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Smoking as a risk factor of onset and relapse of Multiple Sclerosis — a review

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ABSTRACT

Introduction and objective. Multiple Sclerosis (MS) is a chronic demyelinating disease caused by damage to myelin in the brain and spinal cord. The cause of the disease is unclear, but it is probably correlated with dysregulation of the immunological system, as well as non-modifiable and modifiable risk factors.

Unfortunately, there is no cure for MS. However, the course of the condition has been shown to be modifiable by treatment and various environmental factors. Cigarette smoking is one of the most common addictions around the world, and may be a key modifiable risk factor in MS. Here, we review data available on Pubmed and Scopus from the last 10 years. The following consecutive key words were used in our search: "multiple sclerosis", "smoking", "cigarette", "impact", "progression", and "tobacco". This search yielded 248 initial articles, 43 of which were included in our review.

Current state of knowledge. In our review, we have examined the impact of smoking on the immunology, course, treatment, relapse, recurrence, quality of life, and changes visualised on MRI among patients with MS in general. We have also explored these patterns in MS subtypes. In general, smoking is reported to have negative effects on MS, including a decrease in quality of life, as well as cognitive and mental state, and an increase in disability, as well as in the frequency of relapses and recurrences.

Clinical implications. Smoking has a widespread negative impact on patients with MS. Thus, it is important to educate patients and to help them to give up smoking to improve their health and quality of life.

Future directions. Further research about the impact of smoking and nicotine on MS and other neurodegenerative diseases is needed; in particular, research on e-cigarettes.

Key words: multiple sclerosis, smoking, cigarettes, tobacco, impact, progression

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Introduction and objectives

Multiple Sclerosis (MS) is a neurological disease caused by a chronic, inflammatory demyelinating process of nervous tissue in the brain and spinal cord. It is estimated that the number of cases of MS in the population is 30.1 per 100,000 people [1]. MS can have a wide range of physical and mental symptoms, including double vision, blindness, ataxia, urination disorders, and cognitive impairment. The pathogenesis of MS is still unclear; however, MS onset is correlated with impaired functioning of the immune system. Thus, it is possible that the onset of MS depends on an occurrence of genetic and environmental risk factors and may be triggered by a viral infection. Environmental and genetic factors have been shown to influence MS onset.

Identifying the factors that have an impact on the development of the disease is critical for preventing the progression of MS. The literature suggests that key factors are likely to include diet, vitamin D deficiency, overweight status, viral infection, stress, and smoking. Importantly, many of these environmental and lifestyle factors can be modified. A diagnosis of MS requires the occurrence of certain symptoms and signs in combination with medical imaging (i.e. magnetic resonance imaging, MRI) and laboratory testing. The McDonald criteria, updated in 2017, are commonly used in the diagnosis of MS [2, 3]. MS remains an incurable condition. However, new

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drugs are available that have shown promise in stunting the progression of the disease for years. The severity of MS can be assessed using the Expanded Disability Status Scale (EDSS) [4]. One key modifiable risk factor for poor outcomes is smoking.

Smoking results in a broad range of harmful effects from the risk of lung cancer and other cancers to autoimmune diseases. Tobacco smoke contains several substances that have been shown to negatively influence biological processes in the body through various mechanisms. In recent years, it has been suggested that smoking may be implicated in MS pathogenesis, and that it may affect the progression of the disease including its severity [5, 6]. Our study comprises a review of the data available on smoking and MS published in Pubmed and Scopus over the past 10 years. The following consecutive key words were used in our search: "multiple sclerosis", "smoking", "cigarette", "impact", "progression", and "tobacco". This search yielded 248 initial articles, 43 of which were included in our review.

Current state of knowledge

Impact of smoking on experimental model of MS in mice

The harmful effects of smoking may be due to the different components of smoke rather than solely related to nicotine itself.

