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The Effect of Smoking and Passive Exposure on Multiple Sclerosis and Correlation with IL17 & IL23 Levels

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ABSTRACT

Introduction: The aim of the study was to investigate whether there is any effect of smoking status or passive exposure on different subtypes of multiple sclerosis (MS) and their association with the IL17 & IL23 levels.

Methods: Blood samples were obtained from patients diagnosed with clinically isolated syndrome (CIS), relapsing remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS) and healthy controls. Smoking habits and passive exposure were questioned via a specifically created questionnaire. Patients and controls were grouped into three subgroups according to smoking status as active smokers, former smokers and never smokers.

Results: There were 60 patients and 20 age and sex-matched healthy controls. Active smoking was associated with a higher relapse rate per year. Smoking was inversely proportional to IL23 levels. Passive smoking was associated with atrophy in the follow-up cranial MRI. In utero exposure was associated with a polysymptomatic disease onset. The onset symptoms differed between patients whose mothers smoked during their childhood.

Conclusion: This study shows the effects of smoking and passive smoking on the presenting symptoms and course of MS. The relationship between these adverse effects and the Th17 pathway is not clear. It is evident that MS patients should be advised against smoking and should be directed to programs for quitting smoking.

Keywords: Childhood exposure, disease onset, IL17, IL23, maternal smoking, multiple sclerosis, onset symptoms, passive smoking

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INTRODUCTION

Tobacco farming has a long history, presumed to have started in the 6000 BC in the Americas and first clues regarding the smoking date back to the Mayans in 1500 BC. However, the calendars were showing as late as 1761 when John Hill suggested that tobacco might in fact be harmful for human health. Now, the harmful effects of smoking are more evident than ever in light of modern science (1).

Multiple sclerosis (MS) is an inflammatory, demyelinating, neurodegenerative disease of the central nervous system with various clinical presentations and course types. It is one of the leading causes of non-traumatic disability in young adults. Despite being defined by Charcot over 150 years ago, many aspects of the disease still remain poorly understood due to its complex clinical and pathological nature, as well as the intricate interactions among genetic, immunological, and environmental factors.

Smoking and passive smoking have been established as risk factors for MS. The Nurses' Health Study I and II investigations have revealed a relative ratio (RR) ranging from 1.4 to 1.8, indicating an increased risk of MS. This risk is proportional to the cumulative dose (2,3) and is also found to be modulated by the personal genetic factors, such as HLA alleles. Hedström et al. have shown that people with both HLA DRB1*15 and A*02 have an even greater risk compared to others (4). NAT1 gene polymorphisms are another important risk factor (5). Passive exposure is also associated with an increase in MS risk; however, the role of in-utero exposure is not apparent in humans (6–9).

Highlights

- **The number of relapses per year was higher in ever smokers among RRMS patients.**
- **Maternal smoking history affects the presenting symptoms in MS patients.**
- **Maternal smoking may be associated with a polysymptomatic onset in the offspring.**

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Numerous studies regarding the effect of smoking on MS have provided evidence of an association of smoking with increased disease activity, faster transition to progressive phase, worse quality of life, increased disability, and mortality (2,10–19). Moreover, there have been suggestions of a negative impact of smoking on treatment response in individuals with MS (20,21).

Differentiation of $CD4^+$T cells into T helper cells is an indispensable step in adaptive immunity. Th17 cells are a distinctive population, playing a role in immunity against bacterial and fungal pathogens in addition to the pathophysiological process of diseases such as psoriasis, Crohn's disease, rheumatoid arthritis, and chronic obstructive pulmonary disease. Differentiation into Th17 cells starts with pathogen activating dendritic cells; these dendritic cells release TGF-β and IL6 in addition to IL23, which can be derived both from dendritic cells and macrophages (22,23). IL23 is a critical part of this differentiation as supported by the lack of ability of Th17 differentiation and resistance against experimental autoimmune encephalomyelitis in IL23 knock-out mice (24). Th17 cells can easily pass through choroid plexus via the chemokine receptors they carry, and are believed to play a major role in persistent inflammation in progressive forms of MS (25,26). The most important cytokines released from Th17 are the IL17 family, known to not only support inflammation, but also hamper remyelination and possibly contribute to the formation of ectopic lymphoid follicles in the central nervous system (27–33).

