

# A Link between Smoking and Age at Onset in Multiple Sclerosis

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## Abstract

**Background:** Smoking has been suggested to increase susceptibility to Multiple Sclerosis (MS) and also disease progression, associated with higher disability and higher risk of conversion to progressive disease phenotypes. However, the effect of smoking and smoking intensity on MS progression remains unclear.

**Objectives:** The aim of this study was to investigate the influence of smoking and smoking intensity on the susceptibility to and progression of MS.

**Methods:** Demographic and clinical data were collected. Patients were divided according to their smoking status at the time of MS onset (non-smokers and regular-smokers) or current smoking status (non-smokers, current-smokers, past-smokers and second-hand smokers). Statistical analysis was performed using SPSSv20.0, and a p-value<0.05 was considered statistically significant.

**Results:** 120 patients (73.3% were female) with a mean age of 44.1 years were included. It was found that regular-smokers had an early onset of disease compared to non-smokers (29.5 vs. 34.2, respectively, p=0.031). Age of disease onset was directly correlated with pre-onset pack-year (r=0.295; p=0.002). A significant difference in the gender distribution was observed among the different smoking status groups (p<0.001). Most females were non-smokers (56.8%), while males were past-smokers (53.1%).

**Conclusions:** Our findings suggest that smoking is associated with an anticipation of the age at onset of MS, reinforcing the role of smoking as a risk factor to MS.

**Keywords:** Multiple sclerosis • Smoking • Risk factor • Anticipation of age at onset

**Abbreviations:** MS: Multiple Sclerosis; RRMS: Relapsing-Remitting Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; EDSS: Expanded Disability Status Scale; MusiQoL: Multiple Sclerosis International Quality of Life questionnaire.

## Introduction

Multiple Sclerosis (MS) is a complex neurological condition characterized by demyelination and axonal loss. Current evidence suggests that genetic background and environmental factors such as Epstein Barr virus infection, low vitamin D or Ultra Violet B light (UVB) exposure, smoking, and obesity [1] are risk factors for MS development [2,3].

MS typically starts as a Relapsing-Remitting (RR) disease, characterized by recurring clinical symptoms followed by complete or partial recovery [4].

MS affects 2.8 million people worldwide in 2020 [5], and the prevalence and incidence of MS are increasing in most countries, highlighting the importance of identifying modifiable lifestyle and environmental risk factors [6].

MS is more common in females, and gender disparity has been increasing, with a current ratio of nearly 3:1 (F:M) in most developed countries. The increased incidence of MS in female may be partially explained by changes in smoking habits, as the rise in female smokers has paralleled the growing gender disparity in MS [7]. Smoking is also more prevalent in patients with MS than in the general population [8].

Various case-control and population cohort studies suggest that smoking cigarettes increases the susceptibility to MS [9,10] and MS progression [11-13], being associated with higher disability and higher risk of conversion to progressive disease phenotypes [8].

Smoking also increases the risk of developing neutralizing antibodies against biologic agents used in the treatment of MS [14]. In addition, smoking is associated with an increased risk of other inflammatory diseases. Smoking shows a relevant interaction with MS-associated HLA risk genes [6].

Second-hand exposure to smoke has also been associated with increased risk for MS, which suggests that even minor "lung irritation" may be significant [15]. Smoking has also been associated with physical status and health-related quality of life [16].

However, the causal relationship between these associations is unclear, and several pathophysiologic mechanisms have been proposed [3].

This study aimed to understand the influence of smoking and smoking intensity on the susceptibility to, and progression of, MS.

## Materials and Methods

### Setting and participants

Patients with MS regularly followed at the Neurology Department of Centro Hospitalar e Universitário de Coimbra were recruited consecutively from follow-up consultations. All patients were diagnosed with definite MS according to the revised 2017 McDonald criteria and presented either a Relapsing-Remitting MS (RRMS) or a Secondary Progressive MS (SPMS) clinical subtype. Patients with a phenotype of primary progressive disease were excluded.

According to the Declaration of Helsinki, all participants provided written informed consent previously approved by the local Institutional Review Board.

Clinical and demographic data of participants were collected through the use of medical records and thorough, face-to-face, questionnaires. Data included gender, age, disease subtype, age of disease onset and age of secondary progression onset, Expanded Disability Status Scale (EDSS score) and number of relapses in the previous year.