Gao et al. examined the impact of nicotine and the non-nicotine components in cigarette smoke on MS using an experimental autoimmune encephalomyelitis (EAE) model in mice. They found that nicotine moderated the severity of EAE, as evidenced by reduced demyelination, increased body weight, and attenuated microglial activation. After the development of EAE symptoms, nicotine administration prevented further disease exacerbation, suggesting that it may have therapeutic utility for EAE/MS. Importantly, the other (non-nicotine) components of cigarette smoke, delivered as cigarette smoke condensate (CSC), were shown to accelerate and increase the adverse clinical symptoms during the early stages of EAE. Among the non-nicotine compounds, acrolein was identified as the key potential mediator. The protective role of nicotine may be explained by its immunomodulatory functions. Within the nervous system, nicotinic receptors are primarily expressed on microglia, which relate to their immune-regulatory functions. CSC infusion into the spinal cord has been shown to correlate with microglial activation. Moreover, therapeutic nicotine administration has been shown to attenuate EAE symptoms. Nicotine has also been shown to demonstrate anti-inflammatory properties [7].

For example, Enzmann et al. examined the impact of specific genetic factors on the effects of smoking using the EAE model. Using Swiss Jim Lambert (SJL/J) mice, a transgenic model of relapsing-remitting MS (RRMS), the authors observed a very low incidence of EAE in both the smoke-exposed and control groups. In a model of optico-spinal encephalomyelitis (OSE) in C57 Black 6 (C57BL/6) mice, a double transgenic model, the early onset of EAE precluded a meaningful evaluation of the effects of cigarette smoke. In EAE models induced by immunisation, daily exposure to cigarette smoke caused a delayed onset of EAE followed by a protracted disease course in SJL/J mice. In contrast, cigarette smoke exposure was shown to ameliorate the EAE clinical score in C57BL/6J mice. Taken together, the influence of cigarette smoke on MS has been shown to depend on the type of transgenic mouse [8].

To date, the literature remains unclear about which components of cigarettes are harmful. Research suggests that nicotine administered alone may actually have a protective role in the course of MS. The other components of cigarette smoke may contribute to the detrimental effects of smoking in MS.

Correlation between smoking and immunology, biochemistry

Smoking has been shown to impact upon various features of the immune system in MS patients. According to Paknejad et al., Calcium binding protein B (S100B) plays a role in the pathogenesis of the disease via detection of specific T cells against S100B in the peripheral blood of MS patients. Based on these findings, levels of S100B in serum is considered to be a sensitive biomarker of disease activity. In one study, the level of S100B was significantly higher among smokers with RRMS compared to non-smokers [9]. Socha et al. examined the impact of smoking on selenium concentration (Se), glutathione peroxidase (GSH-Px) activity, and total antioxidant status (TAS) in serum drawn from patients with RRMS. Patients with MS had lower Se, GSH-Px, and TAS compared to individuals in the control group. Moreover, in that study, a significant decrease in TAS was observed in the serum of smokers compared to non-smokers. Thus, the immune system may be affected by low levels of antioxidants. Oxidative stress is an important factor involved in the pathogenesis of MS, including speeding up the production of reactive oxygen species. The generation of reactive oxygen species has been linked with both demyelination and inflammation [10].

A study by Tao et al. demonstrated a link between a history of tobacco smoking and symptom onset 3.05 years later. This result is consistent with the recognised notion that smoking is a risk factor of MS. The anti-inflammatory effects of nicotine on T-cells, B-cells, and dendritic cells might provide some answers. Tobacco smoking may have a greater influence on neurodegeneration rather than inflammation itself. A greater effect on neurodegeneration than inflammation may play a role in the onset of a subset of cases [11]. Another line of research has examined the role of perfluorinated alkylated substances (PFASs). PFASs are synthetic chemical compounds that have both immunosuppressive and immunotoxic effects. However, after running the experiment, the authors concluded that PFAS exposure is not an important risk factor for MS. Nevertheless, they observed cellular immune activation among smokers, evidenced by: 1) a lower frequency of CD8+ T cells characterised

by the expression of CD26 and; 2) CD161, which presumably defines mucosal associated invariant T (MAIT) cells; and 3) an increased percentage of inducible T cell costimulatory (ICOSL+) plasmacytoid dendritic cells (pDC). MAIT cells express proinflammatory and protective functions in MS.

In this context, lower levels of MAIT cells observed in smokers may be associated with their migration to the lungs. The impact of this phenomenon on the relapse of MS is still unclear. Furthermore, levels of ICOS+ Tfh cells in patients with RRMS have been shown to be higher than levels reported in healthy individuals. Smokers have also been shown to have increased levels of the co-stimulatory molecules ICOSL and CD86 on antigen presenting cells, including pDCs and B cells. ICOSL interacts with ICOS and plays a crucial role in the development of Tfh cells. Moreover, smoking induces APC with higher T-cell activation [12].

