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Association between active and passive smoking and the clinical course of multiple sclerosis and neuromyelitis optica spectrum disorder

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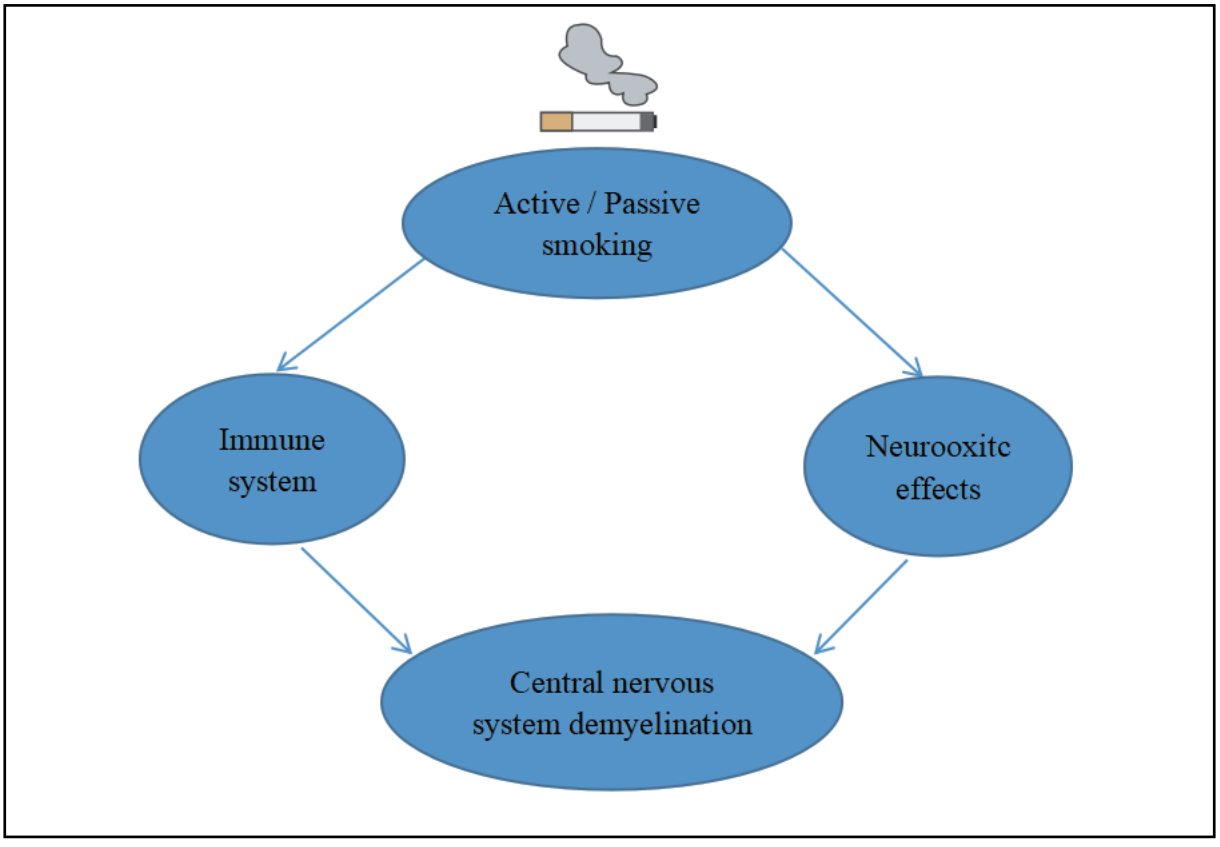
Graphical abstract



The mechanism of cigarette smoke affecting demyelinating diseases.

Public summary

■ We evaluated the impact of passive smoking on multiple sclerosis (MS) relapse and disability progression.

■ Compared to never-smokers, patients with MS who actively smoke have a significantly increased risk of relapse.

■ In MS, compared to never-smokers, active smokers experience accelerated disability progression.

