Smoking and Health-Related Quality of Life in Patients With Multiple Sclerosis From Latin America

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Running head: Smoking, HRQOL, and MS in Latin America

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Practice Points

- Smoking is a relevant, modifiable environmental risk factor for multiple sclerosis (MS) that has a critical impact on quality of life.
- Individuals with MS from Latin America who smoke tobacco had higher fatigue scores and worse quality of life compared with those who never smoked.
- Approximately one-third of treating neurologists do not discuss smoking cessation with their patients.
- Smoking cessation should be a priority for neurologists treating individuals with MS.

Abstract

Background: Tobacco smoking is an important, modifiable, environmental risk factor for multiple sclerosis (MS) with a relevant impact on health-related quality of life (HRQOL). We aimed to assess the use of tobacco in individuals with MS from Latin America (LATAM), and its impact on HRQOL.

Methods: We conducted a cross-sectional study based on a LATAM web-based survey. Demographics, social and clinical data, information on physical disability, and HRQOL scores were collected using the MS Impact Scale-29 (MSIS-29), the Fatigue Severity Scale (FSS), and the Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Individuals with MS were classified at the time of the survey as follows: never-smokers (ie, patients who reported they had never smoked), past smokers (those who had smoked tobacco but not during the past year), or current smokers. For the analysis, groups were compared.

Results: 425 patients (74.6% female) from 17 LATAM countries were included, mean age 43.6 ± 11 years and median Expanded Disability Status Scale score 2. There were 122 (28.7%) current smokers, 178 (41.9%) past smokers, and 125 (30.4%) never-smokers. Current smokers had significantly higher MSIS-29 physical (physical worsening), FSS (fatigue), and HADS-A (anxiety) scores compared with past and never-smokers after being adjusted for covariables. No significant differences were observed in any of the other analyzed demographic, clinical, and therapeutic variables. Thirty percent of the current and past smokers groups had never had their neurologists discuss smoking cessation with them.

Conclusions: Individuals with MS who were current smokers had higher fatigue and anxiety scores and worse HRQOL compared with past and never-smokers. *Int J MS Care*. 2024; XX:XXX-XXX.

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, immune-mediated, and neurodegenerative disease of the central nervous system (CNS). It usually affects health-related quality of life (HRQOL), especially among young adults during their critical years of social and work productivity.[1] Although the etiology of MS is not completely understood, there are several studies that support the hypothesis that autoimmunity plays a critical role in the genesis of this disease.[2] As in other autoimmune diseases, there is relevant evidence suggesting that MS arises from complex interactions between genetic susceptibility and environmental factors.[3,4] In this context, cigarette smoking is an important and well-known modifiable environmental risk factor for MS with a high impact on HRQOL in affected patients.[5,6] In addition, cigarette smoking has been associated not only with a higher risk of MS, but also with greater MS inflammatory activity and progression.[7] Cigarette smoking may also increase the risk of premature mortality[8] and could affect the effectiveness of disease-modifying therapies (DMTs) for MS.[9] The lack of awareness of and treatment for this habit can lead to worse patient outcomes. Several studies have recommended that smoking cessation should be a priority for neurologists who treat MS in clinical practice.[10] However, there is limited information about patient knowledge about the impact of smoking tobacco and the unmet needs of MS patients regarding smoking cessation and its relationship with MS.[11,12] Thus, we aimed to assess cigarette smoking and its impact on HRQOL and neuropsychological aspects in individuals with MS who reside in Latin America (LATAM).

Methods

A cross-sectional study was conducted between January and March 2022. A large cohort of MS patients from LATAM were sent a web-based, self-administered, voluntary, and anonymous questionnaire from treating neurologists and 2 MS organizations, Asociación de Lucha contra la Esclerosis Múltiple (ALCEM) and the Latin American MS Organizations Network (LATEM). The survey was developed in Spanish and underwent a pilot process to

ensure that the items accurately addressed the research questions. We were not able to calculate a response rate due to the study design and the diffusion of the survey.

This study was approved by the Hospital Alemán Ethics Committee, Buenos Aires, Argentina. All participants signed an electronic informed consent form before data collection.

Screening Instruments

Sociodemographics and Clinical Data

Data on age (at time of survey), sex, MS course (relapsing-remitting MS [RRMS], primary progressive MS [PPMS], secondary progressive MS [SPMS]), MS duration, MS relapses in the past 6 months, employment status, education level, and use of DMTs were collected.

