ± 4.09
EDSS	1.68 2.1

EDSS: Expanded Disability Status Scale, LOMS: late-onset multiple sclerosis

of our participants regarding the use of stimulants or hallucinogens.

The prevalence of alcohol consumption was significantly higher in the LOMS cases (24.1% vs. 11.6%). After adjusting for age, the results showed that the odds of developing MS in people with a history of alcohol consumption were significantly higher than that of those without a history of alcohol consumption (OR = 2.45, 95% CI: 1.26–4.76, $p = 0.008$). Specifically, wine (OR = 3.30, 95%CI: 1.41–7.71, $P = 0.006$) and beer consumption (OR = 3.12, 95%CI: 1.45–6.69, $P = 0.003$) were associated with an increased LOMS risk (Table 4 and 5).

Discussion

The present population-based case-control study reported the characteristics of 83 LOMS patients and 207 healthy controls in an Iranian population and assessed the possible role of exposure to cigarette and waterpipe smoking, drug abuse, and alcohol consumption in the risk of LOMS development. Since various risk factors can influence the age of onset and differ across various age groups, as well as different populations, we have

Table 5 Comorbidities of of LOMS cases and general population controls

Comorbidities	Case *N* (%)	Control *N* (%)
HTN	9 (10.8%)	20 (9.6%)
Diabetes mellitus	6 (7.2%)	24 (11.5%)
Coronary artery disease	1 (1.2%)	6 (2.8%)
Hypothyroidism	11 (13.3%)	36 (17.4%)
Hyperthyroidism	3 (3.6%)	6 (2.9%)
Rheumatoid Arthritis	6 (7.2%)	13 (6.3%)
Lupus	0 (0%)	0 (0%)
Psoriasis	2 (2.4%)	2 (1%)
Leukemia	1 (1.2%)	0 (0%)
Melanoma	0 (0%)	1 (0.5%)
Skin cancer	0 (0%)	1 (0.5%)
Bladder cancer	0 (0%)	1 (0.5%)
Breast cancer	0 (0%)	1 (0.5%)
Ovarian Cancer	0 (0%)	1 (0.5%)
Gastrointestinal Cancer	0 (0%)	2 (0.9%)
Other disease (Anemia, Urinary disease, Hyperlipidemia…)	24 (28.9%)	45 (21.7%)

undertaken to explore the potential influence of tobacco smoking, alcohol consumption, and substance abuse as risk factors for LOMS. For all we know, this is the first research to examine these factors in a relatively large-scale Iranian population, which makes it stand out from other national studies. Besides, the inclusion of a large control group adds to the robustness of the analysis, enhancing the reliability of the results.

The mean ± SD EDSS score was 3.68 ± 2.1 in cases, indicating a moderate level of disability. Interestingly, there was no significant difference between the two groups concerning marital status which aligns with the findings of Alsharie et al. [1] who examined PPMS cases and controls, where they also found no significant differences in marital status ($P=0.02$). Moreover, in our study, we observed that the LOMS cases had significantly lower levels of education and self-rated health compared to the control group. This finding echoes the results of studies on PPMS [1] and NMOSD [4], which reported a higher self-rated health score in controls compared to NMOSD cases. These results collectively suggest that educational attainment and self-perceived health may have an impact on various neurologic diseases, including LOMS, PPMS, and NMOSD. The differences in education levels and self-rated health between cases and controls highlight the potential influence of social and quality-of-life factors in the development and progression of neurologic conditions.

The current study also confirms the correlation between smoking cigarettes and increased odds for LOMS. The age-adjusted OR of developing LOMS was 2.57 in ever smokers and 4.33 in current smokers. However, the results could not show an association between ex-smokers and the risk of LOMS. Smoking for more than 20 years had 3.45 times the odds of developing LOMS. Although passive smoking was more prevalent in LOMS with OR of 1.79, the statistical analysis was unable to demonstrate a significant difference between the two groups. These findings broadly support the study on individuals with MS aged 40 to 69 years who reported increased OR of current smoking but not passive smoking [21]. Conversely, in a prospective cohort, current or former smoking was not significantly linked with the risk of LOMS [22].