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Abstract: *Objective*: Active and passive smoking are common environmental risk factors, but there is no definite conclusion about their effects on relapse and disability progression in multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). *Methods*: This was a retrospective cohort study. Patients were included from four centers. Demographic and clinical data were extracted from the clinical database, while data involving environmental exposures during daily life, relapse, and disability progression were obtained through telephone follow-up interviews. Determinants of relapse were assessed by Cox proportional models, and disability progression was assessed by linear regression. Kaplan–Meier survival was used to estimate relapse within five years after the first attack. *Results*: A total of 130 MS patients and 318 NMOSD patients were included in this study, and females accounted for 60% and 79.6%, respectively. MS patients with an active smoking history had a higher risk of relapse, for which the association became borderline significant after accounting for covariates (aHR=1.52, 95% CI=1.00, 2.31; p=0.052). The relapse risk between ever-smokers who smoked more than 10 cigarettes per day and smokers who smoked less than 10 cigarettes per day was not significantly different (aHR=0.96, 95% CI=0.63, 1.47; p=0.859). However, exposure to passive smoking was associated with a reduced risk of MS relapse (aHR=0.75, 95% CI=0.56, 1.00; p=0.044) compared with never-exposed patients. No associations were observed between active smoking/passive smoking and the risk of NMOSD relapse, but patients with a history of smoking were associated with a lower annual progression rate by Expanded Disability Status Scale (EDSS) (aβ=−0.20, 95% CI=−0.38, −0.01; p=0.036) and Multiple Sclerosis Severity Score (MSSS) (aβ=−0.23, 95% CI=−0.44, −0.03; p=0.028). *Conclusion*: Our research shows that active smoking increases the relapse risk of MS and has a negative impact on disability progression; thus, smoking cessation should be encouraged.

Keywords: smoking; relapse; disability; multiple sclerosis; neuromyelitis optica spectrum disorder

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1 Introduction

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are common autoimmune and neurodegenerative diseases of the central nervous system (CNS)[1]. NMOSD was originally considered to be a subtype of MS until the discovery of an aquaporin-4 antibody specific for NMOSD[2]. In addition to trauma, they are the most common causes of permanent disability among young people, resulting in huge social and economic burdens[3].

The etiology is unknown, but the interplay between genetic and environmental factors plays an important role in their pathogenesis[4, 5]. In MS and NMO, relapse, symptom deterioration, and disability are inevitable, and the progression of the disease (including relapse and symptom deterioration) often leads to more severe disabilities. However, some environmental factors can promote or inhibit these processes, so attention should be given to the relevant factors that affect the progression of patients' disease.

As a common environmental exposure, smoking is considered to be a key risk factor for disease onset and progression. A large amount of evidence suggests a link between smoking and the incidence of MS[4, 6], while knowledge of the influence of smoking on relapse and disability is sparse. Although some studies have suggested that smoking may be related to the clinical relapse rates in MS, no definite conclusion has been reached[7–13]. Weiland et al.[10] found no significant association between smoking and relapse rate or disease activity (when the specialist-determined relapse rate in the preceding 12 months exceeded the 5-year annualized relapse rate, disease activity was categorized as increasing) controlling for age and gender. Similarly, Kvistad et al.[11] found that smokers did not display more relapse or Expanded Disability Status Scale (EDSS) progression. Another prospective

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study found that smoking was not associated with relapses during cohort observation[7]. However, two other studies showed that the clinical relapse rate of MS patients who smoke was higher than that of patients who do not smoke[8, 13]. For NMOSD, a recent study showed that the annualized relapse rate was not significantly different between ever-smokers and never-smokers[5]. To the best of our knowledge, no study has yet analyzed the relationship between passive smoking and the course of MS and NMOSD.

In this study, we used a multicenter cohort to examine the relationship between active and passive smoking and the course of MS and NMOSD (relapse and disability).

2 Methods

2.1 Study population and patients

This is a multicenter retrospective cohort study. Patients were hospitalized and treated in four centers (The First Affiliated Hospital of USTC; Jinling Hospital, Medical School of Nanjing University; Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine; and The First Affiliated Hospital, Sun Yat-sen University) from January 2015 to December 2021. All cases were examined and diagnosed by the neurologist of the unit, and patients were required to fulfill the MS[14, 15] and NMOSD[16] diagnostic standards. Patients under 16 years of age or with incomplete baseline data were excluded. Finally, 130 MS patients and 318 NMOSD patients were enrolled.

