TOBACCO INFLUENCE IN THE CLINICAL PROGRESSION OF MULTIPLE SCLEROSIS

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Tobacco smoking has already been linked to an increased risk of MS but the association between smoking and progression of MS has not been fully clarified. The aim of this study was to investigate the effects of smoking on MS disability progression and quality of life.

A total of 120 patients 73,3% female (n=88), underwent a structured interview to assess smoking history and completed the MusiQoL questionnaire. There was a male predominance in past-smokers (63,0%) while in the other groups female were predominant. Age of MS onset was lower in regular-smokers compared to non-smokers (29,53 ±10,04 vs 34,19 ±10,10; *p*=0,031). The age of smoking initiation (standardized b 0,40; R^2 change 0,14 ; *p*=0,001) and pack-year before disease onset (standardized b 0,73; R^2 change 0,32 ; *p*<0,001) were the only predictors for the age of disease onset. There was a significant correlation of increasing EDSS with disease duration (r=0,673; *p*<0.001), pack-year after disease onset (r=0,214; *p*=0.028) and smoking duration after disease onset (r=0,387; *p*=0,026). In the group of secondary-progressive (SPMS) patients the median EDSS was significantly higher in ever-smokers (7.0) and second hand-smokers (6.8) compared to non-smokers (5.5) (*p* =0,013). Moreover, current and second hand-smokers presented worse scores in the Relationship with Family (*p*=0,019) and the Sentimental and Sexual Life (*p*=0,030) MusiQoL dimensions, when compared to past and non-smokers. In SPMS the second hand-smokers had the lowest mean scores followed by the ever-smokers and the non-smokers in the Activity of Daily Living (*p*=0,010) and Relationship with Family (*p*=0,001) dimension.

This study suggests that smoking is associated with an earlier MS onset and worse long term prognosis, accumulating more disability and presenting inferior quality of life. In addition, smoking cessation is associated with a beneficial effect in the disease evolution.

Key-words

Multiple sclerosis, Smoking, Progression, Quality of Life

RESUMO

A esclerose múltipla (EM) é uma doença inflamatória desmielinizante do sistema nervoso central (SNC). O hábito tabágico já foi associado a um risco aumentado de EM, mas a associação entre o tabagismo e progressão da esclerose múltipla ainda não foi claramente esclarecida.

O objetivo deste estudo foi investigar os efeitos do tabagismo sobre a progressão clínica de EM e a qualidade de vida. Um total de 120 pacientes 73,3% mulheres (n=88), foram submetidos a uma entrevista estruturada para avaliar hábitos tabágicos e realizar questionário de MusiQoL. Encontramos uma predominância do sexo masculino nos ex-fumadores (63,0%) enquanto que nos outros grupos o sexo feminino foi o mais prevalente. A idade de início da EM foi menor em fumadores-regulares em comparação com não-fumadores (29,53 ±10,04 vs 34,19 ±10,10; *p*=0,031). A idade de início de fumar (padronizado b 0,40; R^2 change 0,14; *p*=0,001) e U.M.A (unidade maço/ano) antes do início da doença (padronizado b 0,73;

R^2change 0,32; p<0,001) foram os únicos preditores para a idade de início da doença. Detectámos uma correlação significativa entre o EDSS com a duração da doença (r=0,673; p<0,001), U.M.A após o início da doença (r=0,214 ; p=0,028) e a duração de fumar (em anos) após o início da doença (r=0,387 ; p=0,026). No grupo de doentes com EM secundária progressiva (EMSP) a mediana de EDSS foi maior nos alguma vez-fumadores (7,0) e fumadores-passivos (6,8) em comparação com os nunca-fumadores (5,5) (p=0,013). Adicionalmente, os fumadores e fumadores-passivos apresentaram piores pontuações nas dimensões de Relação Familiar (p=0,019) e de Vida Sexual e Sentimental do MusiQoL, quando comparados com os não-fumadores e ex-fumadores (p=0,030). No grupo de doentes com EMSP os fumadores-passivos tiveram pontuações médias mais baixas seguidos dos alguma vez e nunca-fumadores nas dimensões para Atividade de Vida Diária (p=0,010) e Relação Familiar (p=0,001).