Ammitzbøll et al. examined immune cells from three groups: healthy smokers, healthy non-smokers, and non-smokers with MS. There was a significant increase in the number of granulocytes, monocytes, B cells, CD4+ and CD8+ T cells among smokers. Smokers also showed lower levels of MAIT cells. Based on these results, the authors suggest that smoking exerts proinflammatory effects rather than specific immunological ones [13]. Ammitzbøll et al. examined the expression of the class A orphan G-protein coupled receptor (GPR15) gene. Expression of GPR15 was increased among healthy smokers as well as non-smokers and smokers with RRMS. Expression of GPR15 was normal among patients with progressive MS. GPR15 may function as a chemoattractant receptor and has been associated with effector T cells in inflammatory processes. Smokers show higher expression of GPR15 on their CD4+ T-cells. Based on these results, the authors put forward the hypothesis that higher GPR15 expression on CD4+ T-cells is observable in RRMS upon activation. Moreover, GPR15+ CD4+ T cells were shown to produce higher levels of IL-17, which defines Th17 cells, suggesting a crucial role in the pathogenesis of MS. RRMS smokers had increased level of GPR15+ cells detected in their cerebrospinal fluid (CSF), which might explain the observed harmful effects of smoking in MS [14].

It is thus possible that smoking could have a comprehensive influence on immune system functions by changing levels of certain proteins or enzymes. Smoking may also affect the distribution of immune cells and growth factors.

Correlation between smoking and different forms of MS

MS is divided into a few types based on its course, severity, occurrence of relapse, recurrence, and remission. Smoking can have different effects on different types of MS.

In general, there are three clinical forms of MS: RRMS, primary progressive MS (PPMS), and secondary progressive MS (SPMS) [15]. Lublin et al. described a distinct, fourth subtype of MS, which is described as a clinically isolated syndrome (CIS). Patients with CIS have been found to frequently transition to other types of MS [16]. Indeed, Van der Vuurst de Vries et al. examined CIS patients during a five year follow-up and examined the risk of clinically definite MS (CDMS) in smoking and non-smoking patients at the time of the first demyelinating event. They found that smoking at the time of CIS was an independent predictor for CDMS diagnosis [hazard ratio (HR) 2.3; $p = 0.002$]. Interestingly, CIS patients who formerly smoked did not have a higher risk for CDMS compared to those who had never smoked. The researchers also found that the number of cigarette packs smoked per year was higher in the group that was diagnosed with CDMS (CIS–CDMS) during follow-up than in the group that remained in the CIS category. Patients who smoked at the time of CIS had a shorter time to CDMS diagnosis than patients who were not active smokers (HR 2.1 $p < 0.001$) [17]. Similar results have been reported in other studies, wherein patients with CIS had significantly higher risks of secondary progressive disease in males (HR 1.83, 95% CI: 1.3–2.7) and in those with a history of smoking (HR 1.4, 95% CI: 1.0–2.0). Progressive disease was found to occur four years earlier in patients who had a history of smoking relative to non-smoking patients [18].

In contrast to the aforementioned studies, Horakova et al. found that active smoking status was not associated with the number of relapses (all p-values > 0.26), progression to CDMS (all p-values > 0.44), or time to first relapse (all p-values > 0.41). However, smoking was associated with observable changes in MRI scans in this study and in other published studies [32, 33]. Arikanoglu et al. also demonstrated that there was no difference between smokers and non-smokers with CIS in relation to rate and time of conversion to CDMS. Nevertheless, smokers presented more changes in white matter [19].

Progression of RRMS to SPMS may be associated with exposure to smoking. According to O'Gorman et al., there were significantly higher risks of secondary progressive disease in males and in patients with a history of smoking. Again, SPMS was found to occur approximately four years earlier in patients with a history of smoking relative to non-smokers. However, smoking was not found to affect the age of onset of primary progressive disease [18]. In other research, a higher proportion of patients with RRMS were found to be smokers compared to non-smokers ($p = 0.001$). Moreover, a greater frequency of SPMS was significantly associated with an increase in the number of cigarettes to more than 10 ($p = 0.001$).

