



Multiple Sclerosis and Smoking

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ABSTRACT

Multiple sclerosis (MS) is a common, severe neurological disease that affects millions of people worldwide. Nevertheless, the actual cause of MS remains unknown. Smoking has been studied with respect to MS development and progression. The objectives of this review were to examine the relationship between smoking and MS and to understand the possible molecular mechanisms underlying the association. PubMed was searched for articles related to the study topic published between 2012 and 2020 using the search terms “multiple sclerosis,” “smoking,” “risk factors,” “cigarettes,” and “molecular mechanisms.” Studies show a significant relationship between smoking and the risk of MS. Furthermore, smoking has been linked to the progression of MS at the patient and population levels. However, the underlying mechanism remains to be explored in further studies; researchers still disagree on how the relationship between smoking and MS arises in different populations. Evidence from randomized controlled trials, systematic reviews, and epidemiological studies shows that smokers have a higher risk of developing MS and experiencing related adverse symptoms and complications.

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KEYWORDS: Cigarettes; Disease activity; Multiple sclerosis; Smoking

INTRODUCTION

Cigarette smoke is a lung irritant believed to induce a proinflammatory cascade in the lungs that can evoke chronic inflammation and, over prolonged exposure, autoimmunity. Chronic inflammation may increase the risk of developing autoimmune diseases such as multiple sclerosis (MS) in a process driven by antigen cross-reactivity between lung antigens and myelin antigens.¹ Genetic factors also play a central role in individual susceptibility to MS.^{2,3} The free radicals, cyanates, and carbon monoxide found in cigarettes are directly neurotoxic.^{4,5} Therefore, patients with MS who smoke cigarettes may have higher disease activity, a faster rate of brain atrophy, and a greater disability burden.⁶ The

evidence documented in the literature to date will be summarized in this study (Figure).

MS is considered among the most common disorders affecting the nervous system. This central demyelinating condition has a complex etiology and can lead to adverse effects on the nervous system and on the health and well-being of the patient.⁷ MS leads to damage to nerve cells in the spinal cord and brain.⁸ Adverse events affect communication among various organs within the nervous system, resulting in a wide range of symptoms, such as mental challenges and psychiatric complications.⁹ Other signs of MS are blindness, double vision, weak muscles, coordination problems, and sensory challenges.¹⁰ Research shows that MS can occur in the form of isolated attacks or as a progressive condition characterized by relapses.^{11,12} In some cases, the symptoms may disappear, only to return days or weeks later. To date, the actual causes of MS have not been identified. However, researchers believe that the underlying mechanism involves the failure of myelin-generating cells and the immune system. According to van der Mei et al,¹¹ MS is a condition with both environmental and genetic underpinnings related to nervous system functions. Thus, the complex interaction of genetic and environmental factors at the individual level contributes to the development and progression of MS.

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Studies have suggested that smoking can affect the development and progression of MS in different populations. Therefore, attempts have been made to understand the possible causal link between smoking and neurological conditions. In recent years, cigarette smoking has become a widespread habit in some regions of the world. Indeed, between 1950 and 2000, the global consumption of cigarettes and other related products increased threefold.¹² Coincidentally, the incidence and prevalence of MS also increased in the same period, leading to further suggestions about the potential connection between smoking and MS. Importantly, the prevalence of smoking tends to vary geographically and regionally. However, the reported rate of smoking is higher among men than among women. In some instances, researchers have examined both the duration and degree of exposure to cigarette smoke among individuals, with the primary goal of understanding how the toxic components of tobacco can affect health and well-being.

Therefore, smoking is viewed not only as a possible environmental causative factor of MS, but also as a risk factor that can influence the progression of MS. Although several studies have been performed to explore the connection between smoking and MS, researchers have yet to provide conclusive evidence on the possible molecular mechanisms underlying this association. The aim of this systematic review is to examine the relationship between MS and smoking and explore the possible mechanisms that underlie the connection between cigarette smoking and neurological disorders.

METHODS

This study entailed locating articles that could be used in understanding the possible association between MS and smoking. Furthermore, articles on the mechanisms underlying the relationships between the 2 variables were identified. The relevant articles were identified via a systematic search of PubMed with the following search terms: “multiple sclerosis,” “smoking,” “risk factors,” “cigarettes,” and “molecular mechanisms.” Boolean operators were used to combine the search terms to locate studies that could help answer the research questions. Additional articles were identified by examining gray literature and the reference lists of the studies that met the inclusion criteria. The search was limited to articles published between 2012 and 2020. At

the end of the search process, 67 articles were identified and subjected to a systematic review, which entailed reviewing the objectives, methodology, results, and limitations of the studies. The findings were then compared to generate insights that could augment the understanding of the possible connection between MS and smoking.

CLINICAL SIGNIFICANCE

- Cigarette smoking is a common addiction and environmental source of toxic exposure.
- Long-term cigarette smoking can have severe repercussions for personal health.
- Cigarette smoking is an additional risk factor for both the onset and progression of multiple sclerosis (MS).
- Cigarette smoke is irritating and toxic to the lungs and can lead to chronic lung inflammation.
- Chronic lung inflammation leads to activation of the immune system.
- Chronic immune activation can lead to the development of autoimmune diseases such as MS.
- While cigarette smoking may not be the only cause of MS, it appears to be a powerful aggravating factor for both MS onset and progression.