Este estudo sugere que o tabagismo está associado a um início mais precoce da EM e a um pior prognóstico a longo prazo, com maior acumulação de incapacidade e pior qualidade de vida. Além disso, deixar de fumar, poderá ter um efeito benéfico na evolução da doença.

BACKGROUND

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) (1). The disease typically begins in the second or third decade of life and has a female predominance of approximately 2:1 (2).

At the onset, nearly 85% of the patients have a relapsing-remitting clinical course (relapsing-remitting MS [RRMS]), and experience alternating episodes of neurological disability defined as relapses, with full or partial recovery, as described by Lublin *et al.* (1996) (2–5). Within 25 years, approximately 90% of the RRMS patients transform into a secondary-progressive disease course (secondary-progressive MS [SPMS]), characterized by steady neurological decline (2,5). About 10% of patients with MS will have a primary progressive course (primary progressive MS [PPMS]), representing a relentless progression from the beginning with no remission and a small minority of MS patients (5%), classified as progressive-relapsing MS (PRMS), suffer from a disease course with progressive neurological decline accompanied by well demarcated acute attacks with or without recovery (6).

The onset is usually isolated in space with signs indicating a lesion in the optic nerve (a common presentation), spinal cord, brainstem or cerebellum, or (rarely) a cerebral hemisphere. However, MS can present with clinical evidence for dissemination in space or with a first episode that is not suggestive of an acute demyelinating inflammatory event in the CNS, as defined above, with symptoms such as cognitive changes, seizures, and encephalopathy (7).

There is growing evidence that the difference between the relapsing-remitting and progressive disease course results from the expression of distinct pathophysiologies (8).

Relapses appear to be related with focal inflammation and demyelination, causing axonal conduction failure at the site of a lesion (9), whereas diffuse axonal degeneration is believed to underlie the progressive disease course (8), ensuing from the lost efficacy of the repair mechanisms, unable to restore functions. Thereby, the neurodegenerative character of the disease surpasses the inflammatory component (9).

MS is regarded as a disease with a multifactorial aetiology, comprising genetic as well as environmental influence (10), which is currently incompletely known (11). Large-scale genome-wide association studies have identified multiple genetic risk loci but by far the most important association in MS susceptibility is with the class II *human leukocyte antigen (HLA)* region, specifically *HLA-DRB1 * 1501* bearing haplotypes (12). Regarding the environmental factors, cigarette smoking seems to contribute to MS susceptibility (13), acting on cellular and humeral components of the immune system, having pro-inflammatory and inhibitory effects as well as direct damage on the cells (14). Furthermore, it has been demonstrated in several studies that smokers have a higher risk of developing MS than non-smokers (15).

Additionally, tobacco has non-immunological effects related to high concentrations of free radicals such as nitric oxide that may directly damage cells (14) cause axonal degeneration or block axonal conduction, especially in axons that are physiologically active (16).

Hernán *et al.* (16) found that ever smokers with RRMS converted to SPMS at a faster rate than non smokers. In contrast Koch *et al.*, in a retrospective study found that cigarette smoking was not significantly associated with the development of secondary progressive MS or progression of clinical disability as measured by the Expanded Disability Status Scale (EDSS) (8).

Since no modifiable risk factors for multiple sclerosis progression have been identified so far, determining whether cigarette smoking affects the course of multiple sclerosis can be taken as

a priority (16). In this study we therefore examine the association between smoking and the course of MS disease, such as the influence of smoking on neurologic disability, on the evolution to a secondary progression course and its impact on quality of life.

MATERIALS AND METHODS

Setting and Participants

The study is comprised with patients regularly followed at Neurology Department of Centro Hospitalar e Universitário de Coimbra (CHUC). Participants with MS were recruited from follow-up consultations during a three-month period from 10/09/2013 to 10/12/2013. All patients were diagnosed with definite MS according to the revised 2005 McDonald criteria (17) and presented either a RRMS or a SPMS clinical subtype.

Clinical and demographic data of participants were collected prospectively through the use of medical records and through thorough, face-to-face, questionnaires. Data included gender, age, disease subtype, age of disease onset and age of secondary progression onset, EDSS score, number of relapses in the last year and use of immunomodulating therapy (IMT) (18).

Smoking History

Information 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 smoked pack-years until participation in this study, before onset of MS and after onset of MS, was calculated for every patient. A pack-year was defined as 20 cigarettes smoked per day for 1 year.

