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Association between chronic tobacco smoking and cognitive function in persons with multiple sclerosis

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Multiple Sclerosis; Smoking; Cognition; Memory; Function

Abstract

Background: Cognitive impairment is common in multiple sclerosis (MS) and can markedly influence individuals' quality of life (QOL). Understanding the factors influencing cognitive dysfunction in MS is essential for developing targeted interventions. Smoking, a modifiable risk factor linked to numerous adverse outcomes in MS, has an unclear relationship with cognitive function. This comparative study with cross-sectional data collection aimed to examine the association between smoking and cognitive performance in persons with MS.

Methods: A total of 152 participants with MS were recruited, comprising 76 smokers and 76 non-smokers. Cognitive function was assessed using the Brief International Cognitive Assessment for MS (BICAMS), which includes the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II), and Brief Visuospatial Memory Test-Revised (BVMT-R). Cognitive impairment was defined as scores below 1.5 standard deviations (SDs) from the mean, and tobacco exposure was quantified in terms of pack-years. Analyses controlled for potential confounders such as age, education, and Expanded Disability Status Scale (EDSS) scores.

Results: Smokers performed significantly worse on the CVLT-II and BVMT-R ($P < 0.05$), while no differences were observed on the SDMT. After adjusting for confounders, only BVMT-R performance remained significantly associated with smoking status ($P = 0.009$, $\eta^2p = 0.049$). Smokers had higher odds of cognitive impairment on the BVMT-R [odds ratio (OR) = 11.8, $P = 0.002$]. Additionally, pack-year exposure correlated with declines in BVMT-R and CVLT-II scores ($P < 0.05$).

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Conclusion: These findings indicate an association between smoking and cognitive performance in MS, particularly in visuospatial and verbal memory domains. Further research is needed to explore underlying mechanisms and inform clinical strategies.

Introduction

Smoking is a well-known and modifiable behavioral risk factor for the development of multiple sclerosis (MS) and the progression of disability.[1-3] Research on smoking in MS has predominantly focused on its association with disease risk and disability progression; however, the number of studies examining various MS symptoms and health-related quality of life (QOL) has also increased over time. For example, several studies on persons with MS have found links between tobacco smoking and increased fatigue, depressive symptoms, anxiety, and a decline in health-related QOL.[4-7] Additionally, some studies have explored the connection between smoking and cognitive function in persons with MS. This is important because cognitive impairment is prevalent in MS, impacting 40%-70% of individuals at some points during their disease progression.[8] Persons with MS with cognitive difficulties are more likely to struggle with everyday functional activities and face unemployment, regardless of the extent of their physical disability.[9] The degree of cognitive impairment varies significantly among persons with MS and is affected by various disease-related factors, comorbidities, and health behaviors.[10,11] Since there is no established treatment, identifying modifiable factors that can prevent or slow cognitive decline is particularly crucial in the management of MS.[12-14]

Current smoking has been identified as a factor associated with cognitive impairment in persons with MS.[15,16] Conversely, Amato et al.[8] and Alirezaei et al.[17] did not observe a significant relationship between smoking and cognitive function in this population. We attribute this inconsistency to methodological differences across these studies. For example, Chow et al. assessed cognitive function using the Brief International Cognitive Assessment for MS (BICAMS) and quantified smoking exposure through pack-years.[16] In contrast, Ozcan et al. employed a comprehensive battery of neuropsychological tests named brief repeatable battery of neuropsychological tests (BRB-N), including the Selective Reminding Test (SRT), Spatial Recall Test (SPART), Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT), and Word List Generation (WLG), categorizing participants as heavy smokers or non-smokers based on pack-years.[15]

Amato et al. limited by missing pack-year data, dichotomized smoking status as yes/no and utilized both the BRB and the Stroop Color and Word Test.[8] Similarly, Alirezaei et al. applied the Minimal Assessment of Cognitive Function in MS (MACFIMS), including the California Verbal Learning Test-II (CVLT-II), PASAT, SDMT, Brief Visuospatial Memory Test-Revised (BVMT-R), Judgment of Line Orientation test (JLO), Controlled Oral Word Association Test (COWAT), and Delis-Kaplan Executive Function System (D-KEFS), and calculated a cognitive index, treating smoking status as a binary variable.[17] Notably, most studies relied on a global cognitive index or impairment measure. However, we argue that identifying the specific cognitive domains most strongly associated with smoking is important. Furthermore, we hypothesize that pack-years play a significant role in this association, as it provides a comprehensive measure of lifetime tobacco exposure by accounting for both the intensity (number of cigarettes smoked per day) and the duration (years of smoking).[18] This metric is particularly relevant in chronic conditions such as MS, where prolonged and cumulative toxic exposures may have profound and lasting effects on brain health and cognitive function. Additionally, the sample sizes across the studies are relatively small. Therefore, our study aims to investigate the relationship between smoking status, pack-years, and distinct cognitive domains such as working memory, visuospatial memory, and verbal memory, which are among the most frequently impaired cognitive functions in a larger cohort of persons with MS.[19]