Evidence on the risk factors of LOMS is limited. However, several studies have established that smoking is a risk factor for developing, and adverse prognosis of MS [23–31]. Duration and intensity of smoking contribute dose-dependent to the hazards of MS and the harmful effects slowly subside after smoking cessation [32]. The attributed effects of smoking might be due to interaction with some genetic variants and subsequent activation of T cells [33]. Smoking enhances inflammatory responses, reduces some immune defenses, and increase vulnerability to infection [11]. Furthermore, smoking acts synergistically with Epstein-Barr virus antibody levels to increases MS risk [34]. In addition, components in cigarette smoke might cause direct toxic effects on neurons [35].

Despite the strong evidence, some studies using Mendelian randomization manifested no clear confirmation of smoking as environmental risk factor for MS susceptibility [36, 37]. In contrast to our findings, some studies have reported that passive smoking and prior smoking increased the risk of MS [13, 20, 38–41]. The frequency of ever waterpipe smoking in the LOMS group was slightly more than the control group; however, the difference was not significant. This limitation is attributed to the small sample size of patients who smoked water pipes and participated in the study. The limited number of participants who engaged in this smoking method precludes definitive conclusions regarding its potential association with the outcome of interest. Contrary to the current results, some studies have reported that waterpipe smoking increases the risk of MS [42–44].

We also observed a significant correlation between opium use and the onset of LOMS. The odds of developing MS in people with a history of opium use was 5.67 times higher than those without a history after adjusting for age.

No study had ever assessed the effect of drugs on the LOMS. However, evaluating the impact of recreational drugs on MS revealed a significant link between drug abuse and MS onset which is in line with our findings for LOMS [45, 46]. Conversely, no connection was observed between the abuse of opium and the onset of MS in a

study, and current or past use of marijuana and MS in another study [47, 48].

It seems that alterations in the endogenous opioid system contribute to the onset and severity of symptoms in MS patients [49]. Studies detected all three Delta opioid receptors (DOR), Mu-opioid receptors (MOR), and Kappa-opioid receptors (KOR) in T cells, B cells, and macrophages [50, 51]. Disruptions in the balance of the T helper cells, especially decreasing the Th1/Th2 ratio are established to play a major role in the immunopathogenesis of MS [52, 53]. Morphine can cause an alteration in Th1/Th2 ratio, cytokine expression, T cell apoptosis, and differentiation [54]. Opium addict patients have higher EDSS scores, increased fatigue severity scale, and memory impairments [55].

In our study, the prevalence of alcohol consumption was significantly higher in LOMS patients compared to healthy subjects. In addition, drinking alcohol, especially wine and beer, during adolescence and young adulthood increased the risk of LOMS. In a large cohort study conducted in England between 1999 and 2011, the risk of developing MS in any type of alcohol use, such as alcohol consumption, alcohol abuse, and dependence, was significantly increased. This investigation supported a noteworthy positive relationship between alcohol use disorders and the risk of MS [56]. However, some population-based studies, have indicated that there is a dose-dependent inverse relationship between MS and alcohol consumption [57].

In previous studies, it has been mentioned that long-term high alcohol consumption has harmful effects on the humoral and cellular immune systems [58]. Furthermore, it seems that alcohol consumption can reduce the frequency of lymphocytes, and this reduction is more pronounced in people with alcohol use disorder (AUD) [59]. Also, alcohol abuse can cause a shift in T cell phenotype by changing the surface antigens and receptors [59]. In addition, due to the augmentation in hematopoietic proliferation, the number of memory T cells may increase and the accumulation of memory T cells in different tissues increases the incidence of chronic inflammatory diseases [60]. Taken together, studies have shown that chronic T-cell lymphopenia following heavy and long-term alcohol consumption leads to increased hemostatic proliferation and activation of T cells, thereby increasing the ratio of memory T cells to naïve T cells, in contrast, moderate alcohol consumption increases the number of lymphocytes [59]. Some studies have suggested that smoking and alcohol consumption can cause increasing immunoglobulin (Ig) levels, and affect the function of microglia and astrocytes, which leads to strengthening the immunogenicity of self-proteins and finally the beginning of autoimmune responses and autoimmune diseases such as MS [61, 62].

Because alcoholic beverages are high in energy and are considered a source of energy for consumers, most AUD suffer from malnutrition such as vitamins deficiency [63]. Likewise, vitamin D deficiency is one of the known risk factors for developing MS [64]. Hence, in AUD the immune system suffers from various methods, such as malnutrition with vitamin deficiency, immune cells (B and T lymphocyte) dysfunction, and barrier defects that can increase the occurrence of chronic diseases such as MS and Alzheimer's [59].