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

Moreover, the smoking status at disease onset was also determined and classified as regular and non-smokers. Since it was no possible to determine accurately the smoking status of the second-hand smokers at the time of disease onset, they were not considered for this purpose.

Evaluation of Quality of Life

The Portuguese version of MusiQol (19) was used to determine the influence of smoking on quality of life. The MusiQoL is a disease-specific questionnaire describing nine dimensions (Activity of Daily Living, Psychological Well-Being, Symptoms, Relationships With Friends, Relationships with Family and Relationships with Health Care System, Sentimental and Sexual Life, Coping and Rejection) and yielding a global index score (0-100).

Data Analysis and Statistics

Categorical variables were characterized by absolute and relative frequencies, ordinal variables by median (minimum and maximum) and continuous variables by mean and standard deviation.

Comparison of groups according the smoking status was performed using the one-way analysis of variance (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-square test was used for categorical data. Pearson's product moment correlation was examined between EDSS and disease duration, pack-year before and after disease onset, age of smoking initiation and smoking duration after disease onset. Forward stepwise linear regression models (entrance criterion $p<0.05$ and exit criterion $p=0.10$) were generated in order to examine the association of age of MS onset with age of smoking initiation, pack-year before disease onset, gender and education level.

All analyses were conducted using SPSS for Windows version 19.0.0.2. (SPSS Inc, Chicago,IL).

Multiple regression and ANOVA models were evaluated using standard procedures to ensure that final models met the underlying assumptions required by these statistical techniques. Significance for hypothesis-testing analyses was set at $p<0.05$.

RESULTS

Subject characterization

The entire sample consisted of 120 patients, all Caucasian, 88 (73,3%) female, with a mean age of 44,05 (±12,56) years. The mean age of disease onset was 32,19 (±10,30) years while the mean disease duration was 12,27 (± 10,35) years. The majority, 87,5% had a Relapsing-Remitting clinical course, with only 12,5% presenting a Secondary-Progressive clinical

course of MS. The mean age of secondary progression onset was 48,80 (±8,59) years after a mean disease duration of 18,9 years (±13,80). The median EDSS was 2,0 (0-7,5).

The demographical and clinical characteristics are summarized in Table 1.

Table 1 - Demographical and clinical characteristics of all patients

N=120		
Gender (FR, %)		
Male	32	26,7
Female	88	73,3
Age (mean, min.-max.)	44,1	18 – 76
Level of Education (FR, %)		
Basic	37	30,8
Secondary	29	24,2
University	54	45,0
Occupation (FR, %)		
Employed	74	61,7
Retired	35	29,2
Student	6	5,0
Unemployed	5	4,2
Clinical Course (FR, %)		
RRMS	105	87,5
SPMS	15	12,5
EDSS (median; min.-max.)	2,0	0,0-7,5
Relapse (FR; %)	33	27,5
IMT (FR,%)		
Beta-interferon	69	57,5
Glatiramer Acetate	14	11,7
IVIG	1	0,8
Natalizumab	11	9,2
Fingolimod	5	4,2
Classic Imunossupressors	13	10,8
Metilprednisolone IV/Monthly	2	1,7
No-treatment	5	4,2