Definition of a Smoker

Respondents were classified based on tobacco use over the past year as "current smoker" (CS), those who currently smoke at least 1 cigarette per day; "former smoker" (FS), those who had smoked tobacco but not during the past year; or "never-smoker" (NS). These classifications are in line with previous studies.[13,14] Another study characterized smokers as never-smokers (those who reported that they had never smoked), past smokers (those who had smoked tobacco but not during the past year), or current smokers.[15] We quantitatively evaluated the use and frequency of smoking, motivators for smoking, and barriers and facilitators to smoking cessation (cessation preferences) of current or former smokers who have MS. Additionally, we evaluated patients' knowledge about smoking tobacco and MS.

Impact of MS (HRQOL in MS)

HRQOL was determined by the MSIS-29 scale, which is a specific measure to evaluate the HRQOL in MS patients.[16] The MSIS-29 is a 29-item self-administered instrument that measures the physical (20 items) and psychological (9 items) impact of MS on daily life over the past 2 weeks from the patient's perspective. Scores for each item range from 1 (not at all) to 5 (extremely). Each of the scales are scored by summing the responses across items; therefore, a physical impact score can range from 0 to 100 and a psychological impact score can range from 0 to 45. The higher the score, the greater the degree of disability.

Fatigue Severity Scale (FSS)

Fatigue was assessed by the FSS, a self-report questionnaire with 9 items. Scores for each item range from 1 (lowest fatigue level) to 7 (highest fatigue level). Patients with total scores ≥45 are diagnosed as presenting with fatigue.[17]

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item self-report measure with 2 subscales that is used as a brief instrument for detecting the intensity of depression (HADS-D) and anxiety (HADS-A) in patient populations.[18] HADS yields scores on a 0 to 21 scale and the presence of anxiety (HADS-A) and depression (HADS-D) is confirmed when individuals with MS score ≥8 on these assessments. In addition, HADS has been shown to have high sensitivity and specificity in relation to clinical surveys and other mood-rating scales in MS patients.

Neurological Disability

Neurological disability was evaluated by a self-administered Expanded Disability Status Scale (EDSS) that is based on the Patient-Determined Disease Steps (PDDS) scale,[19-21] which has proven to be highly correlated with a neurologist-scored EDSS (95% of feasibility and reliability), per findings from Kobelt et al.[22] Patient-reported EDSS scores range from 0 (without disability) to 9 (confined to bed).

Statistical Analysis

Statistical analysis was performed using Stata v13 (StataCorp LP). Clinically relevant variables are presented using descriptive statistics. Categorical variables are shown as frequencies and percentages, and continuous variables are means and standard deviation or median and interquartile range. Normality was assessed via the Shapiro-Wilk test. Univariate comparisons were conducted using a *t* test or a Mann-Whitney U test for continuous variables depending on the normality. Fisher exact tests or χ^2 were used to compare categorical data, as appropriate. The Kruskal-Wallis 1-way analysis of variance, a nonparametric test, was used to estimate differences between more than 2 groups (CS, FS, NS) and a post hoc analysis,

when appropriate, was conducted using Dunn's multiple comparison test. For all the analyses, the significance level was established as $P < .05$.

Results

As shown in **Table S1**, 425 patients from 17 LATAM countries were included in this study. They had a mean age of 43.6 ± 11 years, 317 (74.6%) were female, and their median EDSS was 2 (range 0-9). A total of 122 (28.7%) were CS, 178 (41.9%) were FS, and 125 (30.4%) were NS (**Table 1**).

As shown in **Table 2**, CS had significantly higher MSIS-29 physical, FSS, and HADS-A scores compared with FS and NS. No significant differences were observed in the rest of the analyzed demographic, clinical, and therapeutic variables.

As shown in **Table S2**, there were no significant differences in mean age (43.2 vs 44.5; $P = .26$), phenotype (RRMS 81.6% vs 71.2%; $P = .09$), DMTs received (84.3% vs 81.6%; $P = .23$), or EDSS (2.66 vs 2.52; $P = .65$) were observed after analyzing 300 CS and FS, and 125 NS. However, significant differences were observed in CS and FS vs NS in scores for fatigue (39.4 ± 1.0 vs 32.2 ± 1.1; $P = .01$), MSIS-29 physical (50.3 ± 1.7 vs 45.5 ± 1.2; $P = .01$), and HADS-A (11.1 ± 3.1 vs 6.3 ± 2.3, $P < .001$) when adjusted for covariables.