However, there is considerable evidence that low to moderate consumption of alcoholic beverages such as beer and wine, which contain polyphenols, have beneficial effects on health and the immune system [65]. It was reported that neither all alcohol consumption nor wine or beer drinking, was linked to the risk of developing MS [66]. This contrast seems to be due to the difference in alcohol consumption definition in these studies (at least once per month for more than 6 months in our research versus several categories of alcohol consumption in the mentioned study).

As far as we know, the current study was the first to investigate the risk factors of LOMS in a relatively large population in the region with well-matched controls; however, it should be noted that due to the retrospective nature of case-control studies and the possibility of recall bias, no causation can be made and further studies are needed to address these limitations, to confirm the findings and to provide additional information on the topic.

Conclusion

It is critical to identify the risk factors contributing to the development of LOMS. In our study, cigarette smoking, alcohol consumption, and substance abuse have been recognized as possible risk factors for LOMS. However, waterpipe smoking did not demonstrate any association with LOMS. Individuals who have smoked cigarettes for more than 20 years face an elevated risk of developing LOMS. Furthermore, the consumption of alcohol, particularly wine and beer, during adolescence and young adulthood has been linked to higher odds of experiencing LOMS. According to the global increase in cigarette smoking and alcohol use, these results highlight the need for interventional preventive programs.

Acknowledgements
Not applicable.

Author contributions
Naghmeh Abbasi Kasbi: Data curation, Investigation, Writing – original draft, Writing – review & editing, Validation. Sajjad Ghane Ezabadi: Data curation, Investigation, Writing – original draft, Writing – review & editing. Kosar Kohandel: Data curation, Investigation, Writing – original draft, Writing – review & editing. Faezeh Khodaie: Data curation, Investigation, Writing – original draft, Writing – review & editing. Amir Hossein Sahraian: Data curation, Investigation, Writing – original draft. Sahar Nikkhah Bahrami: Writing- revision, review & editing. Mahsa Mohammadi: Data curation, Investigation, Writing

– original draft. Amir Almasi-Hashiani: Methodology, Formal analysis, Writing – review & editing. Sharareh Eskandarieh: Project administration, Resources, Supervision, Validation, Writing – review & editing. Mohammad Ali Sahraian: Conceptualization, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Funding
This study did not receive any specific grant from any funding agency.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Each participant was thoroughly informed about his/her role in the study as well as the purpose of the research, and their probable questions about the study were answered. All participants were required to give verbal consent to be informed that their personal information is kept secure. Those who were unwilling to take part in our study were excluded. The ethics committee at Tehran University of Medical Sciences approved the current study by the code: IR.TUMS.NI.REC.1402.028. Furthermore, all the steps taken in this study adhere to the principles outlined in the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Hasan Abad Sq., Tehran, Iran
[2]Department of Epidemiology, School of Health, Arak University of Medical Sciences, Arak, Iran
[3]Student Research Committee, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran

Received: 21 January 2024 / Accepted: 20 August 2024
Published online: 06 September 2024