### Smoking history

Data on smoking history included current smoking status, age of starting and quitting, and average number of cigarettes smoked per day. Patients were divided into four groups according to their current smoking status: Non-smokers, current-smokers, past-smokers and second-hand smokers.

Past-smokers and current smokers reported average daily cigarette consumption during the years they smoked. With this information, the number of pack-years until participation in this study, before onset of MS and after onset of MS, was calculated.

The non-smokers are those who never smoked in their lives or smoked only incidentally (less than one half pack-year in their entire lives). Patients were considered second-hand smokers if they had been exposed to daily tobacco smoke for a prolonged period of time (at least 1 year).

Moreover, the smoking status at disease onset was also determined and classified as regular smokers and non-smokers. Since it was not possible to accurately determine the smoking status of second-hand smokers at the time of disease onset, they were not considered for this purpose.

The Portuguese version of the Multiple Sclerosis International Quality of Life (MusiQoL) questionnaire was used to determine the influence of smoking on quality of life.

### Collected variables

Demographic data (sex and age), disease subtype, age at diagnosis, disease duration, age of disease onset, number of relapses in the

previous year, current EDSS score, smoking habits (onset and current) and pack-year units were collected. The EDSS score (range 0-10) was used to quantify the neurological disability of MS patients. The formula of a pack-year unit is defined by:

$$\text{Pack-year} = (\text{number of cigarettes per day} / 20) \times \text{number of years}$$

Pack-year load was adjusted for age. For the purpose of analyses, patients were divided into two groups: Never smoker/second-hand smoker and smoker past or current.

### Statistical analysis

Categorical variables were described using absolute and relative frequencies, and continuous variables using mean and standard deviation.

Comparison of groups according to smoking status was performed using ANOVA for continuous variables with normal distribution. The Mann-Whitney U-test was used for ordinal variables or continuous variables that were not normally distributed, and the  $\chi^2$  test or Fisher's exact test was used for categorical data. Pearson's product moment correlation was used to examine correlations between EDSS, disease duration, pack-year before and after disease onset, age of smoking initiation, and smoking duration after disease onset.

All analyses were conducted using SPSSv20.0, and a p-value < 0.05 was considered statistically significant.

## Results

### Participants characterization

One hundred and twenty patients with MS were included in this study. Table 1 describes the demographic and clinical characteristics of the total cohort. Most patients were female (73%) with a mean age of 44 years. Regarding disease phenotype, more than 80% of the patients had RRMS, with a mean age at onset of approximately 32 years and a mean of 12 years of disease duration. The mean EDSS score was 2.76 (Table 1).

**Table 1:** Demographic and clinical characteristics of the total cohort

Variable	Total cohort (n=120)
Gender (female; n (%))	88 (73.3)
Age (years; mean $\pm$ SD)	44.05 $\pm$ 12.60
Subtypes (n (%))	
Relapsing-remitting	103 (85.8)
Secondary-progressive	17 (14.2)
Age at diagnosis (years; mean $\pm$ SD)	34.78 $\pm$ 10.19
Disease duration (years; mean $\pm$ SD)	12.27 $\pm$ 10.40
Age of disease onset (mean $\pm$ SD)	32.19 $\pm$ 10.30
Relapses in the previous year (mean $\pm$ SD)	0.38 $\pm$ 0.71
Current EDSS score (mean $\pm$ SD)	2.76 $\pm$ 1.88
Total MusiQoL (mean $\pm$ SD)	67.81 $\pm$ 17.65

**Note:** SD: Standard Deviation

### Smoking status characterization

Regarding the current smoking status, 57 (47.5%) patients were non-smokers, 27 (22.5%) were past-smokers, 22 (18.3%) were current-smokers, and 14 (11.7%) were second-hand smokers. From the 27 past-smokers, 17 (63.0%) patients had quit smoking before the onset of the disease and 10 (37.0%) stopped smoking a mean of

10.60 ( $\pm$  8.59) years after disease onset. The mean age of tobacco smoking initiation was 17.16 ( $\pm$  3.50) years.

### Smoking status at the time of MS onset

At disease onset, 32 (30.2%) were regular-smokers and 74 (69.8%) were non-smokers. The age of disease onset was significantly lower in the regular-smokers group than in the non-smokers group ( $p=0.031$ ).

