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Waterpipe and cigarette smoking and drug and alcohol consumption, and the risk of primary progressive multiple sclerosis: A population-based case-control study

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Keywords
Primary Progressive Multiple Sclerosis; Cigarette; Waterpipe; Alcohol Abuse; Substance-Related Disorders; Risk Factors

Abstract

Background: Multiple sclerosis (MS) is a chronic central nervous system disease, and primary progressive multiple sclerosis (PPMS) is one the main types of MS, has unknown environmental risk factors. The present study was conducted with the aim to identify the association of waterpipe and cigarette smoking, substance abuse, and alcohol consumption with the risk of PPMS development.

Methods: A population-based, case-control study was conducted in Tehran, Iran, on 146 PPMS cases and 294 controls. PPMS cases were diagnosed and confirmed by neurologists. Standard random digit dialing was used to select sex-matched healthy control participants from the same source population as the cases. Logistic regression analysis was used to estimate unadjusted and adjusted odds ratios (OR).

Results: In total, 440 subjects participated in the study.

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PPMS was associated with ever smoking cigarettes [OR = 2.48; confidence interval (CI) = 1.44-4.27], and passive smoking (OR = 2.20; CI = 1.34-3.62). However, having ever smoked waterpipe was not significantly associated with PPMS risk (OR = 1.19; CI = 0.62-2.26). Those who had all 3 types of smoking had an additive OR that was 10.45 times higher than that in individuals without any type of smoking (OR: 10.45; 95% CI = 3.5-31.2). We did not find any significant association between PPMS risk and substance abuse and alcohol consumption.

Conclusion: Cigarette smoking and being exposed to passive smoking are important risk factors for developing PPMS; in addition, the use of 3 types of smoking, showed an OR higher than that in those without any smoking. Considering the global increase in tobacco smoking, this finding emphasizes the importance of interventional programs for the prevention of tobacco smoking.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and immune-mediated disorder of the central nervous system (CNS) described by the demyelination of neurons with uncertain etiology.[1] It is considered one of the most common causes of disability in patients with chronic diseases.

MS is a worldwide disease, with higher prevalence in Europe (142.81 per 100000) and lower prevalence in the Western Pacific region (4.79 per 100000).[2] The prevalence of MS in Iran is estimated to be about 51.52 per 100000 people,[3] and Tehran is among the cities with a high prevalence of MS in Asia.[4] Primary progressive multiple sclerosis (PPMS) is one of the main clinical types of MS, which is seen in 10-15% of patients with poor prognosis.[5] It is characterized by persistent clinical progression with no history of relapse or remission. It is reported that the mean age of PPMS occurrence is about 40-50 years.[5]

It is believed that both genetic and environmental factors are involved in the pathogenesis of MS.[6] MS, like any other autoimmune disease, may be relevant to smoking, and substance and alcohol abuse.[7] There are many studies regarding the relation between tobacco smoking and development of MS. In the study by Abdollahpour et al., current smoking was an environmental factor associated with increased risk of MS incidence among relapsing remitting MS (RRMS) cases.[8] Moreover, previous researches showed passive smoking is a significant factor in the development of MS, especially for people who carry the specific HLA genotypes such as HLA-DRB 1*15.[9,10]

Although PPMS has some differences with other types of MS in term of pathogenesis or its age of onset,[11] the evidence showed that, like MS, exposure to environmental factors like smoking, substance abuse and drinking alcohol are effective in the incidence of RRMS, and they may be the potential risk factors that increase the incidence or progression of PPMS.[12,13] Moreover, due to the characteristics of PPMS and its more severe morbidity than other types, it is necessary to study this type of MS and determine the risk factors associated with it.

In addition, cigarette smoking, waterpipe smoking, alcohol drinking, and substance abuse are emerging global risk behavior, and there are serious concerns about their increasing use in the world.[14-16] Although the etiology of RRMS has been evaluated in many studies, there is crucial need for evidence for assessing the risk factors increasing prevalence of PPMS.

To the best of the authors' knowledge, there is no case-control study on identification of PPMS environmental risk factors focusing on smoking, substance abuse, and alcohol consumption. Therefore, the present study was conducted to discover the possible association of cigarette smoking, waterpipe smoking, substance abuse, and alcohol consumption with PPMS risk.

Materials and Methods

Study design: A population-based, case-control study was conducted from 2019 to 2020 at Sina Hospital, a tertiary care referral center in Tehran, Iran.