This study was approved by the Ethics Committee of the First Affiliated Hospital of USTC (2023-RE-411). Besides, the authors have declared that the ethical guide line of the 1975 Declaration of Helsinki was rigorously adhered to in this study. This study is fully compliant with the regulation of relevant ethical about research involving in human participants.

2.2 Data collection

Participants were recruited through the use of medical records. By searching the keywords “multiple sclerosis” and “optic neuromyelitis”, we obtained the basic information of relevant patients in each center and screened them according to the time of admission. Demographic data, such as age, sex, BMI, education level, and social status, were extracted from the clinical database, while environmental exposure during daily life, relapse, and disability progression were obtained through telephone follow-up interviews. During the follow-up, a staff member used EDSS to score the degree of disability of the patients and confirm the relapse events.

2.3 Definition of smoking habits

Information regarding lifestyle factors and different exposures was collected using a standardized questionnaire[17]. Information on smoking was obtained by asking about current and previous smoking habits, including duration of smoking and average number of cigarettes smoked per day. Information on exposure to passive smoking (i.e., exposure to environmental tobacco smoke) was obtained by asking whether patients were exposed to environmental tobacco smoke at home or at work on a daily basis.

Based on answers, patients were divided into never-smokers and ever-smokers. Never-smokers were defined as patients who never smoked during their disease course or prior to disease onset. Ever-smokers referred to patients who smoked during the course of the disease and before the onset of the disease and quit or still smoked at the time of follow-up. We further categorized the smokers into groups based on the number of cigarettes smoked: more than 10 cigarettes per day and less than 10 cigarettes per day.

Data on passive smoking were evaluated as a dichotomous variable divided into ever-exposed or never-exposed.

2.4 Measurement of relapse and disability progression

Relapse was defined as the second onset of neurological symptoms lasting more than 24 h without other potential explanatory factors, followed by partial or complete stabilization or remission[14].

Disability was assessed by EDSS at the follow-up[18]. From this, the Multiple Sclerosis Severity Score (MSSS) was estimated using previously described functions[19]. Annualized changes in both were evaluated with the follow-up disability value divided by the duration in years since the first demyelinating event.

2.5 Data analysis

Quantitative variables are described as the mean and standard deviation, median, and interquartile range. Categorical variables are described as frequencies or percentages. Normal distribution assumption was checked using the Shapiro–Wilks test and the Q-Q plot.

To examine episodes of relapse as an outcome, relapse event survival analysis was used to calculate hazard ratios for relapse events. All covariates of interest satisfied the proportional hazards assumption. Risks were reported as hazard ratios (HRs) along with their 95% confidence intervals (CIs). We also plotted the Kaplan–Meier survival curve to estimate relapse within five years after the first attack. Predictors of annualized change in EDSS and MSSS were evaluated using a multivariate linear regression model, adjusted for whether participants had a relapse at follow-up.

All analyses were adjusted for age, sex, and BMI because these factors were previously found to be related to the disease[20, 21]. In addition, when analyzing the impact of active smoking, we adjusted for the status of passive smoking, and vice versa. All statistical analyses were performed using Stata 16.0. A p value <0.05 was considered statistically significant.

3 Results

3.1 Participant characteristics

The characteristics of the MS cohort (n=130) and NMOSD cohort (n=318) are shown in Table 1. The median age at study entry of MS and NMOSD patients was 43 and 48 years, respectively, and female patients accounted for 60% and 79.6%, respectively. In the MS cohort, 26.2% of patients had a smoking history, and 18.5% of patients had been exposed to passive smoking, while in the NMOSD cohort, the proportions were 13.2% and 24.8%, respectively. The median duration of the MS course was 3.9 years compared with 3.3 years for NMOSD.

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JUSTC, 2024, 54(3): 0303

Table 1. Demographic and clinical characteristics.