Over and beyond this, smokers have been shown to be at increased risk for progression of RRMS to SPMS compared to non-smokers (HR 2.25, $p = 0.004$). Also, the risk of SPMS was 2.43 ($p = 0.007$) times higher for an increase in the number cigarettes smoked per day, compared to the risk of SPMS among non-smokers [20]. On the other hand, Kvistad et al. demonstrated that, in the case of RRMS, smoking was not associated with the occurrence of new changes in MRI, relapses, or progression in EDSS [21]. Javizian et al. examined the impact of smoking on disease activity in PPMS. The median

time to EDSS 4 was four years in ever-smokers and five years in never-smokers (p = 0.27). The median time to EDSS 6 was nine years in both ever-smokers and never-smokers (p = 0.48). Smoking did not increase the risk of faster progression to EDSS 4 or EDSS 6, or the progression from EDSS 4 to 6.

Hence, cigarette smoking does not appear to influence disability accumulation in PPMS [22]. Taken together, smoking might have an impact on the earlier occurrence of CDMS in patients with CIS. However, the findings are mixed. Smoking can also increase the odds of progression of RRMS to SPMS.

Correlation between smoking and occurrence of relapses in MS

The age at onset of MS can vary, and depends on genetic profile, type of disease, and environmental factors. In MS, relapses and the progression of symptoms and disability are inevitable. However, there are factors that can promote or stifle these processes.

According to Briggs et al., MS patients who had been smokers had an 8.2% younger age-at-onset than non-smokers, which equated to an approximate 2.6-year difference (p = 5.7 × 10−10). Another study suggested that smoking can increase the risk of early relapse (p = 0.053) [23]. Smokers may also be more liable to develop a more severe type of MS, and MS patients with RRMS more likely to develop SPMS. According to Roudbari et al., compared to non-smokers, current and former smokers showed a relative risk of 2.43 and 3.55 respectively for the progression of MS after one year. When age at disease onset, number of relapses per year, and gender were taken into account, the hazard ratio for smokers compared to non-smokers was 2.25 (p = 0.004) [20].

The impact of smoking on the occurrence of relapses and disease activity is unclear. A study by Weiland et al. found no significant association between smoking and relapse rate or disease activity controlling for age and gender. No significant differences in 12-month self-reported physician-diagnosed relapse rates or disease activity were found according to smoking status, amount currently smoked, or time since smoking cessation. However, disease activity was reduced among patients who gave up smoking more than 10 years ago (p = 0.046) and 1–10 years ago (p = 0.047) [24].

On the other hand, a separate line of research showed no link between smoking and severity of MS. According to Kvistad et al., there was no association between cotinine (the main metabolite of nicotine) levels and MRI activity among smokers. In that same study, smokers did not display more relapses or EDSS progression [21]. In another article, active smoking was not associated with the number of relapses, progression to CDMS, or time of first relapse. However, smoking was associated with an increased number, and volume, of contrast-enhancing lesions (CEL) during a two year study period [25]. Kinga et al. examined the impact of smoking on the EDSS annualised relapse rate (ARR). They found no significant differences in EDSS ARR among smokers vs. non-smokers [26].

Thus, the findings regarding the impact of smoking on occurrences of relapses are contradictory. Some studies have reported a higher risk of relapse among smokers with MS, whereas other studies have shown no increased risk.