References

1. Piggott T, Nonino F, Baldin E, Filippini G, Rijke N, Schünemann H, Laurson-Doube J. Multiple Sclerosis International Federation guideline methodology for off-label treatments for multiple sclerosis. Multiple Scler J - Experimental Translational Clin. 2021;7(4):20552173211051855.
2. Chwastiak LA, Ehde DM. Psychiatric issues in multiple sclerosis. Psychiatr Clin North Am. 2007;30(4):803–17.
3. Maroufi H, Mortazavi SH, Sahraian MA, Eskandarieh S. Environmental risk factors of multiple sclerosis in the Middle East and North Africa region: a systematic review. Curr J Neurol. 2021;20(3):166–84.
4. Hellwig K, Verdun di Cantogno E, Sabidó M. A systematic review of relapse rates during pregnancy and postpartum in patients with relapsing multiple sclerosis. Ther Adv Neurol Disord. 2021;14:17562864211051012.
5. Ghadiri F, Sahraian MA, Razazian N, Ashtari F, Poursadeghfard M, Nabavi SM, et al. Late-onset multiple sclerosis in Iran: a report on demographic and disease characteristics. Mult Scler Relat Disord. 2023;70:104493.
6. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med. 2000;343(20):1430–8.
7. Polliack ML, Barak Y, Achiron A. Late-onset multiple sclerosis. J Am Geriatr Soc. 2001;49(2):168–71.
8. Correia I, Marques I, Sousa L. História Natural Da Esclerose Múltipla–Revisão Natural History of multiple sclerosis–review. Sinapse®. 2014:38.
9. Lotti CBC, Oliveira ASB, Bichuetti DB, Castro Id, Oliveira EML. Late onset multiple sclerosis: concerns in aging patients. Arq Neuropsiquiatr. 2017;75:451–6.
10. Martinelli V, Rodegher M, Moiola L, Comi G. Late onset multiple sclerosis: clinical characteristics, prognostic factors and differential diagnosis. Neurol Sci. 2004;25:s350–5.
11. Alrouji M, Manouchehrinia A, Gran B, Constantinescu CS. Effects of cigarette smoke on immunity, neuroinflammation and multiple sclerosis. J Neuroimmunol. 2019;329:24–34.
12. Morabia A, Bernstein M, Antonini S. Smoking, dietary calcium and vitamin D deficiency in women: a population-based study. Eur J Clin Nutr. 2000;54(9):684–9.
13. Mortazavi SH, Naser Moghadasi A, Almasi-Hashiani A, Sahraian MA, Goudarzi H, Eskandarieh S. Waterpipe and cigarette smoking and drug and alcohol consumption, and the risk of primary progressive multiple sclerosis: a population-based case-control study. Curr J Neurol. 2023;22(2):72–81.
14. Manouchehrinia A, Tench CR, Maxted J, Bibani RH, Britton J, Constantinescu CS. Tobacco smoking and disability progression in multiple sclerosis: United Kingdom cohort study. Brain. 2013;136(Pt 7):2298–304.
15. Abdollahpour I, Nedjat S, Mansournia MA, Sahraian MA, van der Mei I. Lifestyle factors and multiple sclerosis: a population-based incident case-control study. Multiple Scler Relat Disorders. 2018;22:128–33.
16. Song J, Westerlind H, McKay KA, Almqvist C, Stridh P, Kockum I, et al. Familial risk of early-and late-onset multiple sclerosis: a Swedish nationwide study. J Neurol. 2019;266:481–6.
17. Ayoubi S, Asadigandomani H, Bafrani MA, Shirkoohi A, Nasiri M, Sahraian MA, Eskandarieh S. The National multiple sclerosis Registry System of Iran (NMSRI): aspects and methodological dimensions. Mult Scler Relat Disord. 2023;72:104610.