	MS	NMOSD	*p* value
Total	130	318	
Female (*n*(%))	78 (60.0)	252 (79.2)	<0.001
BMI (mean±SD)	22.7±3.4	22.9±3.9	0.409
Age at study entry (median(IQR))	43 (31−51)	48 (36−58)	<0.001
Duration (median(IQR))	3.9 (1.8−6.6)	3.3 (2.2−5.7)	0.881
Number of relapses during study (median(IQR))	2.0 (1.0−3.0)	2.0 (1.0−4.0)	0.157
Annualized relapse rate (median(IQR))	0.4 (0.2−0.8)	0.5 (0.3−0.8)	0.279
EDSS（median(IQR)）	2.0 (1.0−4.0)	2.0 (2.0−4.0)	0.172
Annualized change in EDSS（median(IQR)）	0.4 (0.2−0.8)	0.4 (0.4−0.8)	<0.001
Annualized change in MSSS（median(IQR)）	0.5 (0.2−1.0)	0.5 (0.4−1.0)	<0.001
Active smoking (*n*(%))			0.001
Never-smokers	96 (73.8)	276 (86.8)	
Ever-smokers	34 (26.2)	42 (13.2)	
Smoking volume (d^{-1})			0.181
≤10	15 (11.5)	25 (7.9)	
>10	19 (14.6)	17 (5.3)	
Passive smoking (*n*(%))			0.145
Never-exposed	106 (81.5)	239 (75.2)	
Ever-exposed	24 (18.5)	79 (24.8)	

3.2 Association between active smoking and passive smoking and the hazard of relapse in MS

In the MS cohort, the median number of relapses was 2, and the annual relapse rate was 0.4 (Table 1). Compared with never-smokers, patients with a history of smoking had a 52% increased risk of relapse (aHR=1.52, 95% CI=1.00, 2.31; p=0.052), albeit of borderline significance. However, there was no difference in the risk of relapse between ever-smokers who smoked more than 10 cigarettes per day and smokers who smoked less than 10 cigarettes per day (aHR=0.96, 95% CI=0.63, 1.47; p=0.859). After accounting for covariates, MS patients with passive smoking had a reduced risk of relapse (aHR=0.075, 95% CI=0.56, 1.00; p=0.044), and the results were statistically significant (Table 2).

The time to relapse after the first attack between never-smokers and ever-smokers was not significantly different (see Fig. 1a). In the early stage of the disease, however, ever-smokers had a slightly higher risk of relapse than never-smokers. Similarly, no significant difference in time to relapse was observed between ever-exposed and never-exposed patients (see Fig. 1b).

3.3 Association between active smoking and passive smoking and annualized disability progression in MS

In the MS cohort, patients with a history of smoking were associated with higher annual disability progression after adjusting for confounding factors (aβ=0.06, 95% CI=−0.12, 0.25; p=0.494), and patients who smoked more than 10 cigarettes per day had higher annual disability progression. Although it was not as obvious as active smoking, exposure to