Smoking and range of disability in MS

The natural course of MS inevitably correlates with gradually progressing disability. However, environmental factors can alter this course by either stifling or promoting the progression of disability. A study by Briggs et al. examined disability by using the Timed 25-Foot Walk, a marker of lower limb disability, and the Performance Scales Sum, a measure of global disability. Compared to non-smoking MS patients, smoking MS patients showed a slower walking speed as well as higher global disability. Smoking status and insurance payer had the largest impacts on global disability as measured by the Performance Scales Sum [27]. Marck et al. implemented an educational intervention to MS patients that focused on healthy lifestyles, including giving up smoking. The researchers examined adherence to healthy behaviours after three years of education. They found that patients who followed the new healthy lifestyle reported improved physical and mental health [28]. Tanasescu et al. examined the effects of smoking cessation over time on reaching Expanded Disability Status Scale (EDSS) scores 4 and 6 among smokers with MS. They found that participants who gave up smoking had a 0.96 times lower risk of reaching EDSS 4 each year, and a 0.97 times lower risk of reaching EDSS 6 each year. Furthermore, they found that non-smokers had a significantly lower level of disability in all of the self-reported measures compared to current smokers. Relative to a patient who had continued smoking, a patient who gave up smoking 10 years earlier had a 33% and a 26% lower risk of reaching EDSS scores 4 and 6, respectively [29]. Similar results were described by Manouchehrinia et al. In that study, almost 1,000 patients were examined. MS patients who had a lifetime history of smoking were 1.34 and 1.25 times more likely than never-smokers to reach EDSS scores 4 and 6, respectively. A higher risk of reaching EDSS scores 4 and 6 was found for current smokers compared to non-smokers. Former (but not current) smokers had a significantly lower risk of reaching EDSS scores 4 (0.50–0.83) and 6 (0.53–0.90) than current smokers. There were also no significant differences in the time to EDSS scores 4 and 6 between patients who stopped smoking before MS onset, and those who stopped after developing MS.

Other studies have examined the effects of daily smoking on the Multiple Sclerosis Severity Score (MSSS). Average MSSS was increased by 0.04 for each additional cigarette smoked per day [30]. According to Ivashynka et al., the median MSSS was higher (3.2 vs. 2.3, p = 0.002) in patients with a lifetime history of smoking vs. patients without a lifetime history. Patients with a lifetime history of smoking were almost twice as likely to fall into the upper MSSS tertile compared to smoking-naïve patients. Similar to the effects of age and

sex, smoking habit increased the risk of falling into the worst MSSS tertile by 10.81 ($p < 0.01$) [31]. Ektan et al. examined the impact of smoking on respiratory problems and level of functioning. Among MS patients, smoking was associated with decreased functioning of the respiratory system compared to non-smokers. Smokers with MS reduced their daily walking distances. Respiratory failure was also shown to decrease the level of functioning among patients with MS [32].

Briggs et al. evaluated global disability among MS patients using the Patient Determined Disease Steps (PDSS) and Item Response Theory (IRT) summed score. They found that active smokers had significantly higher disability scores as measured with the IRT than non-smokers had. Global disability assessed by the PDDS did not differ between active smokers and non-smokers, although there was evidence of female smokers reporting higher disability than female non-smokers [33]. Ballesteros et al. found an increased risk of disability progression in daily smokers compared to non-smokers and ex-smokers (3.56 times and 2.32 times, respectively) [34]. According to Weiland et al., current smokers showed an almost doubled odds of requiring major mobility support (e.g. bilateral support, wheelchair, becoming bedridden) compared to never-smokers. In that same study, former smokers showed a 1.24 times increased odds of requiring major mobility support compared to patients who had never smoked. No association was observed between smoking and relapse rate, or between smoking and disease activity, after controlling for age and gender. Nevertheless, among former smokers, a longer duration of smoking cessation was associated with reduced disease severity. In another study, smokers had significantly lower HRQOL than never smokers and former smokers, and heavier smoking was associated with greater decreases in HRQOL [24]. On the other hand, according to the available data, the impact of smoking on disability can differ according to the type of MS. For example, in progressive onset MS, the consumption of alcohol, coffee, tea, fish, and cigarettes did not have a significant effect on the time to reach EDSS 6. However, in relapsing onset MS, smoking has been associated with an increased risk of reaching EDSS 6 [35]. Those results are in agreement with other research. Indeed, Javizian et al. examined more than 400 patients with PPMS and demonstrated that patients who had a history of smoking had a median time of about four years to progression to EDSS 4. The median time to progression to EDSS 4 was five years in MS patients without a history of smoking ($p = 0.27$). Median time to progression to EDSS 6 was the same (nine years) in patients with and without histories of smoking ($p = 0.48$). In that study, smokers were not at increased risk of faster progression to EDSS 4 or 6, or progression from EDSS 4 to 6. Age at disease onset, however, was the strongest risk factor for progression to EDSS 4 and 6, and from EDSS 4 to 6 [22].

Kvistad et al. examined a group of 87 patients with RRMS every six months over a two-year period. EDSS and MRI changes were analysed. Tobacco users did not have more relapses or EDSS progression. This could suggest that RRMS progression might be mediated by other factors [21].