18. Ezabadi SG, Sahraian MA, Maroufi H, Shahrbaf MA, Eskandarieh S. Global assessment of characteristics of multiple sclerosis registries; a systematic review. Mult Scler Relat Disord. 2022;63:103928.
19. Pugliatti M, Casetta I, Drulovic J, Granieri E, Holmøy T, Kampman MT et al. A questionnaire for multinational case-control studies of environmental risk factors in multiple sclerosis (EnvIMS-Q). Acta Neurol Scand Suppl. 2012(195):43–50.
20. Abdollahpour I, Nedjat S, Mansournia MA, Sahraian MA, van der Mei I. Lifestyle factors and multiple sclerosis: a population-based incident case-control study. Mult Scler Relat Disord. 2018;22:128–33.
21. Kleerekooper I, Chua S, Foster PJ, Trip SA, Plant GT, Petzold A, Patel P. Associations of Alcohol Consumption and Smoking with Disease Risk and Neurodegeneration in individuals with multiple sclerosis in the United Kingdom. JAMA Netw open. 2022;5(3):e220902.
22. Pommerich UM, Nielsen R, Overvad K, Dahm CC, Tjønneland A, Olsen A, Dalgas U. Diet quality is not associated with late-onset multiple sclerosis risk-A Danish cohort study. Mult Scler Relat Disord. 2020;40:101968.
23. Manouchehrinia A, Huang J, Hillert J, Alfredsson L, Olsson T, Kockum I, Constantinescu CS. Smoking attributable risk in multiple sclerosis. Front Immunol. 2022;13:840158.
24. Poorolajal J, Bahrami M, Karami M, Hooshmand E. Effect of smoking on multiple sclerosis: a meta-analysis. J Public Health (Oxf). 2017;39(2):312–20.
25. Degelman ML, Herman KM. Smoking and multiple sclerosis: a systematic review and meta-analysis using the Bradford Hill criteria for causation. Mult Scler Relat Disord. 2017;17:207–16.
26. O'Gorman C, Broadley SA. Smoking and multiple sclerosis: evidence for latitudinal and temporal variation. J Neurol. 2014;261(9):1677–83.
27. Nishanth K, Tariq E, Nzvere FP, Miqdad M, Cancarevic I. Role of smoking in the pathogenesis of multiple sclerosis: a review article. Cureus. 2020;12(8):e9564.
28. Arneth B. Multiple sclerosis and smoking. Am J Med. 2020;133(7):783–8.
29. Handel AE, Williamson AJ, Disanto G, Dobson R, Giovannoni G, Ramagopalan SV. Smoking and multiple sclerosis: an updated meta-analysis. PLoS ONE. 2011;6(1):e16149.
30. Asadollahi S, Fakhri M, Heidari K, Zandieh A, Vafaee R, Mansouri B. Cigarette smoking and associated risk of multiple sclerosis in the Iranian population. J Clin Neurosci. 2013;20(12):1747–50.
31. O'Gorman C, Bukhari W, Todd A, Freeman S, Broadley SA. Smoking increases the risk of multiple sclerosis in Queensland, Australia. J Clin Neurosci. 2014;21(10):1730–3.
32. Hedström AK, Hillert J, Olsson T, Alfredsson L. Smoking and multiple sclerosis susceptibility. Eur J Epidemiol. 2013;28(11):867–74.
33. Jacobs BM, Noyce AJ, Bestwick J, Belete D, Giovannoni G, Dobson R. Gene-environment interactions in multiple sclerosis: a UK Biobank Study. Neurol Neuroimmunol Neuroinflamm. 2021;8(4).
34. Hedström AK, Huang J, Brenner N, Butt J, Hillert J, Waterboer T, et al. Smoking and Epstein-Barr virus infection in multiple sclerosis development. Sci Rep. 2020;10(1):10960.
35. Rosso M, Chitnis T. Association between cigarette smoking and multiple sclerosis: a review. JAMA Neurol. 2020;77(2):245–53.