No other variable was significantly related to the smoking status at the time of disease onset (Table 2).

**Table 2:** Demographic and clinical characteristics of patients regarding smoking status at the time of disease onset.

Variable	Non-smokers (N=74)	Regular-smokers (N=32)	p-value
Gender (n (%))			
Female	56 (74.7)	19 (25.3)	0.107
Male	18 (58.1)	13 (41.9)	
Age (years; mean $\pm$ SD)	45.59 $\pm$ 13.00	42.28 $\pm$ 10.40	0.205
Age of disease onset (years; mean $\pm$ SD)	34.19 $\pm$ 10.10	29.53 $\pm$ 10.04	0.031
Disease duration (years; mean $\pm$ SD)	11.68 $\pm$ 9.43	13.56 $\pm$ 11.14	0.373
Current EDSS score (mean $\pm$ SD)	2.77 $\pm$ 1.83	2.63 $\pm$ 1.86	0.697
Relapses in the previous year (mean $\pm$ SD)	0.43 $\pm$ 0.78	0.28 $\pm$ 0.58	0.326
MusiQoL (mean $\pm$ SD)	69.77 $\pm$ 15.88	64.31 $\pm$ 16.35	0.124

**Note:** SD: Standard Deviation

### Current smoking status

Concerning the current smoking status, a significant difference in the gender distribution was observed ( $p < 0.001$ ). Most females were non-smokers (56.8%), while males were past-smokers (53.1%). None

of the other evaluated variables was significantly related to the current smoking status (Table 3).

**Table 3:** Demographic and clinical characteristics of patients regarding current smoking status

Variable	Smoker (N=22)	Non-smoker (N=57)	Past-smoker (N=27)	Second-hand smoker (N=14)	p-value
Gender (n (%))					
Female	15 (17.0)	50 (56.8)	10 (11.4)	13 (14.8)	<0.001
Male	7 (21.9)	7 (21.9)	17 (53.1)	1 (3.1)	
Age (years; mean $\pm$ SD)	41.00 $\pm$ 9.35	44.74 $\pm$ 12.98	47.22 $\pm$ 12.72	39.93 $\pm$ 14.07	0.213
Age of disease onset (years; mean $\pm$ SD)	32.36 $\pm$ 8.66	33.19 $\pm$ 10.37	32.26 $\pm$ 11.51	27.71 $\pm$ 9.84	0.907
Disease duration (years; mean $\pm$ SD)	9.59 $\pm$ 6.43	11.98 $\pm$ 9.64	14.96 $\pm$ 12.37	12.43 $\pm$ 13.40	0.165
Current EDSS score (mean $\pm$ SD)	2.00 $\pm$ 0.91	2.82 $\pm$ 1.79	3.15 $\pm$ 2.32	3.00 $\pm$ 2.21	0.081
Relapses in the previous year (mean $\pm$ SD)	0.32 $\pm$ 0.57	0.51 $\pm$ 0.84	0.19 $\pm$ 0.48	0.29 $\pm$ 0.61	0.351
MSSS (mean $\pm$ SD)	2.9 $\pm$ 1.51	3.33 $\pm$ 2.25	3.27 $\pm$ 2.36	3.85 $\pm$ 2.64	0.747
Total MusiQoL (mean $\pm$ SD)	65.28 $\pm$ 18.17	68.48 $\pm$ 16.29	69.59 $\pm$ 16.29	70.95 $\pm$ 19.36	0.646

**Note:** SD: Standard Deviation

### Correlations between clinical and smoking characteristics

Current EDSS was correlated with post-onset pack-year ( $r = 0.124$ ,  $p = 0.028$ ) and disease duration ( $r = 0.673$ ,  $p < 0.001$ ), however pack-year load adjusted for age and disease duration was not correlated with current EDSS, relapses in the previous year, or the total MusiQoL.

The age of disease onset was correlated with pre-onset pack-year ( $r = 0.295$ ,  $p = 0.002$ ). Age at smoking initiation and age at disease onset were not significantly correlated Table 4.