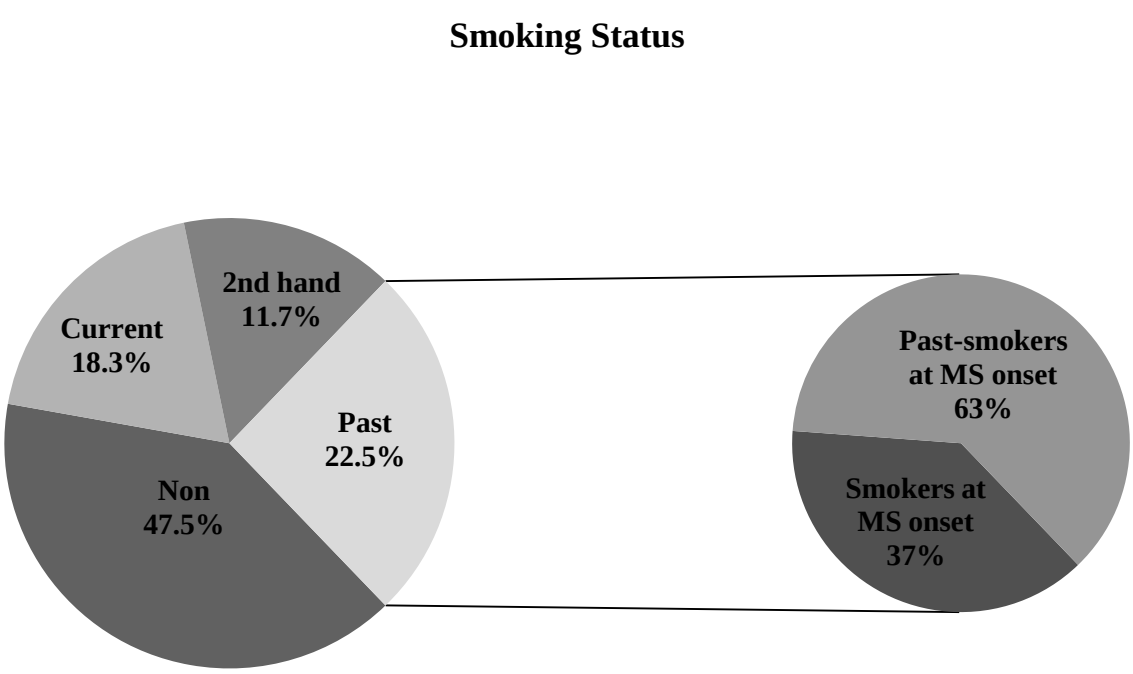
FR=frequency; RRMS=relapsing remitting MS; SPMS=secondary-progressive MS; IMT=immunomodulating therapy; EDSS=Expanded Disability Status Scale

Smoking Status Characterization

Considering the current smoking status, 22 patients (18,3%) were current-smokers, 57 (47,5%) were non-smokers, 27 (22,5%) were past-smokers and 14 (11,7%) were second hand-smokers. Regarding the smoking status at disease onset, 32 (26,7%) were regular-smokers.

From the 27 past-smokers, 17 (63,0%) patients had quitted smoking before the onset of the disease and 10 (37,0%) patients stopped smoking an average of 10,60 (± 8,59) years after the disease onset. (Graphic 1) The mean age of tobacco smoking initiation was 17,16 (±3,50) years.

Graphic 1 - Smoking status



Smoking and Multiple Sclerosis clinical course

1. Smoking status at the time of disease onset

We found that the age of MS onset was significantly lower in the group of regular-smokers at the time of the disease onset (29,53 ±10,04 years) compared to non-smokers (34,19 ±10,10

years), p=0,031. There were no other significant differences between the two groups, regarding the mean age, median EDSS score, clinical subtype or age of progression. (Table 2)

Table 2 - Comparison of characteristics amongst smoking status at disease onset

N=106	**Non-smoker 69,8% n= 74**	**Smoker 30,2% n=32**	***p-value***
Age (yrs) mean (±SD)	45,59 (13,00)	42,28 (10,40)	0,205#
Age disease onset mean (±SD)	34,19 (10,10)	29,53 (10,04)	0,031#
Clinical Course FR (%)			0,482*
RRMS	65 (87,8)	29 (90,6)	
SPMS	9 (12,2)	3 (9,4)	
EDSS median	2,78	2,63	0,697#
Age progression mean (±SD)	50,22 (9,83)	40,67 (7,50)	0,159#

*Chi-Square Test
ANOVA test

The linear regression model used for predicting the age of disease onset in MS patients, retained the age of smoking initiation (standardized β 0,40 ; R^2 change 0,14; p=0,001) and pack-year before disease onset (standardized β 0,73 ; R^2 change 0,32; p<0,001) as the only significant predictors. The other clinical variables, namely gender and education level, were not identified as predictors of age of MS onset.

2. Current smoking status

In our cohort, as shown in Table 3, we found that disease duration was significantly different across the four groups, with current-smokers having a lower disease duration (9,59 ±6,43) compared to non-smokers (11,98 ±9,65), past-smokers (14,96 ±12,37) and second hand-smokers (12,43 ±13,40) with *p*=0,05.

Moreover we found a statistical significant difference in the gender distribution throughout the different statuses. There was a predominance of female patients in all groups except in the past-smokers where there was a male predominance (63,0%).