We found that 15% of all patients (N=425) had never talked with their treating neurologist about smoking. Of CS and FS (n=300), 47% had never had a specific smoking cessation therapy recommended; 35% had received advice or information about smoking cessation; 23% had not discussed smoking cessation; 18% had never discussed their smoking habit; and 17% had not received any recommendation on whether to quit smoking (**Table S3**).

Discussion

This is one of the first studies in the LATAM region that evaluates the impact of smoking tobacco on HRQOL in individuals with MS. Fatigue and anxiety levels are higher in individuals with MS who are CS compared with FS or NS. Smoking also has more of an impact on daily life, as individuals with MS who are CS had higher MSIS-29 physical scores.

The higher scores were not related to disease severity nor to treatment received. Interestingly, according to 14.5% of individuals with MS who smoke, their treating neurologist did not ask about current tobacco status during clinical evaluations.

Currently, more than 1.3 billion people smoke cigarettes worldwide, and each year, about 30 million people become new smokers.[23,24] The average proportion of daily tobacco users in LATAM as a whole is around 25%,[25] but is higher in Argentina at 33.4%.[26] Based on these reports, the percentage of CS (28.7%) is in line with previous data.

Women have an increased risk of developing MS and some studies show that the female-to-male sex ratio in MS has increased over the last few decades;[26] thus, the increase in female smokers may be associated with the increase in the female-to-male ratio for individuals with MS.[27]

Previous studies have shown the effect of tobacco on MS. In a population-based case-control study (2455 cases and 5336 controls), Hedström et al[10] assessed the risk of developing MS related to different categories of tobacco smoke exposure. The authors also evaluated the risk attributable to passive smoking. Both active and passive smoking contribute to MS risk in a dose-dependent manner. Overall, 20.4% of all cases in the cohort were attributable to smoke exposure (active or passive). Active smoking was responsible for 33% of the MS cases, and among NS exposed to passive smoking, 12% of the cases were attributable to passive smoking, consistent with what was found in the present study. Passive smoke exposure was associated with an increased MS risk in a dose-dependent manner among NS ($P = .006$). Active smoking was also associated with a dose-dependent increased risk of MS ($P < .0001$). Members of the Swedish cohort who reported smoking more than 10 pack-years (ie, number of packs per day multiplied by the number of years an individual has smoked) or exposure to passive smoking for more than 20 years had a nearly 3-times higher risk of developing MS compared to members of the cohort who reported no exposure to tobacco smoke (OR = 2.7, 95% CI, 2.0-3.8).

Hedström et al[10] also explored the genetic aspect and the presence of HLA-DRB1*15 and absence of HLA-A*02; in the study, 41% of MS cases (ie, 23 of 55 of the cases) were attributable to smoking.[10] Another study from Sweden found that the risk of MS in participants who were CS or FS was 41% (95% CI, 1.33-1.50) higher than that of never-smokers.[28] Notably, the population-attributable fraction[28] of MS was less than 1% (0.6%;

95% CI, 0-2) in ex-smokers, indicating the beneficial effects of smoking cessation.[29] After evaluating HLA and non-HLA risk scores, the study indicated that at least 13% of MS cases might be prevented through the avoidance of tobacco smoking.[28]

A recent systematic review evaluated the association between tobacco smoking and depression and anxiety in MS patients,[30] specifically whether CS or FS are at an increased risk of depression and/or anxiety compared to NS. A total of 13 studies reporting on 12 individual studies were eligible for research inclusion, with 2 studies analyzing data from the same study both cross-sectionally and 1 prospectively.[30] In studies by Jasielski et al[31] and Gascoyne et al,[32] 4 prospective studies provided evidence supporting a causal smoking-depression relationship, with a 1.3- to 2.3-fold higher depression prevalence in CS than NS. The possible mechanism could be related to CNS impairment and/or inflammatory damage that may exacerbate mental health disorders in individuals with MS. CNS inflammation may partially explain the role of smoking in increased MS activity via chronic lung inflammation and increased proinflammatory cytokines and/or neurotoxic components. Returning to Vong et al,[30] 3 cross-sectional studies found no smoking-depression association and 4 studies found current smoking was associated with anxiety, with 3 indicating that anxiety prevalence was around 20% higher in CS. Past smoking was associated with an increased prevalence of depression, but not anxiety. The authors concluded that there is strong evidence for increased depression prevalence in individuals with MS who are either CS or FS. However, only CS were associated with an increased prevalence of anxiety based on the studies.

