REVIEW ARTICLE

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Environmental determinants of multiple sclerosis – a focused review

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Abstract

Introduction and Objective. Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) involving immune-mediated damage to myelin and axons. Its etiology is not fully understood, but both genetic susceptibility and environmental factors contribute to disease risk. The aim of the review is to summarize current knowledge on the most relevant environmental risk factors associated with MS.

Review Methods. This review is mainly based on meta-analyses and original studies identified in PubMed and Google Scholar database using key words such as 'multiple sclerosis', 'risk factors', 'environmental', and 'pathogenesis', published between 2020 – 2025. Relevant studies investigating environmental determinants of MS were selected and analyzed.

Brief description of the state of knowledge. Prior infection with Epstein-Barr virus (EBV) shows the strongest association with MS (odds ratio [OR] ~3.3). Other established risk factors include vitamin D deficiency, tobacco smoking (OR ~1.6), and obesity (OR ~1.2). These factors may contribute to MS development through immune dysregulation, chronic inflammation, and neurotoxic effects. Exposure during critical developmental periods, particularly childhood and adolescence, appears to be especially important. Additional factors, such as psychological stress and other viral infections, have been suggested, but current evidence remains limited.

Summary. Environmental factors play a significant role in MS pathogenesis, likely through cumulative and interacting effects. A better understanding of these factors may support the development of preventive strategies in the future and improve early risk assessment.

Key words

multiple sclerosis, risk factors, environmental, pathogenesis

INTRODUCTION AND OBJECTIVE

Multiple sclerosis (MS) is a chronic, progressive, inflammatory disease of the central nervous system (CNS) characterized by demyelination and neurodegeneration within axons. The exact pathomechanism of the inflammatory process leading to demyelination in MS remains incompletely understood, however, it is believed to involve an autoimmune response, particularly mediated by T-cells directed against CNS autoantigens, resulting in ongoing inflammation [1–4]. Demyelinating lesions in MS accumulate in both the white matter and gray matter throughout the CNS – in the brain, optic nerves, and spinal cord. Clinical manifestations are heterogeneous and depend on the location of the lesions. Some pathological changes remain clinically silent and do not cause noticeable symptoms [1, 3]. The clinical course of MS is also variable, and several disease phenotypes are recognized. The relapsing-remitting form (RRMS) is characterized by reversible episodes of neurological deficits (relapses) that are followed by remissions, during which neurological status stabilizes. Over time, recurrent relapses and the development of irreversible neurological deficits may lead to progressive disability, which is referred to as secondary progressive MS (SPMS). Less commonly, patients experience primary progressive MS (PPMS), in which the disease progression occurs from onset, without distinct relapses or remissions [1, 5]. A clinical relapse is defined as the occurrence of new or recurrent neurological symptoms reflecting CNS demyelination and resulting in neurological deterioration. To be classified as an MS relapse, symptoms must last for at least 24 hours in the absence of concurrent infection or other medical conditions [3].

In recent decades, the prevalence and incidence of MS have increased, and more than 2.9 million people worldwide are affected by the disease. [6] MS most commonly develops between the second and fourth decades of life, although in some cases symptoms may appear earlier, even during childhood [1, 2]. Therefore, MS is the most common cause of non-traumatic disability among young adults [1, 5]. The disease is more frequently observed in women than in men, which may be partly explained by environmental factors that mainly affect women, such as smoking, and obesity [1, 3]. The incidence of MS is also noticeably dependent on latitude. The disease occurs more frequently in regions located further from the equator, with the highest incidence reported in Northern and Western Europe and North America. MS is most common among white people of European ancestry and less frequent in Asians, Native Americans, African Americans, and Middle Easterners [3, 7, 8, 9].

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Although the direct cause of MS is currently unknown, it is well established that both environmental factors and genetic predisposition contribute to disease risk. The best-known risk factors for MS include past infection with the Epstein-Barr virus (EBV), vitamin D deficiency, exposure to tobacco smoke, and obesity (elevated body mass index, BMI). Additional, less well-established factors include psychological stress, excessive alcohol or caffeine consumption, and low physical activity levels [1, 4]. Epidemiological studies indicate that the strength of association varies between these factors, with odds ratios (OR) of approximately 3.3 reported for prior EBV infection and around 1.2 for obesity, suggesting a substantially stronger effect of EBV on MS risk (Tab. 1). Evidence also suggests that the timing of exposure is critical. The period from childhood to adolescence appears to be the most sensitive window during which environmental factors may contribute to the development of MS, such as EBV infection or obesity during adolescence [1, 4, 10].

The aim of this review is to provide a comprehensive, updated overview of the most relevant environmental risk factors implicated in the development of MS, based on an analysis of the available literature.