In this study, our objective was to enhance our understanding of the relationship between smoking and MS by investigating their interplay. Additionally, we aimed to explore the potential role of the IL17/IL23 pathway in this interaction. By examining these aspects, we hope to shed light on the complex mechanisms underlying the effects of smoking on MS and gain valuable insights into the involvement of the IL17/IL23 pathway in this context.

METHODS

This study has been approved by the Cerrahpasa Medical Faculty ethical committee (approval number 2015/221015).

Patient selection and demographic/clinical data collection

Consenting healthy controls and consecutive patients diagnosed with clinically isolated syndrome (CIS), relapsing remitting MS, secondary progressive MS, and primary progressive MS according to the McDonald 2017 criteria were included in the data collection. Patients and healthy controls with active infections, recent (within 6 weeks) relapses, autoimmune/inflammatory comorbidities, or those currently using medications which may alter their cytokine levels, or who were pregnant or lactating, were excluded.

Patients were asked to fill out a survey on their smoking habits and beliefs regarding smoking, as well as paternal and maternal smoking habits during their conception and childhood, past and current passive exposure at home or workplace.

Demographic data and clinical data were collected from patient files in a retrospective manner. All clinical and laboratory data were reviewed by at least two of the authors (ADE and AA) before being entered into the database, and all neuro-radiological images were re-evaluated by these authors to reach a consensus.

The patients and controls in this study were categorized into three groups based on their smoking status: never smokers, former smokers, and active smokers.

Laboratory tests

Blood samples of 8 ml were collected from the antecubital vein into acid citrate dextrose tubes. These samples were centrifuged for 5 minutes at 300 rpm and stored in propylene tubes in -70°C degrees. Commercial kits (BioSource IL17 Cytoscreen kit, Nivelles, Belgium; Affymetrix human IL23 platinum ELISA, eBioscience, Vienna, Austria) were used according to the firms' directives to detect IL levels.

Statistical analysis

All data collected in this study were analyzed using IBM Statistical Package for Social Sciences (SPSS) program version 21 software. Categorical values were summarized as numbers and percentages, continuous measurements were summarized as mean and standard deviation or median and minimum-maximum where appropriate. Categorical values were tested via Chi-square and Fisher's exact test. The Mann-Whitney U test was utilized for two independent samples without normal distribution whereas the t-test was utilized if the distribution was normal. For comparisons including more than two groups, Kruskal-Wallis test was chosen for samples without a normal distribution and one-way ANOVA was chosen for the ones with normal distribution. Continuous variables were studied via the Spearman Correlation test. Kaplan-Meier Method was employed in order to predict mean time to an endpoint. Statistical significance was set to $p<0.05$ in all tests.

RESULTS

Sixty MS patients and 20 healthy controls were recruited. Demographic data and smoking habits are summarized in Table 1a-b. The age and gender distributions were statistically similar between patients and controls (p=0.460 & 0.80). The age of smoking onset was also similar in patients versus controls and between patient subgroups for former and ever smokers (p=0.365 & 0.747).

Smoking and clinical course of MS

The relationship between MS subtypes and smoking habits was evaluated, and a statistically significant difference was observed between the groups (p=0.024). Further post-hoc analysis revealed that this difference primarily stemmed from the primary progressive MS (PPMS) patients, none of whom were smokers. None of the other criteria regarding disease onset were found to be significantly associated with smoking (Supplementary Tables).

For the disease activity and disability, multiple sclerosis severity score (MSSS), EDSS increases per year, time to reach EDSS 3 or 6 were not found to be associated with smoking status (p=0.209 & 0.560). We found that the number of relapses per year was significantly higher in ever smokers in RRMS patients compared to never smokers and former smokers (p=0.039) (Figure 1).