Participants: From the source population, patients with definite clinical diagnosis of PPMS based on the latest criteria were selected. All participants were residents of Tehran, who had referred to the specialist MS Clinic of Sina Hospital in Tehran.[11] The PPMS diagnoses were confirmed by neurologists. The control group participants included healthy individuals of 18-60 years of age who were selected from among all residents of the 22 municipal districts of Tehran. The controls were healthy individuals without any history of neurological diseases. They were selected randomly from the same source population as the cases (residents of one of the 22 municipalities of Tehran) through the standard method of random digit dialing (RDD).[17,18] The Kish method was used to select a subject from among all eligible

people in one household.[19]

Similar to the PPMS cases included in the current study, all participants in the control group were residents of Tehran. Cases and controls were matched in terms of gender and adjustment for the year of recruiting participants was considered.

The study exclusion criteria included being pregnant, younger than 18 years of age, and older than 60 years of age, and having a memory dysfunction or cognition disorder.

Data collection protocol: The interviews of both case and control participants were done via telephone by 6 qualified and experienced interviewers. At the start of each interview, the main purpose of the study was explained to the participant. The study protocol was approved by the institutional review boards (IRB) at the ethics committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1399.728).

Measurements

A structured questionnaire was designed in the MS research center of Tehran University of Medical Sciences. The questionnaire was prepared to measure various variables including demographic variables (age, sex, marital status, education level, parental ethnicity, and self-rated health status), and lifestyle variables (cigarettes smoking, water pipe, alcohol, and substance abuse). The risk factors were measured using the questionnaire designed for multinational case-control studies of Environmental Risk Factors in MS (EnvIMS-Q).[20]

The content validity and reliability of the Persian version of this questionnaire were approved.[21] To reduce potential selection or response bias, subjects were informed that all collected information would be processed anonymously and that no potential legal consequences could arise concerning their responses.

Socioeconomic status (SES): The participants were asked about their SES in their adolescence.[22] This variable was measured on a visual ladder with 10 steps, asking them "Where would you place your SES during your adolescence considering the ladder from 1 to 10?" accompanied by the following explanation according to the MacArthur Scale of Subjective Social Status:[23]

"The visual ladder represents the SES of every person in our society regarding money, education, and job. The highest level of the ladder (step 10) is for ones with the most money, highest educational levels, and best jobs. At the bottom of the ladder, the lowest level (step 1) shows the least money, lowest educational levels, and worst jobs or unemployment."

Lifestyle characteristics: The participants were asked whether they ever smoked waterpipe at least once a week for a minimum of 6 months.[24] More information was obtained on the duration and amount (average frequency per week) of use, and age at the first use. The total amount of waterpipe used was calculated by multiplying the average frequency per week and the duration (years). Information was also obtained on cigarette use,[25] and participants were asked whether they ever smoked cigarettes at least once a week for a minimum of 6 months. Related information including total cigarettes smoked, average amount smoked per day, and converted to pack-years, passive smoking [ever lived with anyone who regularly smoked, duration (years), and timing (before/after or during 13–19 years)], and maternal smoking history in pregnancy were collected. We also obtained information about alcohol and drug abuse. Information was obtained about drinking of any type of alcohol (whisky/vodka, beer, and wine), and abuse of any types of drug and substances (opioid, cannabis, stimulants, and hallucinogen) at least once a month for a minimum of 6 months.[26]

Categorical and continuous variables are presented as number (percentage) and mean [standard deviation (SD)], respectively. The likelihood-ratio chi-square test and two independent t-test were used to compare the demographical characteristics between the two groups of PPMS cases and controls. To assess the association between the examined risk factors and risk of PPMS, crude and adjusted OR were calculated using logistic regression models.

An asset-based approach was used to calculate the SES. For this purpose, principle component analysis (PCA) was used, and the studied assets included personal car, refrigerator-freezer, washing machine, TV, LED/LCD, vacuum cleaner, personal computer, dishwasher, microwave, and smartphone.

The main assessed exposures in this study were tobacco smoking, waterpipe smoking, and passive smoking, and both independent and joint effects of these variables on PPMS were investigated. The effect size, adjusted OR, and their 95% CI were calculated. To detect the potential confounding factors, prior knowledge was used, and based on the limited sample size, we adjusted the models for age (in continuous form), SES (low, moderate, and

high), and sex. Due to the low prevalence of smoking in women, we were unable to control the effect of gender in the analysis. All analyses were performed at a significance level of 0.05 using Stata software (version 13; Stata Corp., College Station, TX, USA).