**Table 4:** Correlations between clinical and smoking characteristics.

Variable	p-value	Correlation coefficient
Current EDSS score vs. post-onset pack-year	0.028	0.214
Current EDSS score vs. disease duration	<0.001	0.673
Disease duration vs. post-onset pack-year	<0.001	0.452
Age of disease onset vs. pre-onset pack-year	0.002	0.295
Relapse in the previous year vs. post-onset pack-year adjusted for age	0.454	-0.072
Age of smoking onset vs. age of disease onset	0.964	-0.006
Total MusiQoL vs. post-onset pack-year adjusted for age	0.18	-0.18

## Discussion

This study aimed to understand the influence of smoking on the susceptibility to, and progression of, MS. In this Portuguese cohort with MS, the age of disease onset was younger in the regular-smokers compared to non-smokers, supporting the well-known role of smoking as a risk factor to MS [10,17,18]. Indeed, meta-analyses have found an effect estimate of approximately 1.5 fold [8,19-21], and smoking has been reported to increase the risk of MS between 40% [7] and 50% [8]. Moreover, we found a correlation between the pre-onset pack-year and the age of disease onset. This was also reported in previous studies that demonstrated increasing MS susceptibility with increasing numbers of cigarettes smoked. Quantitative measures include patient-reported pack-years, packs of cigarettes per day, cigarettes per day, years of cigarette smoking, and levels of nicotine metabolites [3], which hinder the comparison between studies [19]. However, an interaction between susceptibility and dose is essential to establish causality of any environmental factor [19].

However, although smoking is associated with MS susceptibility, this environmental factor alone is unlikely to account for the global variation in prevalence [19], which is highly dependent on genetic context, latitude or vitamin D levels [6].

Studies are less clear regarding the effect of smoking on MS progression, with some studies suggesting an increased risk of progression [22] and others showing no effect on progression. Handel et al. showed no statistically significant association between smoking and SPMS risk [19]. Degelamn et al. found a statistically significant association between smoking and MS risk and the conversion from RRMS to SPMS. However, no association was found between smoking and the progression from Clinically Isolated Syndrome (CIS) to Clinically Definite MS (CDMS) [8]. Also, Koch et al. [23] reported that smoking does not influence disease progression or accumulation of disability in MS. Similarly, in our study we found no association of smoking with disease progression or with quality of life.

These contradictory findings reported in the literature may be partially explained by different population characteristics which can modulate the MS progression, since the consequences of cigarette smoking seem to have a larger effect in older patients [8].

This study found no correlation between relapses in the previous year and pack-year adjusted for age, which is corroborated by two studies that found similar results [24,25]. However, some studies have found an association between relapses in the previous year and pack-year adjusted for age [16]. These different results may be due to individual characteristics, namely the relationship between inflammatory disease activity and smoking, which continues to have inconsistent findings [26].

Some studies report that smoking cessation can reduce the probability of achieving disability milestones [27]. However, the duration of follow-up might partly explain the heterogeneous results reported in various studies, since the detection of reaching disability

milestones is more frequent in studies with more extended follow-up periods (between 2 to 5 years) [16]. Even so, patients with MS are strongly advised to quit smoking because the disease course may be worsened by continued smoking [12] and also due to the risk of developing neutralizing antibodies against biologic agents used for treating MS [6]. However, the impact of smoking can continue even after quitting, since some studies also associate past smoking with a worse prognosis [13].

The prevalence of female with MS in this study confirms the ratio of 3:1 (Female: Male) that is frequently reported [28]. During the last century, smoking habits in female have been changing, which, combined with risk factors, may explain a trend in the increasing sex ratio observed in MS [7,19].

This study has some limitations since this is not a multicenter study, and the patients included may not represent the MS population. However, the center where the patients were recruited is a reference center for MS, and the number presented is considerable.

## Conclusion

In this Portuguese cohort, smoking was associated with an anticipation of the age at onset supporting its well-known role as a risk factor to MS. However, no association was found with the progression of MS. This may be related to different genetic backgrounds, environmental factors and lifestyles.

## Credit Authorship Contribution Statement

CL and SB: Conceptualization; data curation; formal analysis; investigation; methodology; writing - original draft; final approval of the version of the manuscript to be published. RM, ZA, IC, CCN, MCM and LS: Data curation; investigation; methodology; writing - review and editing; final approval of the version of the manuscript to be published.

## Conflicts of interest

None to declare.

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