RESULTS

Smoking and MS

During the last decade, the number of studies examining the association between smoking and MS has markedly increased.^{8,9} Furthermore, attempts have been made to understand the manner in which smoking can affect susceptibility to MS. Research shows that the prevalence of smoking is related to the global risk of MS development and progression at a population level.¹⁰⁻¹² Furthermore, studies have concluded that individuals who smoke have an increased risk of suffering from, and experiencing rapid progression of, MS. In these studies, researchers focused on collecting data on the prevalence of MS, the diagnosis of MS, and exposure to smoking to achieve their objectives.¹³⁻¹⁶ While

some of these studies involved small sample populations, the general consensus supports a potential link between smoking and the risk, prevalence, and progression of MS among people of different age groups and sexes.¹⁷⁻¹⁹

The current review shows that previous studies have identified a clear link between cigarette smoking and the risk of developing MS.^{19,20} Furthermore, research has demonstrated that the risk of MS is higher for smokers than for nonsmokers,²¹⁻²³ and evidence gathered from epidemiological studies in the last decade demonstrates a critical link between MS and smoking habits.²⁴⁻²⁷ Studies have also reported a possible dose–response effect regarding the risk of MS; individuals who consume tobacco products have a higher risk of suffering from neurological disorders.²⁸⁻³⁰ In addition, a potential relationship between cigarette smoking and genetic and environmental risk factors has been established in MS studies. Epidemiological studies and systematic reviews have revealed that smoking may interact with other factors—such as ultraviolet radiation exposure, causative genes, and Epstein-Barr virus—to increase the risk of MS.³¹⁻³³

Another recent research focus area is the means by which smoking can affect the progression of MS in different patients. Systematic reviews, randomized controlled trials, and epidemiological studies have shown that relapse is common among patients with MS and can persist in some