Materials and Methods

Participants: This comparative study with cross-sectional data collection included 152 participants diagnosed with MS. We analyzed baseline data from an ongoing study titled "Monitoring the Balance, Walking, Hand Functions and Cognitive Functions in Persons with Multiple Sclerosis: A Prospective Cohort Study". The study protocol was approved by the Noninvasive Research Ethics Board of Dokuz Eylül University, Izmir, Turkey (protocol number: 6418-GOA, approval number: 2021/17-05), adhering to the Declaration of Helsinki (Brazil, 2013). Participants were evaluated yearly through clinical, physical, psychosocial, and cognitive assessments to monitor cohort progress.

All patients with MS visiting the clinic, regardless of disease duration or disability level, were enrolled upon providing written consent. Data were recorded in the iMed electronic patient registry system (version 6.1, Merck Serono SA, Geneva, Switzerland), utilizing custom fields specifically created for this study.

For this analysis, we extracted data from patients with a neurologist-confirmed diagnosis of MS according to the revised McDonald criteria. Exclusion criteria were pregnancy, cardiovascular, respiratory, or neurological disorders other than MS, and incomplete smoking or cognitive function data.

As this was a secondary analysis, we did not perform an a priori sample size calculation. However, a post hoc power analysis was conducted to guide future research.

Assessments

In addition to demographic data, disease duration and Expanded Disability Status Scale (EDSS) scores were collected. The EDSS was used to quantify the participants' neurological disability. This clinician-based, 10-point scale ranges from 0, indicating a normal neurological exam, to 10, representing death due to MS.[20] All EDSS scores were determined by the same neurologist based on their neurological examination.

Cognitive assessment: Cognitive function was assessed using the BICAMS, a validated tool specifically designed to evaluate cognitive impairment in persons with MS.[19] All BICAMS assessments were conducted by a psychotherapist. BICAMS includes three tests: the SDMT, the CVLT-II, and the BVMT-R. The Turkish version of BICAMS has been demonstrated to be a valid tool for assessing cognitive impairment.[21] The SDMT measures processing speed and working memory by requiring participants to match symbols with corresponding numbers as quickly as possible within a 90-second period. The CVLT-II evaluates verbal learning and memory by asking participants to recall a list of words over multiple trials and after a delay. The BVMT-R assesses visual learning and memory through the recall of complex geometric figures presented during three learning trials and a delayed recall trial. Each participant's raw scores were converted to Z-scores using normative data adjusted for age, gender, and education level reported in a previous study.[21] Cognitive impairment in a specific domain was defined as a Z-score of -1.5 or lower on the relevant BICAMS subtest.

Smoking exposure: Smoking status (current smoker or non-smoker) was self-reported, with non-smokers defined as participants who were not actively smoking at the time of assessment. Exposure was quantified using pack-years, calculated as the number of packs of cigarettes smoked per day multiplied by the number of years the participant had smoked.

Data normality was assessed using the Kolmogorov-Smirnov test and visual inspection of histograms. Chi-square tests were employed to compare the presence of cognitive impairment between groups. For comparisons of BICAMS subtest scores between groups, independent t-tests and analysis of covariance (ANCOVA) were conducted, controlling for potential confounders including age, education level, and EDSS scores. Logistic regression models were used to explore the relationship between smoking status (smoker vs. non-smoker) and the likelihood of cognitive impairment, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). Linear regression analyses evaluated the association between pack-years and cognitive function scores, adjusting for the same confounders. Statistical significance was set at $P < 0.05$. All data analyses were performed using SPSS software (version 25.0, IBM Corporation, Armonk, NY, USA).