After examining the relationship between neuro-radiological findings and smoking status, it was determined that there were no significant associations between smoking status and various factors. These factors included the baseline cranial MRI status (normal/abnormal but not diagnostic/abnormal and diagnostic), presence of contrast-enhancing lesions in the baseline cranial MRI, baseline spinal MRI findings, increased T2 load, presence of contrast-enhancing lesions, and atrophy in follow-up cranial and spinal MRIs. Detailed information is presented in Supplementary Table 1.

IL17 & IL23 levels

Interleukin 17 and 23 levels were not only similar between patients and controls (p=0.519 & 0.214), but also between MS subgroups (p=0.699 & 0.598). On the other hand, smoking led to interesting differences, IL17 levels of former smokers were lower compared to never smokers

Table 1a. Demographic data

	MS patients	Never smokers	Former smokers	Active smokers	Controls
N	60	25	17	18	20
Age	39.02 (±9.05)	36.52 (±8.39)	41.29 (±11.15)	40.34 (±6.51)	37.35 (±7.03)
Female/male	35/25 (58%)	17/8	6/11	12/6	11/9 (55%)
Onset age of MS	29.95 (±8.93)	28.08 (±9.17)	30.29 (±8.88)	33.23 (±8.01)	-
Onset age of smoking	19.06 (±5.33)	-	17.82 (±5.23)	20.23 (±5.17)	22.27 (±8.20)

MS: Multipe sclerosis

Table 1b. Demographic data

	Age	Gender (F/M)	Never smokers (n)	Former smokers (n)	Active smokers (n)	Treatments
Controls	37.35 (±7.03)	11/9	9	4	7	-
CIS	35.83 (±8.68)	4/2	2	0	4	5 NT 1 IFβ-Ib
RRMS	37.97 (±8.64)	22/12	12	10	12	14 IFβ-Ia im 6 GA 4 IFβ-Ib 5 IFβ-Ia sc 4 NT 1 GA & IFβ-Ib
SPMS	40.47 (±8.70)	9/6	9	4	2	2 GA 2 IFβ-Ia im 2 IFβ-Ia sc 2 IFβ-Ia sc & AZA 2 IFβ-Ib & AZA 1 IFβ-Ib 1 IFβ-Ib & AZA & CP 1 GA & AZA & CP 1 AZA 1 NT
PPMS	45.6 (±11.02)	0/5	2	3	0	1 AZA 1 GA & AZA 1 GA 1 IFβ-Ia sc & AZA & CP 1 NT

AZA: azathioprine; CIS: clinically isolated syndrome; CP: cyclophosphamide; GA: glatiramer acetate; IFβ-Ia: interferon beta 1a; IFβ-Ib: interferon beta 1b; im: intramuscular; NT: no treatment; PPMS: primary progressive MS; RRMS: relapsing remitting MS; sc: subcutaneous; SPMS: secondary progressive MS.