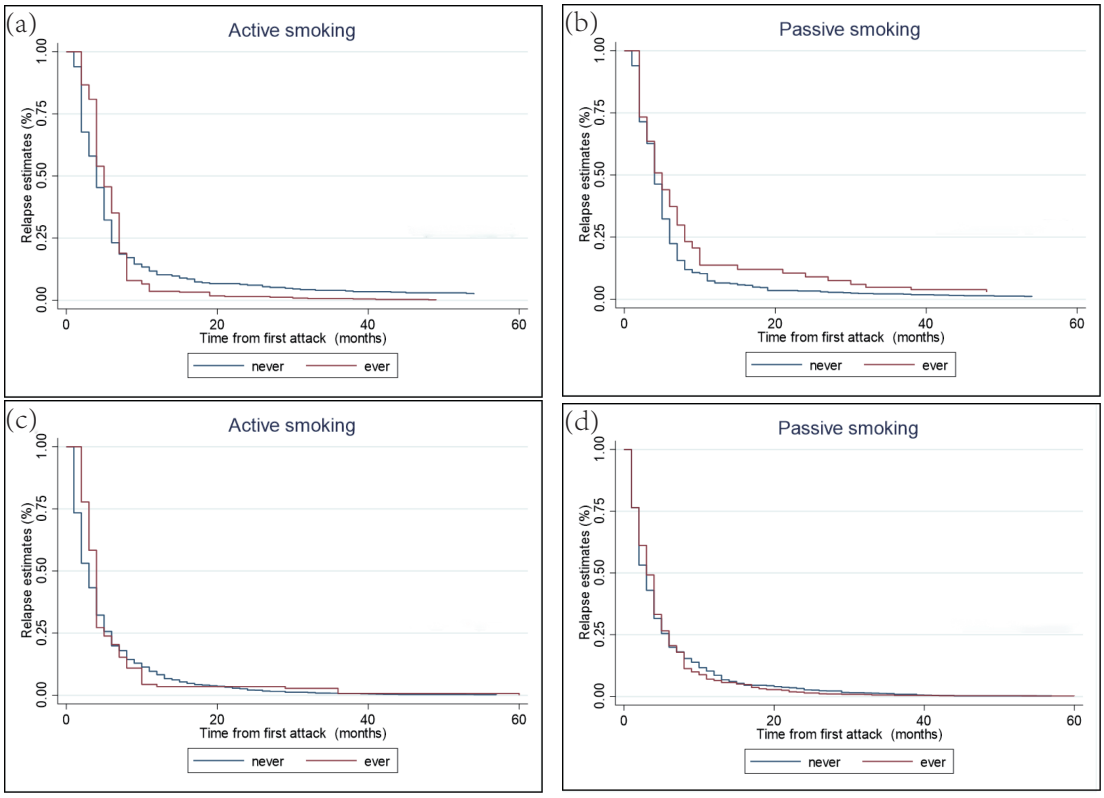

Fig. 1. Kaplan–Meier analysis of (a, b) time to relapse in the MS cohort and (c, d) time to relapse in the NMOSD cohort.

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JUSTC, **2024**, 54(3): 0303

passive smoking was also related to a higher annual progress rate (aβ=−0.17, 95% CI=−0.39, 0.04; p=0.116) (Table 3).

3.4 Association between active smoking and passive smoking and the hazard of relapse in NMOSD

In the NMOSD cohort, the median number of relapses was 2, and the annual relapse rate was 0.5 (Table 1). Active smoking did not appear to be associated with relapse risk in NMOSD. Compared with never-smokers, the risk of relapse in ever-smokers did not increase or decrease. However, the relapse risk of patients who smoked more than 10 cigarettes per day was significantly higher than that of patients who smoked less than 10 cigarettes per day (aHR=1.65, 95% CI=1.10, 2.47; p=0.016), indicating that the relapse of NMOSD may be related to smoking volume. No association was found between passive smoking and the risk of NMOSD relapse (Table 2).

There was no significant difference in time to relapse between never-smokers and ever-smokers (see Fig. 1c). The same results were observed for passive smoking (see Fig. 1d).

3.5 Association between active smoking and passive smoking and annualized disability progression in NMOSD

In the NMOSD cohort, a history of smoking and active smoking was associated with lower annual disability progression. The annual progression rates of EDSS and MSSS in ever-smokers decreased by 0.20 (95% CI=−0.38, −0.01; p=0.036) and 0.23 (95% CI=−0.44, −0.03; p=0.028), respectively, and the results were statistically significant. Compared with patients who smoked less than 10 cigarettes per day, patients who smoked more than 10 cigarettes per day had higher annual disability progression.

No association was found between passive smoking and NMOSD annualized disability progression (Table 3).

4 Discussion

In this multicenter retrospective cohort study, we assessed the role of active and passive smoking in the course of MS and NMOSD, including relapse and disability progression. We found that active smoking and passive smoking were associated with MS relapse but not with NMOSD relapse; active smoking was negatively correlated with the annual disability progression of NMOSD, but no association between exposure to passive smoking and disability progression was seen in patients with MS and NMOSD.

Studies have determined that smoking contributes to the onset of MS[6, 12, 17]. However, few studies have investigated the impact of smoking on disease relapse and disability progression, and the results are contradictory. Some studies have reported that smokers with MS had a higher risk of relapse[8, 13], while other studies have shown no increased risk[7, 10, 11]. In our study, active smoking was associated with a 52% increased hazard of relapse, which is consistent with the conclusions of previous investigations[8, 12]. A cross-sectional study of 929 cases found that smoking increased the risk of early relapse (RR=1.12, 95% CI=1.00, 1.25)[12]. Another study investigated the relationship between smoking and relapse during treatment with IFN-β in 834 RRMS patients[8]. Participants received neurological examination every 3 months after the start of treatment, followed by annual visits. The study concluded that smoking increases the relapse rate in IFN-β–treated patients with RRMS after adjusting for sex, age at the start of treatment, and pretreatment relapse rate (RR=1.20, 95% CI=1.02, 1.42). Weiland et al.[10] found that there was no significant correlation between smoking and relapse rate or disease activity after controlling for age and sex. However, among patients who quit smoking for >1 a, the relapse rate was reduced (p=0.046 for >10 a; p=0.047 for 1–10 a), which is suggestive of an underlying effect of smoking on relapse.