Results

A total of 152 participants were included in the study, comprising 76 smokers and 76 non-smokers. Table 1 summarizes the baseline characteristics of smokers and non-smokers. The two groups were similar in age ($P = 0.994$), sex ($P = 0.051$), and EDSS scores ($P = 0.117$). Educational level differed significantly ($P = 0.048$), with non-smokers more frequently attaining university education (55.3% vs. 34.2%). Disease course distributions were comparable between groups ($P = 0.717$), with relapsing-remitting MS (RRMS) predominating in both.

Independent t-tests initially indicated that smokers demonstrated significantly poorer performance on the CVLT-II ($P = 0.017$) and the BVMT-R ($P < 0.001$), with no significant differences observed in the SDMT ($P = 0.651$) (Table 2). However, further analysis using ANCOVA revealed a significant main effect of smoking status only on BVMT-R performance ($P = 0.009$, $\eta^2p = 0.049$), whereas no significant associations were found for CVLT-II ($P = 0.240$) or SDMT ($P = 0.261$) after controlling for age, education, and EDSS scores (Table 3).

Table 1. Descriptive characteristics of the participants

	Smokers (n = 76)	Non-smokers (n = 76)	P
Age (year) (mean ± SD)	35.97 ± 10.23	35.96 ± 11.65	0.994
Sex [n (%)]			
Women	48 (63.2)	59 (77.6)	0.051
Men	28 (36.8)	17 (22.4)	
Education level [n (%)]			
Primary school	10 (13.7)	10 (13.2)	0.048*
Secondary school	11 (15.1)	5 (6.6)	
High school	27 (37.0)	19 (25.0)	
University (including undergraduate and postgraduate)	25 (34.2)	42 (55.3)	
EDSS (mean ± SD)	2.16 ± 1.95	1.68 ± 1.76	0.117
Disease course [n (%)]			
Relapsing remitting	66 (86.8)	69 (90.8)	0.717
Secondary progressive	9 (11.8)	6 (7.9)	
Primary progressive	1 (1.3)	1 (1.3)	

*P < 0.05

EDSS: Expanded Disability Status Scale; SD: Standard deviation

Chi-square tests confirmed that cognitive impairment was more prevalent among smokers on the CVLT-II (χ^2 = 5.335, P = 0.02) and BVMT-R (χ^2 = 18.494, P < 0.001) compared to non-smokers, while no significant differences were detected for SDMT (P > 0.05) (Figure 1).

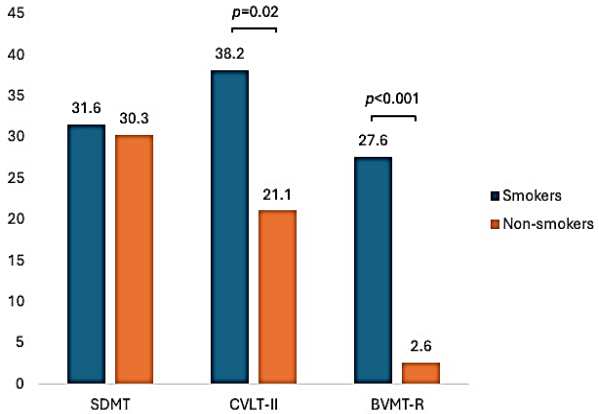

Figure 1. Presence of cognitive impairment according to different cognitive domains in smokers and non-smokers (values represent percentage)

Logistic regression analyses indicated that smokers had significantly higher odds of cognitive impairment on the BVMT-R, with an OR of 11.8 (95% CI = 2.5-55.8, P = 0.002), after controlling for the same variables (Table 4). Additionally, pack-year exposure was significantly associated with cognitive performance on the BVMT-R and CVLT-II, after controlling for age, education level, and EDSS scores. Each additional pack-year was linked to a decline in BVMT-R scores [B = -3.785, standard error (SE) = 1.474, β = -0.184, t = -2.569, P = 0.011], explaining 25.8% of the variance in BVMT-R performance. A similar negative association was observed with CVLT-II scores (B = -4.450, SE = 2.085, β = -0.149, t = -2.134, P = 0.035, adjusted R^2 = 0.281), with each pack-year resulting in an estimated reduction of 0.149 points in CVLT-II performance. However, no significant relationship was found between pack-year exposure and SDMT scores (B = 2.541, SE = 1.850, β = 0.08, t = 1.374, P = 0.172), suggesting that smoking may have a more pronounced effect on memory-related cognitive functions than on processing speed.

Discussion

In this study, we aimed to explore the relationship between smoking status, pack-years, and specific cognitive domains in persons with MS.