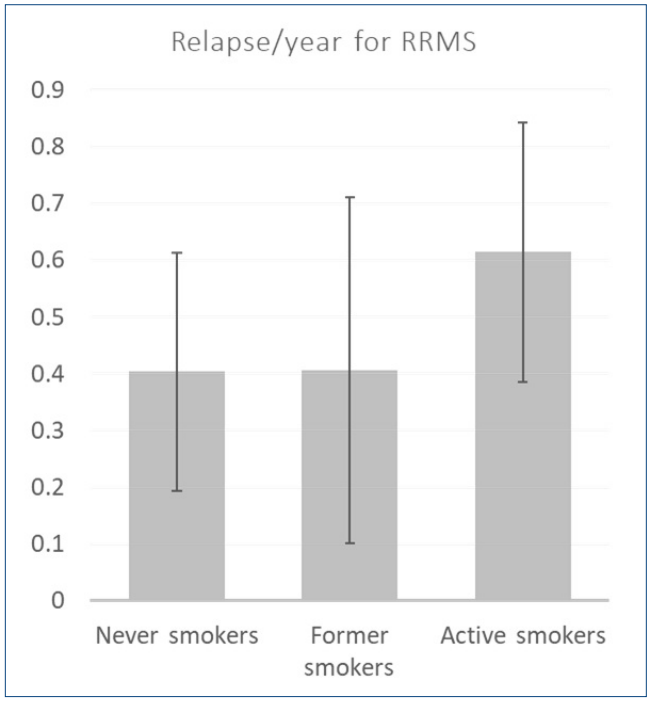
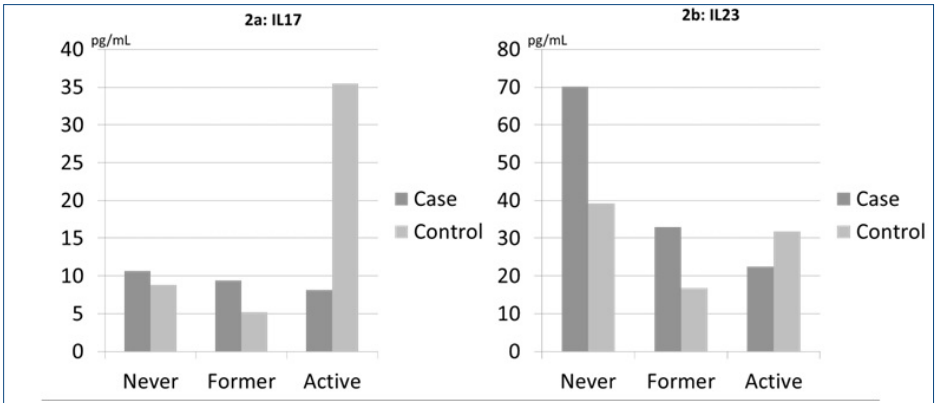


Figure 1. Relapse per year according to smoking status.

and active smokers (p=0.047). Additionally, smoking was associated with lower IL23 levels amongst patients and controls (p<0.00). Upon examining MS patients alone, same profile was observed, and it was statistically significant (p<0.001). Despite demonstrating a similar trend in MS patients for IL17 levels, this did not reach statistical significance (p=0.175) (Figure 2a and 2b). Upon comparing the IL17&23 levels among patients and controls depending on their smoking status, levels of IL23 were revealed to be higher in never-smoker MS patients compared to the never-smoker control group (p=0.048) (Figure 2c).

In a detailed examination of disease-related factors, the following findings emerged:

- Age of disease onset showed a weak but statistically significant negative correlation with IL17 levels (p=0.002, r=-0.392).
- For patients with relapsing remitting MS (RRMS), there was a similar negative correlation between IL23 levels and the number of relapses per year (p=0.040, r=-0.354).
- An interesting finding was the association between IL23 levels and follow-up cervical spinal MRI findings. Patients who showed an increase in their T2 load on the cervical spinal MRI had higher IL23 levels (p=0.029).



2c		Never smokers	Former smokers	Active smokers
IL17	MS	10.66 (±8.57)	9.39 (±12.43)	8.12 (±6.08)
pg/ml	Control	8.83 (±2.60)	5.18 (±1.15)	35.53 (±47.24)
	p value	0.708	0.985	0.801
IL23	MS	70.13 (±63.75)	32.91 (±26.10)	22.46 (±11.57)
pg/ml	Control	39.21 (±30.16)	16.80 (±2.14)	31.81 (±24.29)
	p value	***0.048***	0.206	0.482

Figure 2. IL17 and IL23 levels according to smoking status.

However, no statistically significant relationships were found between IL levels and the remaining studied factors related to disease onset, subgroup, activity, and progression. Detailed information is presented in Supplementary Table 1.