Results

Table 1 compares the distribution of demographic variables between cases and controls. We did not observe significant differences between the two groups in terms of sex (P = 0.847), education level (P = 0.227), and SES (P = 0.157). The distribution of marital status was significantly different between the two groups (P = 0.008), and in the case group, the mean age was significantly higher (P = 0.001), and the mean of self-rated health was lower (P = 0.001).

Table 2 shows the adjusted OR (with 95% CI) for the association of tobacco smoking, waterpipe smoking, and passive smoking with PPMS. After controlling for appropriate confounders, waterpipe smoking and maternal smoking during pregnancy did not show a significant relationship with PPMS.

The results of the study showed that ever smokers were at significantly higher risk of developing PPMS than never smokers (OR: 2.48; 95% CI: 1.44-4.27; P = 0.001). Moreover, PPMS was associated with current smoking (OR: 1.98; 95% CI: 0.98-3.97; P = 0.055) and past smoking (OR: 3.23; 95% CI: 1.54-6.79; P = 0.002). Furthermore, the analysis revealed that there is a significant dose-response association between the duration and cumulative amount of tobacco smoking and PPMS.

The obtained results suggested that living with someone who smokes increases the odds of PPMS. The odds of PPMS among passive smokers was 2.2 times higher than that among those who had never been a passive smoker (95% CI: 1.34-3.62; P = 0.002). Like tobacco smoking, there is a significant dose-response association between the duration of passive smoking and PPMS, and people who have been passive smokers throughout their life are 2.87 times more likely to get the disease than those who have never been exposed to cigarette smoke.

The association of the consumption of different types of drugs, substances, and alcohol with PPMS was assessed and the results are presented in table 3. The prevalence of substance abuse and alcohol consumption was low in the case group, and the highest prevalence was related to the consumption of beer and wine with 9.6%. The adjusted OR suggested that there is no significant association between substance abuse and alcohol consumption and PPMS.

Since tobacco smoking, waterpipe smoking, and being a passive smoker are interrelated, the joint effects of these three variables were examined and the results are presented in table 4.

Table 1. Demographic characteristics of primary progressive multiple sclerosis (PPMS) cases and general population controls

Variables	PPMS group (n = 146)	Control group (n = 294)	P
Age (year) (mean ± SD)	47.00 ± 9.40	37.70 ± 6.10	0.001
Self-rated health status* (mean ± SD)	2.84 ± 1.04	3.67 ± 0.84	0.001
Sex [n (%)]			0.847
Male	61 (41.8)	120 (40.8)	
Female	85 (58.2)	174 (59.2)	
Marital status [n (%)]			0.008
Single	26 (17.8%)	78 (26.6)	
Married	104 (71.2%)	200 (68.3)	
Widow	5 (3.4)	10 (3.4)	
Divorce	11 (7.5)	5 (1.7)	
Education [n (%)]			0.227
Illiterate or primary school	13 (8.0)	11 (3.7)	
Guidance school	12 (8.2)	31 (10.5)	
High school	55 (37.7)	109 (37.1)	
Associate's or Bachelor's degree	55 (37.7)	114 (38.8)	
Master's degree and higher	11 (7.5)	29 (9.9)	
SES [n (%)]			0.157
Low	59 (40.4)	133 (45.3)	
Moderate	30 (20.6)	73 (24.8)	
High	57 (39.0)	88 (29.9)	

SD: Standard deviation; SES: Socioeconomic status; PPMS: Primary progressive multiple sclerosis
*The self-rated health status ranged between 1 and 5.

Table 2. Association between different types of smoking and primary progressive multiple sclerosis (PPMS)