Table 2. Comparison of cognitive performance between smokers and non-smokers

	Smokers (n = 76) (mean ± SD)	Non-smokers (n = 76) (mean ± SD)	P	Cohen's d	Power
BVMT-R	18.88 ± 10.54	24.97 ± 6.38	< 0.001*	0.698	0.99
CVLT-II	47.79 ± 12.22	52.80 ± 13.39	0.017*	0.391	0.67
SDMT	45.37 ± 13.40	46.93 ± 14.62	0.494	0.112	0.11

*P < 0.05

BVMT-R: Brief Visuospatial Memory Test-Revised; CVLT-II: California Verbal Learning Test-II; SDMT: Symbol Digit Modalities Test; SD: Standard deviation

Table 3. Comparison of cognitive performance by smoking status, adjusted for education, Expanded Disability Status Scale (EDSS), and age

Variables	BVMT-R			CVLT-II			SDMT		
	F	P	η^2p	F	P	η^2p	F	P	η^2p
Smoking	7.09	0.009*	0.049	1.39	0.240	0.010	1.27	0.261	0.009
Education	7.46	< 0.001*	0.139	9.47	< 0.001*	0.170	18.47	< 0.001*	0.288
EDSS	7.88	0.006*	0.054	4.20	0.042*	0.029	2.03	0.156	0.015
Age	0.71	0.401	0.005	2.61	0.109	0.018	25.93	< 0.001*	0.159
Education × Smoking	0.04	0.989	0.001	0.28	0.843	0.006	0.36	0.782	0.008

*P < 0.05

EDSS: Expanded Disability Status Scale; BVMT-R: Brief Visuospatial Memory Test-Revised; CVLT-II: California Verbal Learning Test-II; SDMT: Symbol Digit Modalities Test

Our findings indicate that smoking is associated with poorer cognitive performance, particularly in visual and verbal memory, as evidenced by significant impairments in the visuospatial and verbal memory. However, after controlling for age, education level, and disease severity, only the impairment in the visuospatial memory remained significant. Additionally, our data suggest that pack-year exposure is a significant factor, with higher exposure correlating with greater cognitive decline, particularly in visual and verbal memory tasks, even after controlling for the same possible confounding variables.

In terms of impaired cognitive function and smoking in persons with MS, the literature presents conflicting results. For example, a pioneering study by Ozcan et al. included 44 persons with MS, who were categorized as heavy smokers, defined as those who smoked for at least 10 pack-years, and non-smokers. They used the BRB-N battery to assess cognitive functions and found no significant difference in any BRB-N subtest, including SDMT scores, between the two groups. However, the presence of cognitive impairment, determined by a calculated cognitive index derived from all BRB-N battery subtests, was significantly higher in heavy smokers. A logistic regression model revealed that smoking status was a significant predictor of cognitive impairment, with an OR of 2.327.[15]

Similarly, Chow et al. included 60 persons with primary-progressive MS (PPMS) and used the BICAMS to assess cognitive functions. They found no significant difference in CVLT-II and BVMT-R scores but noted a significant difference in SDMT scores between those who ceased smoking before onset or never smoked and those who smoked after onset. Furthermore, SDMT scores were significantly associated with pack-years.[16]

In our study, CVLT-II and BVMT-R performance was significantly associated with smoking status and pack-years. Our results align more closely with those of Ozcan et al.[15] However, the categorization of participants in terms of smoking status differs across the studies. Ozcan et al. and our study included mostly persons with MS with less disability, while Chow et al.[16] focused solely on primary progressive MS. This variation in participant categorization and disease progression levels may contribute to the differences observed in the findings across these studies. Additionally, the discrepancies could be due to differences in sample sizes and assessment tools.

Some studies did not find any significant associations between smoking and cognitive functions in MS. For example, Amato et al. included 150 persons with MS and used Rao's battery and the Stroop test to assess cognitive functions, and there was no significant difference between the cognitively impaired and cognitively preserved participants in terms of smoking status.[8]

Table 4. Comparison of presence of cognitive impairment according to Brief International Cognitive Assessment for MS (BICAMS) subsets between smokers and non-smokers and logistic regression model

	OR	95% CI (lower-upper)	P	Cox & Snell R^2	Nagelkerke R^2
BVMT-R	11.8	2.5-55.8	0.002*	0.188	0.337
CVLT-II	2.0	0.9-4.7	0.096	0.192	0.274
SDMT	1.2	0.5-3.0	0.637	0.221	0.312

*P < 0.05

Logistic regression model was adjusted for age, education, and EDSS.