No statistical difference was found in the mean age, age of disease onset, clinical course and EDSS median accordingly the actual smoking status.

Table 3 - Comparison of characteristics amongst smoking statuses groups

N=120	**Non-smoker (47,5%) n= 57**	**Current-smoker (18,3%) n=22**	**Past-smoker (22,5%) n=27**	**Second hand-smoker (11,7%) n=14**	***p-value***
Age (yrs) mean (± SD)	44,74 (12,96)	41,00 (9,33)	47,22 (12,72)	39,93 (14,07)	0,320#
Gender FR(%)					0,000*
Female	50 (87,7)	15 (68,2)	10 (37,0)	13 (92,9)	
Male	7 (12,3)	7 (31,8)	17 (63,0)	1 (7,1)	
Age onset mean (±SD)	33,19 (10,37)	32,36 (8,66)	32,26 (11,51)	27,71 (9,84)	0,318#
Duration (yrs) mean (±SD)	11,98 (9,65)	9,59 (6,34)	14,96 (12,34)	12,43 (13,40)	0,050#
Relapses in the last year	0,51	0,32	0,29	0,19	0,231#
Clinical Course FR (%)					0,167*
RRMS	50 (87,7)	22 (100)	22 (81,5)	11(78,6)	
SPMS	7 (12,3)	0 (0)	5 (18,5)	3 (21,4)	
EDSS median	2,82	2,00	3,15	3,00	0,168#

*Chi-Square Test
ANOVA test

When analyzing the relation of EDSS with disease duration, pack-year before and after disease onset, age of smoking initiation and smoking duration after MS onset, we found a strong correlation with disease duration (r=0,673 ; *p*<0,001). Still, the pack-year after MS onset (r=0,214 ; *p*=0,028) and smoking duration after MS onset (r=0,387; *p*=0,026) were also significantly correlated. (Table 4)

Table 4 - Pearson Correlation

	EDSS R	***p-value***
Disease duration	0,673	<0.001
Pack-year before MS onset	0,074	0,454
Pack-year after MS onset	0,214	0,028
Age smoking initiation	-0,011	0,937
Smoking duration	0,387	0,026

When analysing the impact of the current smoking status on the EDSS accordingly the clinical subtype, we did not find any significant association in the RRMS group. However, in the SPMS group the EDSS median was significantly higher in ever-smokers (7,0) and second hand-smokers (6,83) compared to non-smokers (5,50) (*p*=0,013). Although not statistically significant, there was a tendency for an earlier progression in the ever-smoking group with a mean age of 44,60 (±9,66) years, compared to the non-smoking group 50,14 (±10,24) and the second hand-smoking group 52,67 (±8,33). (Table 5)

Table 5 - Comparison of characteristics amongst smoking statuses in SPMS

N=15	Non-smoker n= 7	Ever-smoker n= 5	Second hand-smoker n= 3	*p- value*
Age onset mean (± SD)	32,00 (9,02)	26,00 (10,03)	31,67 (16,44)	0,332#
Duration (yrs) mean (±SD)	26,29 (13,46)	32,20 (11,71)	27,67 (23,46)	0,319#
Age Progression (yrs) mean (±SD)	50,14 (10,24)	44,60 (9,66)	52,67 (8,33)	0,906#
EDSS median	5,50	7,00	6,83	0,013#

ANOVA test

Smoking and Quality of Life

MusiQoL is a questionnaire that assesses quality of life in several aspects of daily routine. In this test the higher the value, the better a patient's quality of life. We compared the mean scores of each dimension as well as the global score of the MusiQoL questionnaire considering the current smoking status groups.

We found no statistical difference in mean Total Index score in the MusiQoL even though there is a tendency of being lower in the current-smoker group when compared to non-smoker, past-smokers and second hand-smokers group.

When analyzing each dimension of the MusiQoL separately, mean score for Relationships with Family dimension was significantly lower in current-smoker (62,30 ±32,13) and second hand-smoker groups (76,92 ±30,08) compared to non-smokers (84,67 ±25,94) and past-smokers (84,30 ±28,12) (p=0,019). Another domain we found statistically significant different was the Sentimental and Sexual Life (Relationships). Worst mean scores were attributed to current-smoker (51,19 ±32,81) and second hand-smoker groups (68,75 ±28,95) when compared with non-smokers (71,39 ±32,49) and past-smokers (76,44 ±21,89) (p=0,030).