Variables		Control group [n (%)]	PPMS group [n (%)]	Adjusted OR* (95% CI), P	Adjusted OR** (95% CI), P
Waterpipe smoking	Never	233 (79.3)	126 (86.3)	1	1
	Ever	61 (20.75)	20 (13.7)	1.29 (0.68-2.43), 0.427	1.19 (0.62-2.26), 0.588
	Current	21 (7.2)	3 (2.0)	0.48 (0.12-1.90), 0.300	0.49 (0.12-1.87), 0.298
	Past	38 (13.0)	17 (11.6)	2.01 (0.98-4.10), 0.055	1.83 (0.89-3.77), 0.096
Waterpipe smoking, duration (year)	Never	233 (79.8)	126 (86.3)	1	1
	≤ 10	40 (13.7)	14 (9.6)	1.76 (0.83-3.73), 0.138	1.55 (0.72-3.32), 0.255
	> 10	19 (6.5)	6 (4.1)	0.92 (0.32-2.66), 0.879	0.95 (0.33-2.74), 0.926
Waterpipe smoking, cumulative amount (pipes), min per week	Never	233 (82.3)	126 (90.0)	1	1
	≤ 60	35 (12.4)	8 (5.7)	0.81 (0.34-1.95), 0.647	0.75 (0.31-1.82), 0.529
	> 60	15 (5.3)	6 (4.3)	1.78 (0.58-5.40), 0.305	1.46 (0.48-4.40), 0.502
Cigarette smoking	Never	241 (82.0)	97 (66.4)	1	1
	Ever	53 (18.0)	49 (33.6)	2.54 (1.48-4.37), 0.001	2.48 (1.44-4.27), 0.001
	Current	35 (11.9)	24 (16.4)	2.03 (1.02-4.06), 0.044	1.98 (0.98-3.97), 0.055
	Past	18 (6.1)	25 (17.1)	3.33 (1.58-7.03), 0.002	3.23 (1.54-6.79), 0.002
Cigarette smoking, duration (year)	Never	241 (82.0)	97 (67.4)	1	1
	≤ 15	35 (11.9)	20 (13.9)	2.43 (1.21-4.87), 0.012	2.43 (1.21-4.86), 0,012
	> 15	18 (6.1)	27 (18.7)	2.48 (1.16-5.28), 0.018	2.36 (1.11-5.03), 0.026
Cigarette smoking, cumulative amount (total pack-years)	Never	241 (82.0)	97 (69.3)	1	1
	≤ 120	38 (13.0)	21 (15.0)	1.36 (0.67-2.75), 0.392	1.35 (0.66-2.72), 0.403
	> 120	14 (4.8)	22 (15.7)	4.86 (2.12-11.2), 0.001	4.81 (2.09-11.07), 0.001
Passive smoking	Never	143 (48.6)	43 (29.4)	1	1
	Ever	151 (51.4)	103 (70.6)	2.03 (1.25-3.31), 0.004	2.20 (1.34-3.62), 0.002
Passive smoking, duration (year)	Never	143 (55.9)	43 (34.7)	1	1
	≤ 10	22 (8.6)	6 (4.8)	0.74 (0.25-2.15), 0.582	0.75 (0.25-2.22), 0.615
	11-20	38 (14.8)	26 (21.0)	2.22 (1.10-4.49), 0.025	2.50 (1.22-5.10), 0.012
	> 20	53 (20.7)	49 (39.5)	2.73 (1.49-5.01), 0.001	2.87 (1.56-5.30), 0.001
Passive smoking, age period	Never	175 (60.3)	63 (43.1)	1	1
	≤ 19 years	44 (15.2)	20 (13.7)	1.14 (0.56-2.32), 0.701	1.29 (0.63-2.66), 0.473
	≥ 20 years	21 (7.2)	9 (6.2)	0.74 (0.29-1.88), 0.530	0.82 (0.32-2.09), 0.680
	Throughout life	50 (17.3)	54 (37.0)	2.96 (1.67-5.24), 0.001	3.01 (1.69-5.34), 0.001
Mother's smoking in the perinatal period	No	284 (96.6)	144 (98.6)	1	1
	Yes	10 (3.4)	2 (1.4)	0.31 (0.05-1.76), 0.190	0.35 (0.05-2.13), 0.258

OR: Odds ratio; CI: Confidence interval; PPMS: Primary progressive multiple sclerosis
*Adjusted for age, **Adjusted for age and Socioeconomic status (SES)

Table 3. Association between consumption of different types of substances and alcohol and primary progressive multiple sclerosis (PPMS)

