Original Article

# Relation Between Smoking and Disability Progression in Iranian Multiple Sclerosis Patients: A Case-Control Study


## Abstract

**Background:** To compare characteristics of patients with multiple sclerosis (MS) between cigarette smokers and non-smokers. **Methods:** A case-control study was performed on patients registered in the Kashani MS center from April 2019 to April 2020 in Isfahan, Iran. In total, 136 smoker patients and 220 non-smokers participated in the study and completed the questionnaire. **Results:** The frequency of male gender in the smoker group was significantly higher than in the non-smokers (64.7% vs. 15%, $P < 0.001$). The mean age at MS onset was 31.5 ± 9.60 years among cigarette smokers and 29.7 ± 9.47 years among non-smokers ($P = 0.794$). Furthermore, 80% of cigarette smokers and 64% of non-smokers had at least one relapse per year (ARR ≥1, $P < 0.001$). The Expanded Disability Status Scale (EDSS) of more than 4.5 was significantly higher in smokers (26.5% vs. 18%, $P = 0.023$). There was a relation between an EDSS of more than 4.5 and an interval between smoking initiation and disease onset ($P = 0.004$). Long duration of smoking was associated with a higher disability scale (16.4 ± 9.5 vs. 9.8 ± 7.3, $P = 0.008$). Men smoked for a longer period of time before developing MS than women (9.24 ± 10.07 vs. 4.47 ± 7.61, $P = 0.002$). The average daily cigarette consumption was 7.74 ± 6.65 in women and 10.84 ± 9.44 in men ($P = 0.024$). Duration of smoking before the onset of the disease was 4.47 ± 7.61 years in women and 9.24 ± 10.07 in men ($P = 0.002$). **Conclusions:** Our data suggest that there is a possible relationship between disability score and the duration of smoking before the onset of MS. It also revealed that the duration of smoking can affect the progression of the disease. Further studies are suggested to confirm these findings.


**Keywords:** *Cigarette, multiple sclerosis, smoking*


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## Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that affects mostly young adults, especially females.[1] MS is the leading cause of disability among young adults worldwide.[1] The prevalence of MS has been increasing in recent years in Iran.[2] Although the etiology of the disease is unknown, previous studies have implicated a combination of genetic and environmental risk factors such as sunlight, ultraviolet light, vitamin D deficiency, and Epstein-Barr virus.[1,3-5]

Some studies have proposed smoking as an environmental risk factor for MS.[6,7] However, other studies found no direct effect of smoking on MS activity.[8]

In a study conducted by Weiland TJ, health-related quality of life was lower in smokers compared to non-smokers, but there was no association between disease activity and smoking.[9] Furthermore, Tanasescu *et al.*[10] demonstrated a significant time-dependent reduction in the risk of disability progression after smoking cessation and noted that early smoking cessation has prognostic value.

Another study by Wang Z showed that although smoking may be an important environmental risk factor for MS, it varies from person to person depending on the type of HLA gene.[11] A study showed that smoking can lead to DNA methylation in peripheral blood cells in MS patients and affect downstream gene expression.[11]

In recent years, the use of cigarettes and hookah has become increasingly common among the population of Iran, especially among young people.[12] There are few studies on the relationship between MS and smoking in our region. A population-based study in 2017 in Tehran found that waterpipe smoking is associated with MS.[13]

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**Table 1: Comparison of demographic data, ARR, EDSS, clinical course**

| | Sex | | Age | Age of onset | ARR | | EDSS | | Clinical course | |
|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | | | 0 | >1 | ≤4.5 | >4.5 | RR | PP-SP |
| Non-smoker | 33 15% | 187 58% | 37.5±10.10 | 29.7±9.47 | 77 (36%) | 136 (63.9%) | 172 (79.6%) | 44 (20.4%) | 170 (78.7%) | 46 (21.3%) |
| Smoker | 88 64.7% | 48 35.3% | 37.0±10.29 | 31.5±9.60 | 81 (59.5%) | 55 (40.5%) | 93 (69%) | 42 (31%) | 91 (68.9%) | 41 (31.1%) |
| *P* | 0.00 | | 0.66 | 0.08 | 0.00 | | 0.023 | | 0.04 | |