Passive exposure

Passive exposure to tobacco smoke has been questioned comprehensively via a questionnaire. Details have been summarized in Table 2. The effect of passive exposure criteria on MS related factors were thoroughly examined (Sup. Table 2). Current passive exposure at home or workplace was found to be associated with atrophy in the follow up CMRIs (p=0.040) and multivariate analysis has revealed that this effect was independent of the smoking status of the patients.

Another interesting association that came to light was between the onset symptoms of MS and in-utero exposure and maternal smoking during childhood. Polysymptomatic onset was associated with maternal smoking during pregnancy (p=0.015). The patients with smoking mothers also had different types of onset symptoms (p=0.027) (Table 3). The disease started mostly in optic tracts or spinal cord in patients who did not have maternal smoking history, whereas the patients with maternal smoking history had a higher chance of supratentorial, spinal, or brainstem-cerebellum involvement as the presenting symptom. No relapses with optic nerve involvement were observed in this group.

Rest of the studied factors regarding disease onset, subgroup, activity, progression and IL levels had no statistically significant relationships with passive exposure criteria (Sup. Table 2).

Table 2. Passive exposure details

Passive exposure	**N (%)**
Current exposure at home or work place	27 (48.3%)
In utero exposure	3 (5%)
Maternal smoking history	12 (20%)
Maternal smoking during childhood	10 (18.3%)
Exposure to other family members' smoking during childhood	38 (63.3%)
Number of cigarettes smoked by household per day during childhood	
<10	18 (30.0%)
>11- <20	7 (11.7%)
>21- <30	3 (5.0%)
>31	9 (15.0%)

Table 3. Maternal smoking and disease onset symptom

		Onset symptom			
		Supratentorial	**Brainstem-cerebellum**	**Optic tract**	**Spinal cord**
Maternal smoking during childhood?	Yes	4	4	0	4
	No	7	6	11	24

DISCUSSION

The current study adds to the expanding body of evidence highlighting the detrimental effects of smoking and passive exposure to cigarette smoke in individuals with MS. Importantly, this study reveals a novel finding by demonstrating that maternal smoking may impact the disease onset in the child. This study provides data on the effects of smoking and passive exposure to cigarette smoke on the levels of IL17 and IL23 in both healthy individuals and different subtypes of MS patients.

Smoking and clinical course of MS

Smoking is one of the most detrimental habits affecting human health, and the MS disease process is not exempt from such effects. The literature, albeit sometimes conflicting on details, largely demonstrates pernicious effects of smoking on MS patients. Cigarette smoking is reported to be associated with an increase in MS risk and earlier disease onset (34). Smoking history may also affect the type of disease onset, as Healy et al. reported an increase of progressive onset risk in smokers, whereas Manouchehrinia failed to replicate such findings (10,14). Our study has failed to support or exclude such claims due to the scarce number of PPMS patients and all PPMS patients being non-smokers. However, none of the rest of the criteria regarding disease onset were found to be significantly associated with smoking either.

Disease activity is another integral facet of MS process. Regarding this, we have found that the number of relapses per year was significantly higher in ever smokers in RRMS patients compared to never smokers and former smokers. This issue is rather controversial; some important studies such as the one by Petersen et al. have shown an increase in the relapse rate associated with smoking status, whereas other robust studies have failed to show such an association (15,34–38). Another international study, one of which that has failed to show association between active smoking and relapse rate has revealed that quitting smoking has led to a prominent decrease in relapse rate, intriguingly (15). Although a definitive conclusion regarding the effect of smoking on relapse rate is still lacking, overall data strongly suggests that termination of smoking should be vigorously targeted.

In our cohort, no significant associations were found between smoking status and neuro-radiological findings related to lesion load, contrast-enhancing lesions, and atrophy. This lack of association was observed in both baseline and follow-up magnetic resonance imaging (MRI) scans. Although the overall consensus is that smoking is associated with not only a greater lesion load but also increased number of enhancing lesions and atrophy, there are some other studies, which have also failed to show such association (35,38). Nonetheless, Healy et al. have reported that T2 lesion load increased faster in active smokers, however, there was no significant difference between former and never-smokers (10). Horakova, on the other hand, failed to reproduce such findings but showed that active smoking was associated with more contrast enhancing lesions, not only higher in number but also higher in volume (16).