Variables		PPMS group [n (%)]	Control group [n (%)]	Adjusted OR* (95% CI), P	Adjusted OR** (95% CI), P
Opioid	No	135 (92.5)	278 (94.5)	1	1
	Yes	11 (7.5)	16 (5.44)	0.98 (0.37-2.32), 0.883	0.90 (0.35-2.29), 0.838
Cannabis	No	141 (96.6)	285 (96.9)	1	1
	Yes	5 (3.4)	9 (3.1)	1.59 (0.47-5.38), 0.453	1.58 (0.47-5.24), 0.451
Stimulants	No	144 (98.6)	286 (97.3)	1	1
	Yes	2 (1.4)	8 (2.7)	0.88 (0.14-5.21), 0.890	0.85 (0.14-4.87), 0.858
Hallucinogen	No	146 (100)	292 (99.3)	1	1
	Yes	0 (0)	2 (0.7)	-	-
Beer intake	No	132 (90.4)	239 (81.3)	1	1
	Yes	14 (9.6)	55 (18.7)	0.64 (0.31-1.32), 0.237	0.61 (0.29-1.26), 0.187
Whisky/vodka intake	No	133 (91.1)	239 (81.3)	1	1
	Yes	13 (8.9)	55 (18.7)	0.74 (0.35-1.53), 0.422	0.71 (0.34-1.49), 0.375
Wine intake	No	132 (90.4)	246 (83.7)	1	1
	Yes	14 (9.6)	48 (16.3)	0.75 (0.36-1.57), 0.455	0.73 (0.35-1.53), 0.413

OR: Odds ratio; CI: Confidence interval; PPMS: Primary progressive multiple sclerosis
*Adjusted for age, **Adjusted for age and SES

Table 4. Analysis of the joint effects of different types of smoking on primary progressive multiple sclerosis (PPMS)

Variables		PPMS group [n (%)]	Control group [n (%)]	Adjusted OR* (95% CI), P	Adjusted OR** (95% CI), P
Tobacco and Waterpipe	Never tobacco or Waterpipe	91 (62.3)	193 (65.6)	1	1
	Only tobacco	35 (24.0)	40 (13.6)	1.63 (0.88-3.02), 0.116	1.60 (0.86-2.97), 0.136
	Only Waterpipe	6 (4.1)	48 (16.3)	0.52 (0.20-1.34), 0.178	0.47 (0.18-1.23), 0.128
	Both tobacco and Waterpipe	14 (9.6)	13 (4.4)	6.78 (2.6-17.49), 0.001	5.94 (2.3-15.34), 0.011
Tobacco and passive	Never tobacco or passive	38 (26.0)	125 (42.5)	1	1
	Only tobacco	5 (3.4)	18 (6.1)	0.66 (0.19-2.24), 0.511	0.71 (0.21-2.39), 0.581
	Only passive	59 (40.4)	116 (39.5)	1.31 (0.75-2.29), 0.339	1.44 (0.81-2.55), 0.211
	Both tobacco and passive	44 (30.1)	35 (11.9)	4.49 (2.28-8.86), 0.001	4.54 (2.29-8.98), 0.001
Waterpipe and passive	Never Waterpipe or passive	41 (28.1)	118 (40.1)	1	1
	Only Waterpipe	2 (1.4)	25 (8.5)	0.39 (0.08-1.86), 0.243	0.35 (0.07-1.66), 0.189
	Only passive	85 (58.2)	115 (39.1)	1.68 (0.99-2.84), 0.054	1.82 (1.06-3.12), 0.029
	Both Waterpipe and passive	18 (12.3)	36 (12.2)	2.82 (1.30-6.12), 0.009	2.74 (1.26-5.94), 0.011
All three types of smoking	Never Waterpipe, tobacco, or passive	37 (25.3)	105 (35.7)	1	1
	Only tobacco smoking	4 (2.7)	13 (4.4)	0.47 (0.12-1.87), 0.289	0.53 (0.13-2.09), 0.367
	Only Waterpipe smoking	1 (0.7)	20 (6.8)	0.21 (0.02-1.74), 0.150	0.20 (0.02-1.64), 0.135
	Only passive smoking	54 (37.0)	88 (29.9)	1.21 (0.66-2.20), 0.533	1.34 (0.72-2.49), 0.343
	Waterpipe and tobacco	1 (0.7)	5 (1.7)	1.43 (0.12-16.0), 0.771	1.18 (0.10-13.81), 0.890
	Waterpipe and passive	5 (3.4)	28 (9.5)	0.88 (0.29-2.68), 0.828	0.85 (0.27-2.64), 0.792
	Passive and tobacco	31 (21.2)	27 (9.2)	2.68 (1.25-5.73), 0.011	2.71 (1.27-5.83), 0.010
	All three types of smoking	13 (8.9)	8 (2.7)	11.36 (3.77-34.2), 0.001	10.45 (3.5-31.2), 0.001