The domains of Activity of Daily-Living, Symptoms, Psychological Well-Being, Relationships with Friends, Coping, Rejection and Relationships with Health Care System did not present any significant difference (Table 6).

Table 6 - MusiQoL means score for all participants

N=120	Non-smoker	Current-smoker	Past-smoker	Second hand-smoker	*p-value*[#]
QoL activities**, mean (± SD)**	63,58 (28,81)	71,88 (22,58)	62,86 (34,25)	60,38 (34,88)	0,648
QoL psychological**, mean (± SD)**	56,50 (28,18)	57,74 (17,89)	64,18 (25,66)	70,67 (25,18)	0,255
QoL symptoms**, mean (± SD)**	63,13 (25,64)	61,61 (33,01)	63,70 (26,64)	76,44 (17,33)	0,289
QoL friends**, mean (± SD)**	71,60 (24,65)	65,87 (33,01)	74,04 (27,92)	75,00 (26,35)	0,724
QoL family**, mean (± SD)**	**84,67 (25,94)**	**62,30 (32,13)**	**84,30 (28,12)**	**76,92 (30,08)**	**0,019**
QoL relationships**, mean (± SD)**	**71,39 (32,49)**	**51,19 (32,81)**	**76,44 (21,89)**	**68,75 (28,95)**	**0,030**
QoL coping**, mean (± SD)**	60,00 (31,14)	59,52 (31,35)	56,00 (32,70)	65,39 (31,93)	0,857
QoL rejection**, mean (± SD)**	79,17 (25,31)	80,92 (24,07)	88,50 (17,65)	77,89 (36,50)	0,457
QoL health care, **mean (± SD)**	77,61 (22,14)	73,02 (25,40)	72,12 (25,70)	84,72 (17,71)	0,397
QoL total Index, mean (± SD)	68,48 (16,29)	65,28 (18,17)	69,59 (14,39)	70,95 (19,36)	0,758

ANOVA test

When analysing the SPMS group separately we found a level of significance for the Activity of Daily Living and Relationship with Family with according *p-values* of 0,010 and 0,001. In Activity of Daily Living the lowest mean was for the second hand-smokers (6,25 ±6,25), following the ever-smokers (10,00 ±12,77) and lastly the non-smoker (39,59 ±19,13) . In the Relationship With Family we found worse mean scores for the second hand-smoker (38,89 ±34,70,) the rest of the groups manifested almost perfect means scores (91,67 ±8,34) for the ever-smoker and (100,00 ±0) for the non-smokers.

The domains of Symptoms, Psychological Well-Being, Relationships with Friends, Sentimental and Sexual Life, Coping, Rejection and Relationships with Health Care System and Total Index did not present any statistical difference (Table 7).

Table 7 - MusiQoL means score for SPMS

N=15	Non-smoker	Ever-smoker	Second hand-smoker	*p-value*[#]
QoL activities**, mean (± SD)**	**39,59 (19,13)**	**10,00 (12,77)**	**6,25 (6,25)**	**0,010**
QoL psychological**, mean (± SD)**	43,75 (26,81)	42,50 (17,34)	52,08 (41,61)	0,882
QoL symptoms**, mean (± SD)**	50,00 (29,05)	63,75 (23,55)	58,33 (14,43)	0,666
QoL friends**, mean (± SD)**	70,83 (18,82)	85,00 (18,07)	44,45 (38,49)	0,103
QoL family**, mean (± SD)**	**100,00 (0)**	**91,67 (8,34)**	**38,89 (34,70)**	**0,001**
QoL relationships**, mean (± SD)**	57,50 (37,08)	70,00 (18,96)	41,67 (38,19)	0,489
QoL coping**, mean (± SD)**	65,00 (22,36)	80,00 (32,60)	50,00 (25,00)	0,418
QoL rejection**, mean (± SD)**	79,17 (25,31)	88,50 (17,65)	33,33 (57,74)	0,252
QoL health care, **mean (± SD)**	84,72 (20,01)	80,00 (17,28)	83,33 (28,87)	0,933
QoL Index total, mean (± SD)	61,50 (15,59)	58,05 (11,03)	45,37 (15,06)	0,297

ANOVA test

DISCUSSION

Cigarette smoking became widespread amongst men in the developed world by the middle of the 20th Century (14) but, it was a relatively new movement among women. Smoking prevalence in women increased while prevalence in men decreased, resulting in a trend towards an increasing female: male ratio in smokers (14). While our study had considerably more female participants, being that MS is mostly a female affecting disease, we confirm that the masculine gender, even when less in size, is more prone to have smoked in the past, being more prevalent in the past-smoker group.