Atrophy is another important neuro-radiological criterion and well-known to be related to the smoking status in MS patients, even in CIS (17,39). We believe the visual evaluation approach in our study has led to our failure to detect such an association and even routine follow up necessitates quantitative measurement methods for evaluating atrophy.

Regarding disability, MSSS, EDSS increase per year, time to reach EDSS ≥3 or ≥6 were not associated with smoking status in our study, which is an interesting and unexpected finding. The literature consistently shows an association with smoking and worse disability levels (12,14,15,17). We believe the explanation may lie in the shorter times to EDSS ≥3 and ≥6 of our tertiary center, with difficult-to-treat patients. Time to reach EDSS ≥3 in our study is 6 years whereas time to reach EDSS ≥6 is 9 years, which is significantly shorter compared to the Turkish average (11 years for EDSS 3 and 18 years for EDSS 6) and other centers (8.4 and 20.1 years for Lyon-France, 7.7 and 16 years for London Ontario, 23 and 28 years for Olmsted County) (40–43). This may be mainly due to the setting of the study being a tertiary center where more serious and treatment-resistant patients are being followed up.

IL17 & IL23 levels

The body of data regarding the importance of Th17 cells in the autoimmune processes and especially MS, is expanding every day (25,44,45). Smoking is also shown to negatively affect Th17 related processes. However, most of our knowledge is based on studies performed in patient groups such as chronic obstructive lung disease, periodontitis and psoriasis and the role of Th17 and related IL, namely IL17 and IL23, has not been extensively studied in relation to smoking in MS. Our cohort revealed that smoking was associated with lower IL23 levels amongst patients and healthy controls. Upon examining MS patients alone, same profile was observed consistently. A similar trend was also observed in IL17 levels. This finding is consistent with the literature showing decreased levels of IL-17 and IL23 in smokers (46–48).

Interleukin-23 is an essential molecule in Th17 maturation, and it has been shown that IL23 knock-out mice cannot produce Th17 cells and experimental autoimmune encephalomyelitis cannot be induced (23,24). Li et al. revealed an increase in IL23 expression by the surrounding microglia/macrophages and dendritic cells in active MS lesions compared to normal appearing white matter, both studies providing powerful evidence regarding the role and importance of IL23 in the disease process (49). Our study revealed an interesting finding that supports the association between IL23 levels and cervical spinal MRI findings. Specifically, we observed that patients who exhibited an increase in their T2 lesion load in follow-up MRIs had higher IL23 levels. Increasing cervical lesion load is relatively associated with worse prognosis and their relation to higher IL23 levels is not a surprising finding, considering this may be pointing to an underlying inflammation. Nevertheless, before considering IL23 levels as a prognostic predictor, this hypothesis should be tested and replicated robustly.

Levels of IL23 were higher in never-smoker MS patients compared to the never-smoker control group. The rate of relapses for RRMS patients was inversely proportional to the IL23 levels; higher levels of IL23 were associated with fewer relapses. The observed paradoxical finding in our study, wherein higher IL23 levels were associated with an increase in T2 lesion load on cervical spinal MRIs, yet with lower relapse rates could potentially be attributed to the treatments received by the patients during blood collection. It is worth noting that a significant portion of the RRMS patients in our cohort (28 out of 34) were receiving disease-modifying drugs, with 24 of them specifically on interferons (50–53). Another possible explanation might be that the levels of IL23 are associated with an inclination towards a progressive course. However, the rather scarce numbers in subgroups of our cohort have prevented us from further exploring these hypotheses. A study with a wider cohort and possibly including CSF samples may be more successful in shedding light on this process.

The age of disease onset was inversely proportional to IL17 levels, higher levels of IL17 were associated with a younger age of onset. This finding is to be expected, as IL17 is known to increase blood-brain barrier permeability, shorten the survival of oligodendrocytes, increase their apoptosis, cause intracellular calcium fluctuations, and aid in the formation of ectopic lymphoid follicles in the central nervous system;

all of which not only support the inflammation, but also disrupt the remyelination (25,29,30,33).