**Table 2: comparison of disabling symptoms in smoker and non-smoker based on EDSS**

| | Motor symptoms | | Sensory symptoms | | Cerebellar symptoms | | Visual Symptoms | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 |
| Smoker | | | | | | | | |
| EDSS ≤4.5 | 73 | 9 | 24 | 58 | 63 | 19 | 59 | 23 |
| EDSS >4.5 | 31 | 10 | 14 | 27 | 20 | 21 | 28 | 13 |
| | 3.973 | | 2.499 | | 11.757 | | 2.545 | |
| sig | 0.137 | | 0.287 | | 0.003 | | 0.280 | |
| Non smoker | | | | | | | | |
| EDSS ≤4.5 | 138 | 32 | 88 | 82 | 146 | 24 | 93 | 77 |
| EDSS >4.5 | 25 | 17 | 18 | 24 | 35 | 7 | 31 | 11 |
| | 9.215 | | 2.064 | | 0.347 | | 5.777 | |
| sig | 0.01 | | 0.356 | | 0.841 | | 0.056 | |

We conducted this study with the aim of investigating the characteristics of MS in smokers and non-smokers in an Iranian population.

## Methods

A case-control study was conducted from April 2019 to April 2020 on MS patients registered in the MS registry system of Kashani Comprehensive MS Center, Isfahan, Iran. The Ethics Committee of Isfahan University of Medical Sciences approved the study protocol (No.: 399589).

Inclusion criteria were diagnosis of RRMS or SPMS based on McDonald criteria[14] and accessibility to patient's data. Patients with incomplete data were excluded.

Out of 1776 MS patients who were registered in our system during this period, 210 patients were smokers (11.66%). In total, 136 smokers agreed to enter the study and complete the questionnaire (64.7% of all smokers.) Among the non-smokers, 220 patients were randomly selected as the control group.

Written informed consent was obtained from all patients. Demographic and clinical information of all patients was completed by questionnaire, and smoking patients were interviewed to complete the information.

To ensure that non-smoking patients are not passive smokers, they were also interviewed in person. The following items were collected: age, sex, age of disease onset, type of drug used, clinical course, annual relapse rate (ARR), the severity of disability measured by the Expanded Disability Status Scale (EDSS), disabling symptoms (sensory, motor, balance, visual), and the interval between the disease onset to the progressive stage.

### Statistical analysis

The data were analyzed by IBM SPSS statistics, version 24 (IBM Corp., Armonk, N.Y., USA). We used an independent *t*-test and repeated measures to compare data between different groups. *P* value < 0.05 was considered as a significance threshold.

## Results

The frequency of male gender was significantly higher in the smoking group than in the non-smoking group (64.7% vs. 15%, $P < 0.001$). This could be due to the Iranian culture, where smoking is unusual for women.

Cigarette smokers comprised 88 males (64.7%) and 48 females (35.3%), and the mean age was 37.0 ± 10.29 years. The non-smoker group consisted of 33 males (15%) and 187 females (85%), and the mean age was 37.5 ± 10.10 years. The mean age at MS onset was 31.5 ± 9.60 years in cigarette smokers and 29.7 ± 9.47 years among non-smokers ($P = 0.794$).

ARR ≥1 was detected in 80% of smokers and 64% of non-smokers ($P < 0.001$).

EDSS score was more than 4.5 in 26.5% of cigarette smokers ($P = 0.023$). Motor disability was more frequent among cigarette smokers ($P = 0.001$). These issues may be indications of more progression of disease in smokers [Table 1].

In our study, the average daily cigarette consumption was 7.74 ± 6.65 in women and 10.84 ± 9.44 in men ($P = 0.024$). The age of smoking initiation was higher in women than in men (23.98 ± 6.26 vs. 20.31 ± 5.49, $P = 0.013$). The mean age at MS onset was 28.45 ± 8.38 and 30.55 ± 8.48 among women and men, respectively ($P = 0.417$). Duration of smoking before the onset of the disease was 4.47 ± 7.61 years in women and 9.24 ± 10.07 among men ($P = 0.002$) [Table 2].