36. Mitchell RE, Bates K, Wootton RE, Harroud A, Richards JB, Davey Smith G, Munafò MR. Little evidence for an effect of smoking on multiple sclerosis risk: a mendelian randomization study. PLoS Biol. 2020;18(11):e3000973.
37. Vandebergh M, Goris A. Smoking and multiple sclerosis risk: a mendelian randomization study. J Neurol. 2020;267(10):3083–91.
38. Oturai DB, Bach Søndergaard H, Koch-Henriksen N, Andersen C, Laursen JH, Gustavsen S, et al. Exposure to passive smoking during adolescence is associated with an increased risk of developing multiple sclerosis. Mult Scler. 2021;27(2):188–97.
39. Sakoda A, Matsushita T, Nakamura Y, Watanabe M, Shinoda K, Masaki K, et al. Environmental risk factors for multiple sclerosis in Japanese people. Mult Scler Relat Disord. 2020;38:101872.
40. Hedström AK, Bäärnhielm M, Olsson T, Alfredsson L. Exposure to environmental tobacco smoke is associated with increased risk for multiple sclerosis. Mult Scler. 2011;17(7):788–93.
41. Zhang P, Wang R, Li Z, Wang Y, Gao C, Lv X, et al. The risk of smoking on multiple sclerosis: a meta-analysis based on 20,626 cases from case-control and cohort studies. PeerJ. 2016;4:e1797.
42. Alkhawajah NM, Aljarallah S, Hussain-Alkhateeb L, Almohaini MO, Muayqil TA. Waterpipe Tobacco Smoking and other multiple sclerosis environmental risk factors. Neuroepidemiology. 2022;56(2):97–103.
43. Abdollahpour I, Nedjat S, Almasi-Hashiani A, Nazemipour M, Mansournia MA, Luque-Fernandez MA. Estimating the marginal Causal Effect and potential impact of Waterpipe smoking on risk of multiple sclerosis using the targeted maximum likelihood estimation method: a large, Population-Based Incident Case-Control Study. Am J Epidemiol. 2021;190(7):1332–40.
44. Abdollahpour I, Nedjat S, Sahraian MA, Mansournia MA, Otahal P, van der Mei I. Waterpipe smoking associated with multiple sclerosis: a population-based incident case-control study. Mult Scler. 2017;23(10):1328–35.
45. Brosseau L, Philippe P, Méthot G, Duquette P, Haraoui B. Drug abuse as a risk factor of multiple sclerosis: case-control analysis and a study of heterogeneity. Neuroepidemiology. 1993;12(1):6–14.
46. Hawkes CH, Boniface D. Risk associated behavior in premorbid multiple sclerosis: a case-control study. Multiple Scler Relat Disorders. 2014;3(1):40–7.
47. Dehghan M, Ghaedi-Heidari F. Environmental risk factors for multiple sclerosis: a case-control study in Kerman. Iran Iran J Nurs Midwifery Res. 2018;23(6):431.
48. Ponsonby A-L, Lucas RM, Dear K, van der Mei I, Taylor B, Chapman C, et al. The physical anthropometry, lifestyle habits and blood pressure of people presenting with a first clinical demyelinating event compared to controls: the Ausimmune study. Multiple Scler J. 2013;19(13):1717–25.
49. Ludwig MD, Zagon IS, McLaughlin PJ. Featured article: serum [Met5]-enkephalin levels are reduced in multiple sclerosis and restored by low-dose naltrexone. Experimental Biology Med. 2017;242(15):1524–33.
50. Ninković J, Roy S. Role of the mu-opioid receptor in opioid modulation of immune function. Amino Acids. 2013;45:9–24.
51. Bidlack JM. Detection and function of opioid receptors on cells from the immune system. Clin Diagn Lab Immunol. 2000;7(5):719–23.
52. Van Langelaar J, van der Vuurst RM, Janssen M, Wierenga-Wolf AF, Spilt IM, Siepman TA, et al. T helper 17.1 cells associate with multiple sclerosis disease activity: perspectives for early intervention. Brain. 2018;141(5):1334–49.
53. Kunkl M, Frascolla S, Amormino C, Volpe E, Tuosto L. T helper cells: the modulators of inflammation in multiple sclerosis. Cells. 2020;9(2):482.
54. Gao M, Sun J, Jin W, Qian Y. Morphine, but not ketamine, decreases the ratio of Th1/Th2 in CD4-positive cells through T-bet and GATA3. Inflammation. 2012;35:1069–77.
55. Ayoobi F, Bidaki R, Shamsizadeh A, Moghadam-Ahmadi A, Amiri H. Impact of opium dependency on clinical and neuropsychological indices of multiple sclerosis patients. Neurol Sci. 2019;40:2501–7.
56. Pakpoor J, Goldacre R, Disanto G, Giovannoni G, Goldacre MJ. Alcohol misuse disorders and multiple sclerosis risk. JAMA Neurol. 2014;71(9):1188–9.
57. Andersen C, Søndergaard HB, Bang Oturai D, Laursen JH, Gustavsen S, Larsen NK, et al. Alcohol consumption in adolescence is associated with a lower risk of multiple sclerosis in a Danish cohort. Multiple Scler J. 2019;25(12):1572–9.
58. Budeč M, Ćirić O, Koko V, Ašanin R. The possible mechanism of action of ethanol on rat thymus. Drug Alcohol Depend. 1992;30(2):181–5.
59. Barr T, Helms C, Grant K, Messaoudi I. Opposing effects of alcohol on the immune system. Prog Neuropsychopharmacol Biol Psychiatry. 2016;65:242–51.
60. Chou P, Effros JB. T cell replicative senescence in human aging. Curr Pharm Design. 2013;19(9):1680–98.
61. Thameem Dheen S, Kaur C, Ling E-A. Microglial activation and its implications in the brain diseases. Curr Med Chem. 2007;14(11):1189–97.
62. Eskandarieh S, Moghadasi AN, Sahraiain MA, Azimi AR, Molazadeh N. Association of cigarette smoking with neuromyelitis optica-immunoglobulin G sero-positivity in neuromyelitis optica spectrum disorder. Iran J Neurol. 2019;18(3):93–8.
63. Manari A, Preedy V, Peters T. Nutritional intake of hazardous drinkers and dependent alcoholics in the UK. Addict Biol. 2003;8(2):201–10.
64. Kočovská E, Gaughran F, Krivoy A, Meier U-C. Vitamin-D deficiency as a potential environmental risk factor in multiple sclerosis, schizophrenia, and autism. Front Psychiatry. 2017;8:47.
65. Diaz L, Montero A, Gonzalez-Gross M, Vallejo A, Romeo J, Marcos A. Influence of alcohol consumption on immunological status: a review. Eur J Clin Nutr. 2002;56(3):S50–3.
66. Massa J, O'reilly E, Munger K, Ascherio A. Caffeine and alcohol intakes have no association with risk of multiple sclerosis. Multiple Scler J. 2013;19(1):53–8.

Publisher's note