OR: Odds ratio; CI: Confidence interval; BVMT-R: Brief Visuospatial Memory Test-Revised; CVLT-II: California Verbal Learning Test-II; SDMT: Symbol Digit Modalities Test

Similarly, a study by Alirezaei et al. included 92 persons with RRMS and used MACFIMS to assess cognitive functions, finding that current smoking was not associated with cognitive function.[17]

Overall, these conflicting findings underscore the complexity of the relationship between smoking and cognitive function in persons with MS. Variations in study design, participant characteristics, and categorization for smoking status, disease progression, and assessment tools may all contribute to the differing outcomes. Further research, particularly longitudinal studies with larger sample sizes and standardized assessment methods, is crucial to better understand the associations between smoking and cognitive function in MS. Understanding these nuances will not only help in refining clinical recommendations but also in developing more tailored interventions for cognitive preservation in this population.

Limitations: Our study has several limitations that should be acknowledged. Firstly, the equal-group recruitment introduces potential selection bias and restricts generalizability. Secondly, smoking exposure in our study was assessed only as current smoker versus non-smoker with self-reported pack-years, without detailed information on age at initiation, duration, or cessation; therefore, temporality cannot be established, and the possibility of reverse causation cannot be excluded. Future longitudinal studies with detailed smoking histories are warranted to establish temporal relationships, clarify causal pathways, and minimize the risk of reverse causation. Thirdly, the relatively small sample size, which may have resulted in few impaired cases, could contribute to large ORs in logistic regression analyses, potentially affecting the reliability and generalizability of the findings. Another limitation is that the reliance on self-reported smoking data could introduce recall bias, potentially affecting the accuracy of pack-year calculations. Additionally, other lifestyle and vascular risk factors – such as alcohol consumption, diet, physical activity, socioeconomic status, hypertension (HTN), and diabetes – were not assessed and may have influenced cognitive outcomes. Psychological factors, including depression, anxiety, and other mood-related issues, were also not evaluated and could act as potential confounders. Variability in disease progression and exposure to disease-modifying therapies among participants may have further affected cognitive performance, and these factors could not be fully controlled in our analyses. Due to the retrospective nature of the study, no a priori sample size calculation was possible. Although post-hoc power analyses indicated adequate power for the BVMT-R outcomes, analyses involving multiple subtests and covariates may have limited sensitivity to detect modest effects. Therefore, the results should be interpreted with caution and considered preliminary until replicated in larger samples.

Despite the limitations, our findings provide insights that may have potential clinical implications. Observed associations between smoking and cognitive performance, particularly in visuospatial and verbal memory domains, suggest that smoking cessation could be beneficial for overall health in persons with MS. For example, Alirezaei et al. reported that former smokers had better cognitive function.[17] Clinicians may consider routinely assessing smoking status and offering resources or support for smoking cessation programs. Additionally, targeted cognitive screening, especially for memory functions, could be considered in smokers with MS to monitor cognitive performance and identify potential early changes, while acknowledging that these recommendations are based on observational data and require further confirmation.

Future research should focus on longitudinal studies to better understand the temporal relationship between smoking, pack-years, and cognitive decline in MS. Investigating the mechanisms underlying the observed associations between smoking and cognitive performance, such as potential contributions of neuroinflammation or vascular factors, could provide valuable insights. Furthermore, larger, multicenter studies with diverse MS populations would help improve the generalizability of these findings. The role of other confounding factors, such as socioeconomic status, comorbidities, and genetic predisposition, should also be explored to provide a more comprehensive understanding of the interaction between smoking and cognitive impairment in MS.

Conclusion

Our study supports the association between smoking, pack-years, and cognitive decline in persons with MS, particularly in visuospatial and verbal memory. While the evidence remains mixed in the literature, our findings underscore the

importance of smoking cessation in managing cognitive health in MS. Addressing smoking as a modifiable risk factor could improve cognitive outcomes and overall QOL in this population. Further research is needed to clarify the mechanisms underlying the observed associations between smoking and cognitive performance in MS, as well as their potential long-term implications, to inform future clinical practice and interventions.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

The study protocol was approved by the Noninvasive Research Ethics Board of Dokuz Eylül University (protocol number: 6418-GOA, approval number: 2021/17-05), adhering to the Declaration of Helsinki (Brazil, 2013).

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