Smoking and level of disability are strongly correlated. The research projects cited above have demonstrated a link between smoking and an increase in disability, as well as a decrease of motor functioning, in patients with MS.

Impact of smoking on cognitive functions and mental state in MS

MS is correlated with an impairment in cognitive functioning. Smoking and body mass index (BMI) display consistent and significant deleterious associations with perceived cognitive impairment (PCI) [36].

Özcan et al. used the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) to assess cognitive functioning in patients with MS. Patients who smoked at least 10 pack-years were considered to be heavy smokers. The researchers found a greater degree of impairment in cognitive functioning among patients who were heavy smokers than non-smoking patients ($p = 0.04$) [37]. In other research, current smoking was associated with severe cognitive symptoms, and smoking increased the risk of occurrence of cognitive symptoms by almost three times. Former smokers were more than twice as likely to experience symptoms compared to non-smokers [38]. Due to chronicity and cumbersome symptoms, patients with MS can have mental health problems such as depression. Briggs et al. examined the impact of prognostic factors among patients with RRMS, using the Patient Health Questionnaire 9 (PHQ-9), a nine-item scale that assesses the presence and severity of depression. Briggs et al. [27] found that patients who smoked had higher depressive scores compared to non-smokers. Taylor et al. assessed the impact of lifestyle factors on the occurrence and onset of depression 2.5 years later, using the Patient Health Questionnaire-2 (PHQ-2) and the PHQ-9. The PHQ-2 is a scale that is commonly used to screen for depression at onset, and examines the frequency of depressed mood and anhedonia over the past two weeks. Taylor et al. found that smokers, in general, had more often depression at the beginning of their disease compared to non-smokers, and that depression was more severe at the follow-up in smokers relative to non-smokers [39].

Another study used the Multiple Sclerosis Impact Scale 29 (MSIS-29). Compared to ex-smokers, smokers showed higher MSIS-29 scores, reflecting a poorer mental state. Smoking has also been associated with increased risk of anxiety and depression among patients with MS [29]. Aetiological pathways in depression among people with MS may be related to the neurotoxic effects of smoking [40]. Jelinek et al. proved that smoking was significantly associated with mental state. In that study, the Mental Health Composite score (MHC) was used, where higher scores correlate with better mental health status. Jelinek et al. [41] found that, relative to smokers, non-smoking MS patients scored 6–7 points better on the MHC.

Anxiety and fatigue have also been associated with restless legs syndrome (RLS) among patients with MS. Contentti et al. found that smoking cigarettes significantly increased ($p = 0.03$) the risk of RLS among patients with MS [42]. Patients with MS who are former and current smokers are more likely to achieve worse results on specific tests, which correlated with a decline in cognitive functioning.

In sum, current and former smokers have been found to experience mental health problems more frequently than non-smokers.

Impact of smoking on lesions found in MRI scans among patients with MS

Smoking among patients with MS has also been shown to influence changes visualised in MRI. Horakova et al. examined the impact of smoking on changes in patients with CIS over a two-year period. Smoking was associated with an increased number of contrast enhancing lesions (CEL) ($p = 0.002$), and a trend towards an increased volume of lesions between baseline and the two-year follow up ($p = 0.014$). The mean number of CEL at two years in the group of smoking MS patients was 0.51, compared to 0.19 lesions in the group of MS patients who were not actively smoking. However, smoking status was not associated with the number of new and newly enlarging T2 lesions ($p = 0.86$) or brain atrophy, as assessed by percentage brain volume change ($p = 0.64$) [25]. According to Durhan et al., a tendency towards greater lesion load in MRI was found in smoking patients. Indeed, T1 hypointense lesions and perilesional white matter had reduced fractional anisotropy and increased mean diffusivity to a similar degree in CIS patients who smoked vs. those did not smoke. Compared to non-MS patients who smoke, CIS patients who smoke had more extensive normal-appearing white matter changes revealed by increased mean diffusivity. Moreover, among CIS patients, the mean diffusivity value in the left superior longitudinal fasciculus was significantly higher in smokers than non-smokers [43].

In other research in patients with CIS, white matter lesions were detected in MRI scans of all of the smoking patients. In non-smoking CIS patients, white matter lesions were identified in a smaller number — only 63.5% (54 of 64) ($p = 0.02$) [19]. Graetz et al. found that patients who smoked showed reduced grey matter fraction, lower brain parenchymal fraction, and increased cerebrospinal fluid fraction compared to non-smoking patients. Nevertheless, no effect was observed on white matter fraction [44].