OR: Odds ratio; CI: Confidence interval; PPMS: Primary progressive multiple sclerosis
*Adjusted for age, **Adjusted for age and SES

Evidence has shown that smoking tobacco and waterpipe at the same time increases the odds of developing PPMS by almost 6 times compared to not smoke either (OR: 5.94; 95% CI: 2.3-15.34; P = 0.011). Participants who had responded positive to both ever smoking and exposure to passive smoking were at a 4.5 times higher risk of PPMS (OR: 4.54; 95% CI: 2.29-8.98; P = 0.001). The odds ratio was 2.7 in participants who smoked waterpipe and were exposed to passive smoking (OR: 2.74; 95% CI: 1.26-5.94; P = 0.011). Finally, the OR of PPMS among those exposed to all 3 smoking types was 10 times higher than those who were not exposed to any (OR: 10.45; 95% CI: 3.5-31.2; P = 0.001).

Discussion

Many studies have been conducted on MS and its risk factors, but there is not enough information about the possible risk factors of PPMS. In this population-based, case-control study, we presented the characteristics of 146 PPMS patients and 294 healthy controls in an Iranian population and evaluated the possible relationships between PPMS risk and cigarette and waterpipe smoking, alcohol consumption, and substance abuse. We identified cigarette smoking and exposure to passive smoking as important risk factors for developing PPMS, but no significant relationships were detected between water-pipe smoking, alcohol consumption, and substance abuse and PPMS.

There was a significant difference between the cases and controls in terms of mean age. In the present study, the mean age of the PPMS group was 47 years and the majority of our cases were women with a female-to-male ratio of 1.39:1. Alonso et al. set up a longitudinal, strictly observational registry in Argentina and all practicing neurologists had access to the registry to provide data.[27] The data were updated until July 2019. They found that 144 of the 2089 registered patients had been diagnosed with PPMS. The mean age of PPMS patients was reported to be 54.65 years and the female to male ratio was 1.08:1.[27] A noticeable difference was observed between cases and controls in terms of marital status. Self-rated health status was significantly lower in PPMS patients. This finding was not in line with that of Abdollahpour et al. who found no significant difference between MS patients and controls in terms of self-rated health status.[28] MS is considered a disabling disease, and it can affect mental and physical health status; however, PPMS is more severe.[29] This difference may be due to the severity of PPMS which influences patients' functions and results in a lower health status in PPMS patients.

Waterpipe smoking is emerging as a global health problem, mostly among the young population of Eastern Mediterranean countries.[30] However, it is rapidly spreading to USA and Europe.[15,31] The present study, for the first time, examined the possible association between waterpipe smoking and PPMS risk. In some previous studies, waterpipe smoking was associated with MS;[8,32,33] however, the results of our study showed that waterpipe smoking was not a significant risk factor for the development of PPMS, and its duration and cumulative amount were not correlated with PPMS. In a case-control study conducted by Abdollahpour et al., waterpipe smoking was considered as a novel risk factor for MS among the RRMS population.[8] The duration and cumulative amount of waterpipe smoking were also reported as significant risk factors for MS. In another case-control study in Saudi Arabia, Alkhawajah et al. reported the same results.[32] In the case-control study by Abdollahpour et al. in 2021, waterpipe smoking of at least 1 time per week for a period of 6 months or more throughout life was considered as a risk factor of MS that could significantly increase the risk of the disease.[33]

In this study, we identified cigarette smoking as a significant risk factor for developing PPMS. We found the odds of developing PPMS to be almost 3 times higher in ever smokers than never smokers. This parameter was reported to be 1.98 and 3.23 for current smokers and past smokers, respectively, compared to never smokers. Moreover, a significant dose-response association was detected between PPMS and the duration and cumulative amount of tobacco smoking. Despite extensive researches considering cigarette smoking as an important risk factor for the incident of MS, a systematic review indicated that cigarette smoking had an indefinite association with the progression of MS.[13] In a nested case-control study conducted in the population of UK, no altered risk for developing RRMS or PPMS was observed in "ever versus never" smokers.[12] However, the population of PPMS patients in this study was too small.[12]