Given that smoking is a modifiable risk factor in MS (development and progression), recommending the cessation of tobacco smoking is a relevant part of clinical care. However, several MS-specific barriers to smoking cessation have been identified in qualitative studies,[33,12] and patients have expressed insecurity about whether nicotine replacement therapy is safe for people with MS or in combination with DMTs. For individuals with MS, smoking cessation reduces the frequency of relapses and slows the transition to SPMS. One study showed that people who quit smoking after their MS diagnosis, who then went on to develop SPMS, did so 8 years later than those who continued to smoke.[34] The findings suggest that neurologists should advise patients to quit smoking in order to avoid aggravating MS-related disability, but our survey results show that 30% of the patients in the CS and FS groups had never had their neurologist talk to them about smoking cessation.

Our study has some limitations. As a cross-sectional web-based study, changes made during follow-up to evaluate causality could not be determined. Notably, self-reported questionnaires may overestimate some values, so these findings should be interpreted within this context. In addition, using a self-administered online survey may lead to potential recall, referral, selection, and social desirability bias. This cohort was limited to patients who have access to the internet and are somewhat familiar with online tools. It is possible that potential respondents may have not responded due to an inherent denial of anything related to smoking. Therefore, this cohort cannot represent the whole LATAM population. Despite these limitations, this is a relevant initial study that evaluated patients' knowledge about the relationship between and impact of smoking tobacco and MS.

Conclusions

We found that individuals with MS who are current smokers have a decreased HRQOL with higher levels of fatigue, anxiety, and disease impact. They also reported that approximately on-third of neurologists do not discuss smoking or smoking cessation during their periodic clinical evaluations. Considering the relevance that smoking has on developing MS, early disease progression, heightened disease activity, and its association with worse HRQOL, clinicians should put a greater focus on this topic in order to provide information and support to their patients.

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Table 1. General Characteristics of the Studied LATAM Population

N	425
Mean age at survey, year, (± SD)	43.6 ± 11
Female, n (%)	317 (74.6)
MS duration, mean ± SD (range) year	8.8 (7.8) years (0-36 years)
MS course, n (%)	
RRMS	334 (78.6)
PPMS	39 (9.2)
SPMS	30 (7.1)
Unknown	22 (5.2)
EDSS, median (range) at survey	2 (range 0-9)
EDSS, mean (± SD) at survey	2.6 ± 2.3
Last relapse, n (%)	
< 6 months	86 (20.2)
Live, n (%)	
Alone	84 (19.8)
With spouse or partner	341 (80.2)
Education level, n (%)	
Primary school	9 (2.1)
High school	130 (30.6)
Tertiary education	111 (26.12)
University	175 (41.2)
Employment status, n (%)	
Employed (full-time)	159 (37.4)
Employed (part-time)	61 (14.3)
Unemployed	41 (9.6)

Self-employed	50 (11.7)
Housewife	29 (6.8)
Retired	23 (5.4)
Retired because of MS	40 (9.4)
Currently studying	22 (5.2)
Fatigue Severity Scale score	
Mean (± SD)	37.8 ± 15
MSIS-29 score	
Physical impact, mean (± SD)	46.3 ± 14.3
Physiological impact, mean (± SD)	27.8 ± 11.4
HADS, n (%)	
Depression	
≥ 8	179 (42%)
Median (± SD)	4.5 ± 4
Anxiety	
≥ 8	158 (37.2)
Median (± SD)	7.5 ± 5.6
Use of medications, n (%)	355 (83.5)
Injectables	
IFN, Pegylated IFN, GA	97 (22)
Oral	
Fingolimod, teriflunomide, dimethyl fumarate	186 (46)
Intravenous	
Natalizumab, alemtuzumab, ocrelizumab	72 (16)
None	70 (16.5)

EDSS, self-administrated Expanded Disability Status Scale; GA, glatiramer acetate; HADS, Hospital Anxiety and Depression Scale; IFN, interferon; MS, multiple sclerosis; MSIS-29, MS Impact Scale-29; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

Table 2. Between Group Comparison of Demographic, Clinical, Neuropsychological, and Health-Related Quality of Life Factors