Passive exposure

Passive exposure is the most widespread source of cigarette smoke exposure and a well-known risk factor for multiple diseases. Most studies report an increase in the risk of MS and a worse prognosis for MS patients, albeit the reports are somewhat controversial due to the diversity of criteria for passive exposure (6,34,54,55). In our cohort, current passive exposure at home or workplace was found to be associated with atrophy in the follow up cranial MRIs, and this effect was independent of the smoking status of the patients. This was consistent with reports in the literature (17,56,57). However, since this study did not implement any volumetric measurements to evaluate atrophy, this finding, albeit consistent with the literature, should be taken with a grain of salt. This statistical relationship may merely be representing the chronic expected course of the disease itself. Nevertheless, we believe this could be an interesting aspect for further delineation and prospective studies specifically targeting this issue.

A novel finding of this study concerns the onset symptoms and in-utero exposure and maternal smoking during childhood. Although maternal smoking is a risk factor for developing MS later in life, the literature on this matter is rather conflicting and there are no details as to whether and how maternal smoking affects the offspring's MS onset and prognosis (8,58–60).

In our cohort, we observed that maternal smoking during pregnancy was associated with a polysymptomatic disease onset in MS patients. Furthermore, these patients also exhibited different onset symptoms compared to those whose mothers did not smoke. Specifically, our study found that among patients with non-smoking mothers, the predominant onset symptoms in MS involved optic tracts or the spinal cord. In contrast, patients with a maternal smoking history had a higher likelihood of presenting with involvement in the spinal cord, the supratentorial regions, or the brainstem-cerebellum. Interestingly, no relapses with optic nerve involvement were observed in this group. These findings suggest that maternal smoking history may influence the initial symptoms of MS and potentially have implications for disease prognosis. It is tempting to speculate that the observed shift in affected areas at onset towards regions associated with a worse prognosis could potentially contribute to a more unfavorable disease course in these individuals.

The main limitations of this study are its retrospective nature, lack of correlation with cotinine levels, empirical evaluation of the atrophy progression and the relatively scarce number of patients especially in the PPMS group. Since the data regarding the smoking status and passive exposure are gathered via questionnaires and semi-structured interviews, there is always the risk of recall bias, and this risk is even higher when it comes to questions regarding maternal smoking history and so forth. The retrospective design in addition to non-uniform MR techniques also hindered our ability to perform a quantitative analysis of the atrophy. A greater number of patients and samples might have led to clearer results not only about the presentation and course of the disease but also about the IL17 & 23 pathway. Correlating these with the cotinine levels could prevent recall and reporting bias.

In conclusion, our study focused on investigating the detrimental effects of smoking on MS patients, as well as exploring the role of interleukins IL17 and IL23 in this context. Our data reveal that the number of relapses per year was significantly higher in ever smokers among RRMS patients compared to never smokers and former smokers. Our study also uncovered a potential association between maternal smoking and a polysymptomatic disease onset in the offspring. Additionally, the presenting symptoms in MS patients with smoking mothers differed from those with non-smoking mothers.

These findings contribute to our understanding of the adverse effects of smoking in MS patients, including its impact on disease activity and potential influence on disease onset and symptom presentation. Such knowledge can aid in developing targeted interventions and preventive strategies to mitigate the negative consequences of smoking in MS.

Ethics Committee Approval: This study has been approved by the Cerrahpasa Medical Faculty ethical committee (approval number 2015/221015).

Informed Consent: Consenting healthy controls and consecutive patients diagnosed with clinically isolated syndrome (CIS), relapsing remitting MS, secondary progressive MS, and primary progressive MS according to the McDonald 2017 criteria were included in the data collection.

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Conflict of Interest: The authors declared that there is no conflict of interest.

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SUPPLEMENTARY

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