In this study we found noteworthy that MS onset was earlier in the regular-smokers at the time of disease onset, suggesting that smoking could be a potential environmental factor involved in the intricate process of MS etiopathogenesis. It is currently known that smoking is a significant factor for the development and progression of several autoimmune diseases (18), by altering the innate and adaptive immune cells, having pro-inflammatory and inhibitory effects. In MS, it has been clearly demonstrated in several studies that smokers have a higher risk of developing the disease (15), by acting on cellular and humoral components of the immune system, having pro-inflammatory and inhibitory effects as well as direct damage on the cells (14).

On the other hand, our study suggests that smoking impact on the prognosis of MS is not significant in the earlier phase of the disease (RRMS), becoming only apparent in the later secondary progressive phase with ever-smokers and second-hand smokers having higher EDSS scores comparing to the non-smokers. Moreover, we found a tendency towards an earlier progression in the ever-smokers. We could hypothesize that this delayed effect of smoking on MS prognosis results most likely from neurotoxic effects of the constituents of cigarette smoke (20), namely the free radical nitric oxide (NO). Cigarette smoking is a major

exogenous source of NO, and nicotine induces the production of NO in the CNS (14). NO metabolites in the cerebral spinal fluid (CSP) may contribute to axonal degeneration (15) and persistently elevated levels of NO metabolites in the CSF are associated with clinical progression of MS (14). These elevated NO levels would contribute to axonal degeneration and thus to the permanent deficits observed in the secondary progressive forms of the disease. Other hypothesized mechanisms relating smoking and multiple sclerosis include chronic cyanide intoxication leading to widespread demyelization along with selective loss of oligodendroglia (16).

Our results are in accordance with the results from an observation by D'hooghe *et al.* (2012) and Manouchehrinia *et al.* (2013) which showed higher risk of reaching a higher EDSS score amongst cigarette consumers. Herman et al. reported a three-fold higher rate of conversion in smokers as compared to non smokers. This finding suggests that cigarette smoking may transform, or hasten the transformation of, relapsing–remitting forms of the disease into progressive forms (15,16). The Sundström *et al.* (2008) study suggests, as well, that ever smokers develop progressive disease earlier after MS onset (21).

As in Manouchehrinia *et al.* (2013), we presented evidence of the potential beneficial effects of smoking cessation on disability progression in patients with multiple sclerosis. While the effect of the pack-year after disease onset on EDSS score in the SPMS patients is significant, there was no relation with the pack year in the past thus, there are positive effects of smoking cessation on disease progression even after multiple sclerosis onset (18). However this is a particularly challenging subject and should be looked at more carefully in future studies.

Finally, we aimed to evaluate the impact of smoking on quality of life of MS patients. It is currently known that MS has a negative impact on the quality of life (22) and therefore it has become an endpoint in clinical trials. In our study, some domains of quality of life were worst

in the current-smoker group when compared with the rest of the patients of the study. The patients with SPMS clinical course had lower mean scores than the ones with RRMS clinical course. As expected the patients with SPMS, due to their advanced disability, led a much more complex everyday life with worst quality of living. We found particularly interesting the fact that the second hand-smokers in the SPMS had worst means in the Family Relationship domain. We can only hypothesise that the family members are the ones exposing them to smoking against their will thus, creating strain among them.

There are some limitations to this study that must be considered, mostly the retrospective methodology and the limited sample size. Prospective adequately powered studies are required to properly confirm these results and find other significant associations. A better assessment and a possible quantification of the smoking dosage exposed in the second hand-smoking should also be considered.

CONCLUSION

In summary, we found that MS seems to start earlier in the smokers and that the long term prognosis is worse, accumulating more disability and presenting inferior quality of life. Moreover, our findings point towards the beneficial effect of smoking cessation even after the disease onset.

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