	Current smoker N=122	**Past smoker N=178**	**Never-smoker N=125**	***P* value**
Age	39.4 ± 3.2	43.2 ± 3.2	44.5 ± 2.1	.35
Female	86 (70.5)	136 (76.4)	95 (76)	.54
Live alone	30 (25)	33 (18.5)	21 (16.8)	.19
RRMS	103 (84.4)	142 (79.7)	89 (71.2)	.06
MS duration	8.3 ± 0.47	8.8 ± 0.56	9.33 ± 0.73	.62
EDSS	2.0 ± 0.5	3.0 ± 0.10	2.52 ± 0.21	.88
FSS	**40.3 ± 1.4**	**36.3 ± 1.3**	**32.2 ± 1.1**	**.008***
MSIS-PHYS	**51.4 ± 2.1**	**46.7 ± 1.3**	**45.5 ± 1.2**	**.007***
MSIS-PSYCH	29.4 ± 3.1	26.8 ± 1.9	25.4 ± 1.1	.23
HADS-D	6.6 ± 2.5	6.2 ± 2.3	5.3 ± 1.8	.24
HADS-A	**12.2 ± 1.6**	**8.4 ± 1.5**	**6.3 ± 2.3**	**< .001***
DMT	105 (86)	148 (83.1)	102 (81.6)	.33

DMT, disease-modifying therapy; EDSS, self-administrated Expanded Disability Status Scale; FSS, Fatigue Severity Scale; GA, glatiramer acetate; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; IFN, interferon; MS, multiple sclerosis; MSIS-PHYS, MS Impact Scale-29 physical; MSIS-PSYCH, MS Impact Scale-29 psychological; RRMS, relapsing-remitting MS.

Note: Bold indicates statistically significant values.

*Significant differences were found between current smokers and other groups.

Table S1. Participating Individuals by Country N = 425

Argentina	294
Chile	5
Colombia	9
Costa Rica	7
Cuba	7
Ecuador	8
Honduras	2
Mexico	2
Nicaragua	3
Panama	2
Peru	5
Dominican Republic	2
Uruguay	69
Venezuela	3

Table S2. Group Comparisons

	Current and former smokers n = 300	**Never smokers n = 125**	***P* value**
Age	43.2 ± 2.3	44.5 ± 2.1	.26
Female	222 (74)	95 (76)	.66
Live alone	63 (21	21 (16.8)	.19
RRMS	245 (81.6)	89 (71.2)	.09
MS duration	8.6 ± 0.44	9.33 ± 0.73	.44
EDSS	2.64 ± 0.15	2.52 ± 0.21	.65
FSS	**39.4 ± 1.0**	**32.2 ± 1.1**	**.01**
MSIS-PHYS	**50.3 ± 1.7**	**45.5 ± 1.2**	**.01**
MSIS-PSYCH	28.4 ± 2.5	25.4 ± 1.1	.09
HADS-D	6.3 ± 2.3	5.3 ± 1.8	.18
HADS-A	**11.1 ± 3.1**	**6.3±2.3**	**< .001**

DMT	253 (84.3)	102 (81.6)	.23

DMT, disease-modifying treatment; EDSS, self-administrated Expanded Disability Status Scale; FSS, Fatigue Severity Scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D Hospital Anxiety and Depression Scale-Depression; MS, multiple sclerosis; MSIS-PHYS, MS Impact Scale-29 physical; MSIS-PSYCH, MS Impact Scale-29 psychological; RRMS, relapsing-remitting MS.

Note: Bold indicates statistically significant values.

Table S3. Survey Questions and Results

Have you ever tried to quit smoking? If you have tried to quit smoking, how many attempts did you have? N=300

1	14%
2	22%
3	11%
4	4%
5	20%
I have not tried.	29%

Were any of these attempts after the multiple sclerosis (MS) diagnosis? N=300

Yes	53%
No	33%
I have not tried.	14%

If you have tried to quit smoking already knowing the diagnosis of MS, how many attempts did you have? N=300

1	35%
2	13%

3	6%
4	3%
5	7%
I have not tried.	36%

How long have you been able to stay without smoking? N=300

More than 1 week	11%
More than 2 weeks	4%
More than 1 month	68%
I have not quit smoking.	17%

Do you think your MS has an impact on how much you smoke? For example, do you smoke more if you have a relapse? N=300

Yes	80%
No	20%

Currently, are you thinking about quitting smoking? N=300

Yes	56%
No	44%

Is MS a motivator to quit smoking? N=300

Yes	66%
No	34%

Do you think that smoking affects the symptoms of MS? N=425

Yes	53%
No	6%
I don’t know	41%

Do you think you have been told enough about the impact of smoking on MS? N=425

Yes	69%
No	31%

Do you know if smoking can make your MS worse? N=425

Yes	52%
No	48%

Has your neurologist ever asked you if you smoked? N=425

Yes	85%
No	15%

Has your neurologist recommended that you should quit smoking? N=182

Yes	60%
No	17%
I have not tried	23%

Have you received advice or information on treatment for smoking cessation? N=195

Yes	37%
No	45%
I have not tried	18%