**Table 3: Comparison of different variables in the case group based on EDSS, ARR and Progression of disease**

| Variable | EDSS ≤4.5 | EDSS >4.5 | *P* | ARR 0 | ARR >1 | *P* | RRMS | PPMS-SPMS | *P* |
|---|---|---|---|---|---|---|---|---|---|
| Number of cigarettes (mean±SD) | 7.4±6.7 | 9.7±7.1 | 0.676 | 79.21±31.60 | 82.83±42.24 | 0.877 | 76.14±33.05 | 77.50±39.26 | 0.000 |
| Duration of smoking before disease onset (year) (mean±SD) | 8.3±6.7 | 15.3±10.1 | 0.004 | 9.19±7.07 | 12.43±10.06 | 0.137 | 7.14±6.87 | 9.75±5.50 | 0.000 |
| Duration of smoking (mean±SD) | 9.8±7.3 | 16.4±9.5 | 0.008 | 1.53±0.70 | 1.67±0.73 | 0.531 | 7.14±5.78 | 21±14.97 | 0.000 |

The association between smoking-related variables and MS characteristics is shown in Table 3. Although the number of cigarettes consumed was higher in patients with EDSS >4.5, there was no significant difference. On the contrary, the duration of smoking before the onset of the disease was significantly longer in patients with EDSS >4.5. (15.3 ± 10.1 vs. 8.3 ± 6.7, $P = 0.004$).

In addition, the duration of smoking was related to disability (9.8 ± 7.3 vs. 16.4 ± 9.5, $P = 0.008$) [Table 3].

## Discussion

Based on our findings, the progression of disability was greater in patients who had smoked for a longer time before the onset of MS. In addition, in our patients, disability score was higher in patients who smoked for a longer period of time, which could confirm the effect of smoking on the incidence of disability progression in MS patients. Therefore, our survey may be in line with a study pointing to the positive effects of smoking cessation on the course of the disease.[15]

These results were consistent with another study[16] that showed a significant relationship between smoking and a faster rate of brain atrophy and a greater disability burden in MS patients; the aforementioned study attributed these effects to the neurotoxic properties of free radicals, cyanates, and carbon monoxide in cigarettes.[16]

Another study by Hernán *et al*.[17] reported that the odds ratio of MS was 1.3 for ever-smokers compared with never-smokers and suggested smoking as a risk factor for transforming a relapsing-remitting clinical course into a secondary progressive course. These data are consistent with our study, which showed that smoking could lead to the worsening of the disease course.

In our study, the male gender was significantly higher in cigarette smokers than in non-smokers (64.7% vs. 15%). In smoking patients, there was no difference in the average age of MS onset between men and women, but men started smoking at a younger age. Moreover, the number of daily cigarettes and the duration of smoking before the onset of MS were significantly higher in men. Other studies have shown varied results regarding gender and smoking in MS patients. Manouchehrinia A *et al*.[7] found that the attributable fraction for MS risk was 10.6% in women and 19.1% in men. Ivashynka reported no significant difference between smokers and non-smokers regarding gender and age.[18] This difference in our study can be due to cultural limitations on smoking in Iran, where smoking is considered socially inappropriate for women.

It is unclear whether the shorter interval between smoking initiation and MS onset among women is related to the higher sensitivity of women to smoking hazards or not. Further studies should be done in this field.

Cigarette smokers had higher ARR (one or more relapses per year) and higher EDSS (>4.5) compared to non-smokers. Ivashynka *et al*.[18] found that cigarette smoking was associated with a more severe disease course and these patients had higher EDSS scores but found no difference regarding relapse rate between smokers and non-smokers. The relationship between cigarette smoking and MS progression has been previously evaluated, but studies in our region are few. On the contrary, Koch and others reported that smoking cigarettes had no significant association with the development and age of secondary progression.[9,19] One study using Mendelian randomization found no association between smoking and the risk of developing MS.[9,20] These differences could be due to variations in the study population and the methods of the study. Although smoking may be a major environmental risk factor for MS, it varies from person to person.[11] Hedström AK *et al*.[21] compared self-reported smoking status and cotinine level among MS patients and concluded that using cotinine level to define smoking may bias studies that investigate the association between smoking and MS.[21]

In terms of disabling symptoms in our patients, cerebellar symptoms were more common among non-smokers and motor symptoms among smokers. This result was contrary to a study that found a higher frequency of cerebellar and sensory symptoms in smokers.[22]

This case-control study had some limitations. First, the smoking status was recorded according to the patient's reports, which may reduce the validity of the data. Second, passive smokers were not enrolled in the study, which may affect the study's findings regarding the long-term effects of smoking on health. More detailed longitudinal studies are recommended to investigate the effect of other confounding risk factors besides smoking.

## Conclusions

Our data suggest that there is a possible relationship between disability score and the duration of smoking before the onset of MS. It also showed that the duration of smoking can affect the progression of the disease. Further studies are suggested to confirm these findings It also

showed that the duration of smoking can affect the risk of developing the disease.

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## Conflicts of interest

There are no conflicts of interest.

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