Most studies have shown that smoking is closely related to

Table 2. Associations of active smoking/passive smoking and the hazard of relapse.

	MS		NMOSD	
	Univariable analysis HR (95% CI)	Multivariable analysis aHR (95% CI)	Univariable analysis HR (95% CI)	Multivariable analysis aHR (95% CI)
Active smoking				
never-smokers	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
ever-smokers	**1.35 (1.00, 1.82)**	1.52 (1.00, 2.31) [a]	0.83 (0.69, 1.01)	0.97 (0.75,1.25) [a]
	***p*=0.049**	p=0.052	p=0.058	p=0.125
Smoking volume (d^{-1})				
≤10	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>10	0.72 (0.45, 1.15)	0.96 (0.63, 1.47) [a]	**1.79 (1.19, 2.70)**	**1.65 (1.10, 2.47)** [a]
	p=0.171	p=0.859	***p*=0.005**	***p*=0.016**
Passive smoking				
never-exposed	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
ever-exposed	0.83 (0.62, 1.11)	**0.75 (0.56, 1.00)** [b]	1.03 (0.88, 1.20)	1.02 (0.88, 1.20) [b]
	p=0.201	***p*=0.044**	p=0.756	p=0.759

[a] Adjusted for sex, age, BMI, passive smoking. [b] Adjusted for sex, age, BMI, active smoking. Figures in boldface denote statistical significance (p<0.05).

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JUSTC, **2024**, 54(3): 0303

Table 3. Associations of active smoking/passive smoking and annualized changes in EDSS and MSSS.

	MS		NMOSD	
	Annualized change in EDSS aβ (95% CI)	Annualized change in MSSS aβ (95% CI)	Annualized change in EDSS aβ (95% CI)	Annualized change in MSSS aβ (95% CI)
Active smoking				
never-smokers	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
ever-smokers	0.07 (−0.14, 0.28) [a]	0.06 (−0.12, 0.25)	**−0.20 (−0.38, −0.01)**	**−0.23 (−0.44, −0.03)**
	p=0.507	p=0.494	***p*=0.036**	***p*=0.028**
Smoking volume (d^{-1})				
≤10	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
>10	0.07 (−0.31, 0.44) [a]	0.12 (−0.28, 0.51)	0.14 (−0.06, 0.35)	0.16 (−0.07, 0.40)
	p=0.726	p=0.545	p=0.169	p=0.161
Passive smoking				
never-exposed	0.00 (reference)	0.00 (reference)	0.00 (reference)	0.00 (reference)
ever-exposed	−0.15 (−0.35, 0.04) [b]	−0.17 (−0.39, 0.04)	0.01 (−0.09, 0.11)	0.02 (−0.10, 0.13)
	p=0.128	p=0.116	p=0.840	p=0.769

[a] Adjusted for sex, age, BMI, and relapse passive smoking. [b] Adjusted for sex, age, BMI, relapse, and active smoking. Figures in boldface denote statistical significance (p<0.05).

the degree of disability[22–25]. Our results suggest that smoking has nothing to do with EDSS and MSSS, and other studies have obtained similar results. According to a prospective cohort study of 87 patients with RRMS conducted by Kvistad et al.[11], there was no correlation between tobacco use, assessed by serum cotinine levels (the main metabolite of nicotine), and MRI activity of smokers. In the same study, smokers did not show more relapse or EDSS progression. Another large prospective study of patients with CIS reached a similar conclusion that cigarette smoking did not appear to influence disability accumulation[9]. In addition, Kinga et al.[26] evaluated the effect of smoking on the annualized relapse rate (ARR) of EDSS. They found that there was no significant difference in EDSS ARR between smokers and nonsmokers.