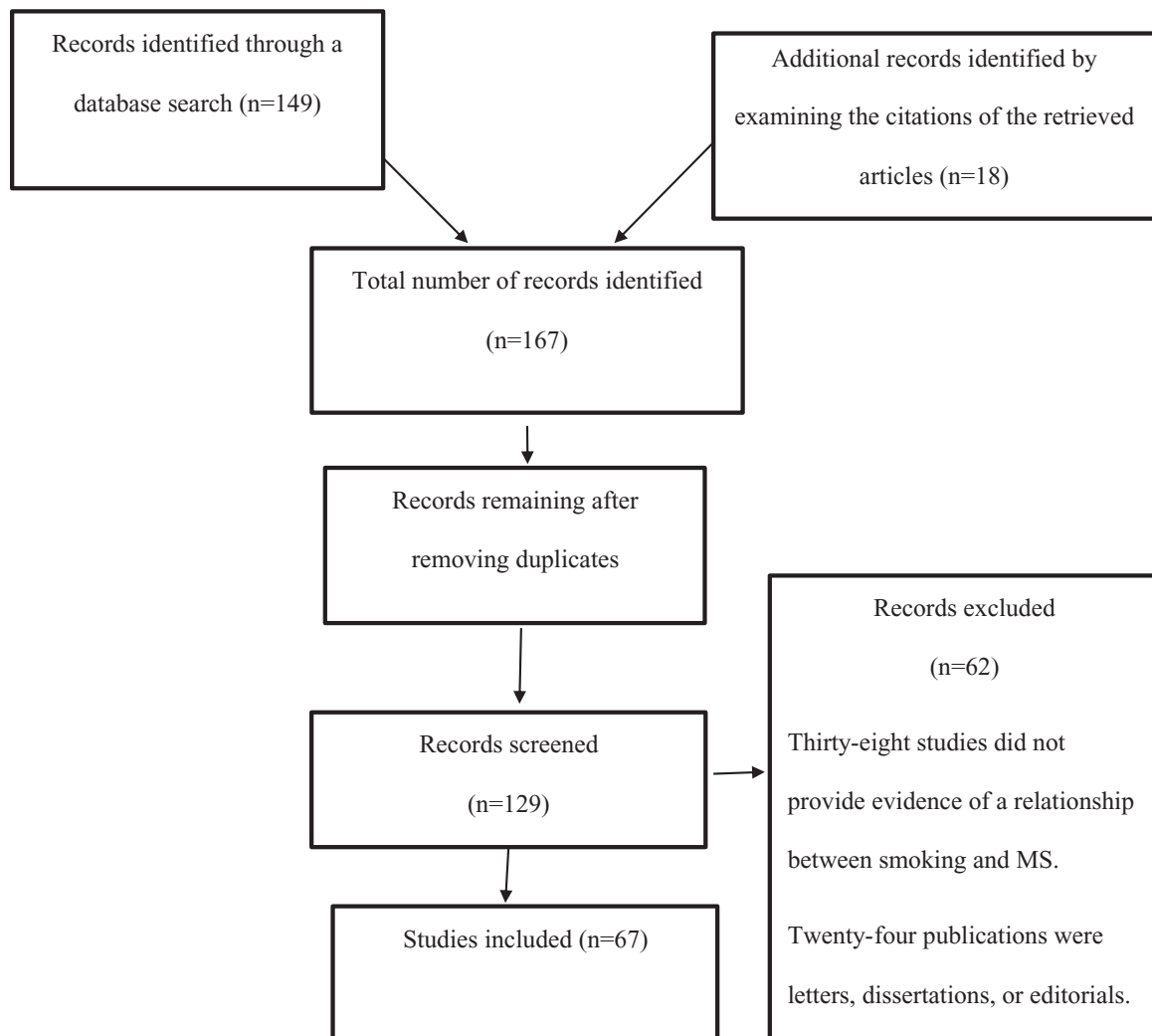


Figure Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram explains in detail the review procedure used.

instances.^{34,35} As the disease progresses, patients are likely to suffer from secondary progressive MS, which is characterized by frequent and steady signs and symptoms resulting from deteriorating immune and brain functions.³⁶⁻³⁸ The association between smoking and disease progression from relapsing-remitting MS to secondary progressive MS has been analyzed in previous studies.^{39,40} Evidence from the investigations shows that smoking accelerates both the development and progression of MS.⁴¹⁻⁴⁴ Thus, MS patients are encouraged to stop smoking after diagnosis.⁴⁵⁻⁴⁷

Molecular Mechanisms

Although MS has been the focus of extensive research, the molecular mechanisms underlying the relationship between MS and smoking remain elusive. A plethora of molecular variables and factors have been associated with MS.⁴⁸⁻⁵⁰ However, researchers have not reached a consensus on the most important variable that may trigger the development of MS and the progression of symptoms. A recent study

showed that compounds found in tobacco can affect the viability of cells at the blood–brain barrier.⁵¹ Similarly, studies have shown that smoking leads to an influx of different permeable solutes and chemokines that affect the blood–brain barrier.⁵¹⁻⁵³ Furthermore, these substances can trigger inflammatory responses that lead to the loss of blood–brain barrier integrity and the eventual development and progression of MS.^{54,55} Other studies have reported that tobacco smoke is a source of hydrogen cyanide and other metabolites, such as thiocyanate, that induce the demyelination of white matter.^{56,57} The results of these studies have been used to examine the possible involvement of cyanide encephalopathy in the development and progression of MS.^{58,59}

Inflammatory and immunomodulatory effects are the other molecular contributors that have been considered in examining the link between smoking and MS.⁶⁰⁻⁶² Research shows that smoking can result in various inflammatory effects, such as the recruitment of inflammatory mediators and cells (eg, macrophages and monocytes).^{11,63,64} In

addition, smoking can affect the levels of interleukin-1 and interleukin-6 in the body. The entry of these mediators into the central nervous system and their interaction with other inflammatory markers affecting the autoimmune response can influence the development of MS.^{65,66} Furthermore, chemicals such as nicotine and acrolein have been linked to immunomodulatory effects that influence MS; these substances can hinder the T-cell response and the function of different antigen-presenting cells in the body.^{11,67} In addition, tobacco can increase Fas expression in CD4⁺ T lymphocytes.¹¹ These events affect T helper cell function and can contribute to the progression of MS.¹¹

DISCUSSION

MS leads to adverse health outcomes and prevents patients from living normal lives. Over the years, researchers have attempted to identify and analyze the possible factors that lead to the development and progression of MS. One risk factor that has been linked to MS is smoking.⁵¹ Evidence from randomized controlled trials, systematic reviews, and epidemiological studies shows a possible link between smoking and the risk of MS.¹¹ The articles reviewed in this paper show that smokers have a higher risk than non-smokers of developing MS and experiencing related adverse symptoms and complications. While the results of previous studies provide vital evidence of a possible correlation between smoking and MS, the underlying mechanism is not fully understood. Researchers suggest that substances in tobacco, such as nicotine, affect the function of the brain and spinal cord through diverse mechanisms, such as immunomodulatory and inflammatory effects and the loss of blood–brain barrier integrity.¹¹

CONCLUSION

Most studies examining the influence of smoking on the development and progression of MS have reported possible adverse effects on various outcome measures. In addition, studies have concluded that smoking can increase the risk of MS and make it difficult for caregivers to manage the condition. However, the actual molecular mechanisms underlying the relationship between smoking and MS remain unknown. Further primary studies are needed to gather data that will lead to a better understanding of the molecular mechanisms underlying the relationship between MS and smoking. The outcomes of such investigations will also offer vital insights into MS pathogenesis and etiology.

Take-Home Messages

- Cigarette smoking is an additional risk factor for both the onset of MS and the MS disease activity.
- Cigarette smoking is irritative and toxic to the lungs, leading to a chronic lung inflammation and activation of the immune system.

- Cigarette smoking might not be the only reason for the emergence of MS, but it seems to be a powerful additional component, aggravating the onset and progression of the disease, if present.

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