In contrast to the aforementioned studies, Kvistad et al. reported no association between tobacco use and the occurrence of new gadolinium-enhancing T1 lesions, new or enlarging T2 lesions, or their aggregate. Furthermore, in that study there was no association between cotinine levels and MRI activity among smokers [21]. In fact, smoking may display a neuroprotective effect. In other research, smoking has been associated with less cortical and deep grey matter damage occurrence and with increased grey matter volumes in several regions of the brain [45].

MS, smoking, quality of life, and prognosis

In general, quality of life is lower among patients with MS compared to individuals without MS. This may be due to chronicity and severity of the disease. Briggs et al. analysed survey data from 950 patients. Health-related quality of life (HRQOL) was assessed via the SF-12v2, which is divided into subscales. HRQOL in smokers was significantly lower than in non-smokers, and current smokers' HRQOL was appreciably lower than HRQOL of former smokers. It is worth noting that the relationship between smoking and HRQOL only reached statistical significance among women, although the non-significant effects in the smaller male sample were in the same direction [33].

Similar results were achieved by Weiland et al. Compared to MS patients who smoked 1–15 or 16+ cigarettes per day, non-smokers had significantly better quality of life across all subscales examined. No significant difference in quality of life tests between patients smoking 1–15 or 16+ cigarettes per day were observed. While time since giving up smoking had no significant impact on the overall quality of life and physical health composite, the number of years since cessation was significantly associated with QOL on the mental health composite and emotional wellbeing subscales [24]. Jelinek et al. used the Multiple Sclerosis Quality of Life-54 (MSQOL-54), which is used to assess physical health-related QOL and mental health-related QOL. Compared to smokers, non-smoking MS patients scored 4–5 points higher in physical health (i.e. PHC) and 6–7 points higher in mental health (i.e. MHC) scales [41].

The mortality rate among patients with MS is generally high; however, some environmental factors can substantially increase this ratio. According to Manouchehrinia et al., the mortality rate was similar between MS patients who had never smoked or formerly smoked and individuals without MS who had never smoked or formerly smoked. However, current smokers with MS had an 84% higher rate of death compared to current smokers without MS. Current smokers with MS had about a ten-year reduction in life expectancy compared to non-smokers with MS [46].

According to Hedström et al., MS risk is correlated with smoking in a dose-dependent manner, and this risk is similar for smoking and exposure to second-hand smoke [47]. On the other hand, Mandia et al. found no significant difference in MS severity between patients who currently smoke and patients who formerly smoked or have no history of smoking. No significant relationship between second-hand smoke and MSSS was found [48]. In general, smokers with MS have been shown to have lower quality of life compared to non-smokers, as measured by various scales. Moreover, smoking MS patients may have a higher mortality rate than non-smoking MS patients. Quality of life and mortality rates are both likely to be associated with the number of cigarettes smoked per day.

Clinical implications

The broadly negative effects of smoking on the metabolism and the proper functioning of the human body are well understood. According to the research data reviewed in this report, cigarettes may have an impact on the onset, course, and effectiveness of treatments for some conditions, including MS.

Most of the reviewed research indicates that smoking has a negative role in MS, by triggering the onset of symptoms, the occurrence of relapse, and activity of drugs. Moreover, exposure to cigarette smoke can impair mental state, quality of life, and cognitive functioning, and increase the severity of disability among MS patients. Smoking might also impact upon changes in the brain, as measured using MRI.

On the other hand, the harmful effect of cigarettes may be moderated by the subtype of MS. Nonetheless, these findings are important points to consider to encourage patients with MS to give up smoking. In particular, healthcare systems should make efforts to provide patients with thorough information on the modifiable factors in MS, particularly smoking, and the impact of these factors on the course of the disease.

The provision of this information could lead to positive changes in both quality of life and efficiency of treatment. Such education may also reduce the social costs of eventual treatment.

Future directions

The role of nicotine and smoking in the pathogenesis of MS and other neurodegenerative disorders remains unclear. However, the potential positive impact of nicotine is promising. Our review found a lack of research about the effects of e-cigarettes on MS.

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