Although not as serious as active smoking, passive smoking has also been suggested to increase the risk of occurrence of MS[6, 27]. To our knowledge, no study has investigated the effect of passive smoking on MS relapse and disability. Our results indicate that passive smoking was negatively correlated with MS relapse but not with the annual progression rates of EDSS and MSSS. A good explanation for these results is challenging. Smoking has complex effects on MS, and some studies have even demonstrated a protective effect[28-30]. A multicenter study of 279 patients conducted by Tao et al.[28] found that tobacco smoking delayed the average age at symptom onset by 4 years. Two other studies have shown similar directions of effect[29, 30]. In addition, a population-basedcase-controlstudyconductedbyHedstrometal.[31]inSweden, including 902 MS patients and 1855 controls, found that the use of Swedish snuff was not associated with an elevated risk of MS. In contrast, taking Swedish snuff for more than 15 years decreased the risk of developing MS (OR=0.3, 95% CI=0.1, 0.8).

Few studies have investigated the relationship between smoking and NMOSD. A recent study evaluated the relationship between smoking and NMOSD relapse and disability[5]. Researchers recruited 101 and 97 NMOSD patients in the UK and South Korea, respectively, and prospectively collected clinical data. The results showed that smoking was associated with worse disability; this result was not due to an increased risk of relapses but was the result of poor relapse recovery. However, our study further showed that both active and passive smoking were not associated with disease relapse, which needs to be verified with a larger cohort.

Many mechanisms of the pathological effects of smoking on inflammatory demyelinating diseases have been reported[4]. Smoking can lead to increased activation of immune function[32]. Studies have shown that compared with inflammation itself, smoking can lead to greater damage and poorer recovery through its impact on neurodegeneration[7]. In addition, the neurotoxic effect of smoke may help to explain the worse disease course of demyelinating patients who smoke[4]. However, the role of nicotine must be noted. The immune cells that play a crucial role in MS can all express nicotinic acetylcholine receptor (nAChR), indicating that nicotine may play an immunomodulatory role in the occurrence and progression of MS[33]. Gao et al.[34] used a mouse EAE model to study the effects of nicotine and nonnicotine components in cigarette smoke on MS and found that nicotine can reduce the severity of EAE by reducing demyelination, increasing weight and reducing the activation of microglia. After the onset of EAE symptoms, nicotine can prevent further deterioration of the disease, indicating that it may have therapeutic effects on EAE/MS. Therapeutic nicotine management has been proven to alleviate EAE symptoms. Nicotine may play a beneficial role in the pathogenesis of MS. Previous studies have shown that nAChR α7 subunits are expressed in $CD4^+$ T cells and upregulated upon activation[35, 36]. Treating these $CD4^+$ T cells with nicotine to induce their Th2 differentiation can reduce the reactivity of Th1 and Th17 cells, ultimately reducing T-cell infiltration into the CNS, and has anti-inflammatory effects on T cells, B cells, and even dendritic cells[37].

The advantages of our study include a multicenter cohort study and careful case confirmation, and we collected data on

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JUSTC, **2024**, 54(3): 0303

both active and passive smoking. Therefore, we can exclude the influence of each other by adjusting for confounding factors in the statistical analysis. Nevertheless, we acknowledge that there exist some limitations to this study. An obvious limitation was a retrospective analysis of data already collected rather than a prospective study, so there may be bias in information collection. Second, the data collected for this study were self-reported, so there may have been inaccuracies due to recall difficulties in less frequent events such as relapse rates or difficulties estimating the amount and frequency of smoking. Finally, we did not adjust for other confounding factors, such as low vitamin D, serum levels, low sunlight, or common infections. Demyelinating diseases of the CNS are complex diseases with many factors affecting the number of relapses. Therefore, the lack of information on other potential confounding factors may affect the results of this study.

We found that active smoking was associated with an increased relapse rate in MS patients, and compared with never-smokers, ever-smokers had a higher progression of disability. Although there is no formal evidence that smoking cessation will reduce the disease activity of MS and NMOSD patients, our findings encourage doctors to inform MS and NMOSD patients of the harmful effects of smoking and focus their attention on quitting smoking.

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Conflict of interest

The authors declared that they had no conflict of interest.

Biographies

Fengling Qu is currently a master's student in the Department of Life Sciences and Medicine, University of Science and Technology of China, under the supervision of Prof. Xinfeng Liu. Her research mainly focuses on relapse and progression of demyelinating diseases.

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