A Swedish cross-sectional study including 17 PPMS patients found that ever smokers, who began smoking before 15 years of age, developed PPMS sooner than never smokers.[34] Although the

mechanism of smoking effect on MS is uncertain, some studies have tried to present some potential theories. Nicotine and acrolein are two important components of cigarettes that can lead to defects in antigen medicated T cell signaling and neurodegeneration.[35,36] The role of free radicals in cigarette smoking, such as nitrogen oxide, is also important. It has been shown that nitrogen oxide can cause axonal damage and is used as a cerebrospinal fluid (CSF) marker for the progression of MS.[37]

In line with other studies, we also detected a significant association between the history of passive smoking and PPMS risk. Participants who had been exposed to smoking were at a 2.2 times higher risk of PPMS than those who had never been exposed to smoking. The results also verified an over twofold higher risk of PPMS in participants who had a history of passive smoking throughout their life compared to those who had never been exposed to smoking. Moreover, passive smoking appears to be a more serious risk factor than active smoking. These findings have also been reported in previous studies. In previous studies in the Iranian population, being a passive smoker has been considered as a risk factor for developing MS,[8,38] but no study was found in the literature which examined the possible relationship between passive smoking and PPMS incidence. In line with our results, several studies reported that sustained exposure to cigarette smoke can increase pro-inflammatory mediators triggering autoimmune disease.[39] Passive smoking is a more serious risk factor than active smoking not only in MS, but also in other autoimmune diseases such as systemic lupus erythematous (SLE) and juvenile rheumatoid arthritis.[40,41]

Evaluation of the possible relationship between mothers' smoking in the perinatal period and development of PPMS was another part of this study. No significant association was observed between mother's smoking in the perinatal period and PPMS incidence. However, due to the small number of PPMS patients in this category, larger studies are recommended for greater statistical power to detect such potential association. Previous studies have observed no statistically significant association between perinatal smoking exposure and risk of MS in the next generation.[42,43] The results of a meta-analysis suggest that active or passive smoking of the mother in the perinatal period does not influence the development of MS.[42]

Additionally, we examined the joint effects of cigarette smoking, waterpipe smoking, and passive smoking on PPMS risk. The results showed that different types of tobacco reinforce each other's effects. The participants who smoked cigarettes and waterpipe were at about 6 time's higher risk of PPMS development than those who did not smoke either. This parameter was reported to be 4.5 and 2.7 in people who were both ever smokers and passive smokers, and people who were waterpipe smoker and passive smokers, respectively. Finally, those who reported all 3 types of tobacco smoking were at a 10 times higher risk than those who did not. In the study by Abdollahpour et al. in 2016, being exposed to 3 types of tobacco smoking increased the odds of developing MS by almost 4 times compared to people who did not smoke either,[8] which is in line with our findings.

Our findings did not support any significant association between the consumption of any types of alcohol and PPMS. Although no study has been conducted to examine the possible relationship between alcohol consumption and PPMS, some studies reported variable information about alcohol and its possible role in MS. In the study by Abdollahpour et al., the consumption of alcohol was considered as a risk factor for developing RRMS.[44] In contrast, Hedstrom et al. conducted a case-control study and reported alcohol consumption as a protective factor in the development of MS.[45]

The results showed no statistically significant association between the use of any types of drugs and substances and the development of PPMS. In contrast to our results, another study conducted in Iran indicated that substance abuse could be considered as a risk factor for developing MS.[44] It has also been reported that cannabis is associated with triples the risk of MS incidence. This difference in the results may be due to the small number of drug users among the PPMS patients and also differences in the nature of MS and PPMS.

As one of the strengths of the present study, it can be stated that this study is one of the first studies investigating the potential role of various risk factors including tobacco, alcohol, and drug consumption in the risk of PPMS incidence. Other strength points include the almost 98% complete response rate of participants, using a random method for the selection of control participants, and more PPMS cases compared to previous researches. However, this study has some limitations. One of the limitations of this study was

that the sample size was relatively small, and because the smoking rate among these individuals is low, the number of people in certain categories of analysis was reduced, which reduced the study power. Moreover, due to the small number of cases in some categories, there is evidence of sparse data bias in the study, which has led to the widening of the confidence intervals. Therefore, given that PPMS is rare, it is recommended that larger prospective studies be conducted with a multicenter design.

Conclusion

For the first time, we assessed the possible risk factors for PPMS development. Cigarette smoking and passive smoking were identified as important risk factors for PPMS. It was observed that tobacco smoking, waterpipe smoking, and exposure to passive smoking can jointly have a significant effect on developing PPMS. Considering the global increase in tobacco smoking, these findings emphasize the importance of interventional programs for the prevention of smoking.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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