REVIEW METHODS

A systematic literature search was conducted in PubMed and Google Scholar using relevant key words, such as 'multiple sclerosis', 'risk factors', 'environmental', and 'pathogenesis'. The analysis primarily included meta-analyses and original research articles published between 2020 – 2025.

Table 1. Established and possible environmental risk factors for multiple sclerosis, based on [4, 10, 29]

Factor	Odds ratio (OR)	Effect during adolescence
EBV	~3.3	Yes
Vitamin D <20 ng/ml	~1.4	Yes
Tabacco exposure	~1.6	Yes
Waterpipe smoking	~1.7	Unknown
Obesity	~1.2	Yes
SLEs	~1.25	Unknown

EBV – Epstein-Barr virus; SLEs – stressful life events

DESCRIPTION OF THE STATE OF KNOWLEDGE

Infectious factors. Infectious agents are considered potential environmental risk factors for MS. However, infection with Epstein-Barr virus (EBV) during childhood and adolescence is one of the most well-established infectious triggers of the disease. Moreover, EBV infection appears to confer the highest risk among all identified environmental factors associated with MS [1, 4, 11].

The Epstein-Barr virus, also known as Human Herpesvirus 4 (HHV-4), belongs to the γ-Herpesviridae family and is a DNA virus. It is one of the most widespread human viruses, infecting approximately 95% of the global adult population. Transmission typically occurs through body fluids, most commonly through saliva. The primary infection is usually asymptomatic, although some people may develop symptomatic infection – infectious mononucleosis. EBV also has oncogenic potential, meaning that it can initiate malignant cellular transformation [12]. The precise mechanism by which the virus can initiate the pathogenic process in MS remains not fully understood, and establishing a definitive causal relationship is challenging. One proposed mechanism is molecular mimicry, which stimulates the development of cross-reactive T-cells and antibodies, thereby inducing inflammation in the central nervous system [1,10]. The antibody that can be detected after EBV infection is the antibody against Epstein-Barr nuclear antigen 1 (EBNA-1). Epidemiological studies conducted in Denmark evaluating the association between EBV infection and MS demonstrated that nearly 100% of patients with MS are seropositive for EBNA-1 antibodies [13]. In some patients, cross-reactivity between ENBA-1 antibodies and CNS autoantigens, such as myelin basic protein, has been observed, further supporting the role of EBV infection in MS pathogenesis [14,15].

The association between EBV and MS has been demonstrated in numerous studies over the years. One of them is a longitudinal study conducted by Bjornevik et al., which analyzed serum samples from U.S. military personnel stored in the United States Department of Defense Serum Repository (DoDSR) to investigate the relationship between EBV infection and MS. The analysis included 801 individuals with MS and 1,566 controls and demonstrated a strong association between EBV infection and the development of MS; among the MS cases, only one individual remained EBV-seronegative, whereas all others underwent seroconversion prior to disease onset. Moreover, the median time from EBV seroconversion to the onset of MS symptoms was approximately 7.5 years, suggesting a long temporal relationship between infection and disease development [16]. Another study examining the relationship between MS and EBV is a case–control study conducted within the German National Cohort (NAKO) by Holz et al. which included 576 patients with MS and 895 controls. The study aimed to identify associations between risk factors and MS development and confirmed that EBV infection increases the risk of developing MS later in life (odds ratio [OR] ~3.33) [4]. Several meta-analyses have also examined MS risk factors. A 2025 meta-analysis including 132 publications from 38 countries demonstrated a positive association between EBV infection and MS, as well as elevated EBNA antibody levels in patients with MS [15] (Fig. 2). Similarly, a 2023 meta-analysis of 134 studies confirmed the impact of EBV infection on MS risk [17]. The literature indicates the presence of a critical time window during which EBV infection may influence MS risk, with infections occurring during adolescence exerting a particularly strong effect. In a meta-analysis conducted in 2025, Vitturi et al. analyzed 87 studies from 20 countries. This analysis which demonstrated that EBV appears to play the most significant role in MS development during the first 20 years of life [18].

Beyond EBV infection, the literature also suggests possible correlations between MS and infection with human Herpesvirus 6 (HHV-6) as well as varicella-zoster virus (VZV). In the aforementioned 2025 meta-analysis, 18 other than EBV infectious factors were examined. In As a result, previous infection with HHV-6 or VZV was found to be associated with an increased risk of developing MS [15] (Fig. 2). This association was also reported in another meta-analysis examining seven viral infections, which identified correlations between HHV-6, VZV, and MS. [17] However,

the previously mentioned meta-analysis focusing on risk factors operating during childhood and adolescence, did not demonstrate a significant association between pediatric HHV-6 or VZV infection and subsequent MS risk [18]. Further research should therefore be conducted to clarify the potential contribution of infectious agents other than EBV to MS risk, as current evidence remains limited and findings across studies are inconsistent.

Vitamin D. Vitamin D is a fat-soluble vitamin that occurs in two main forms: cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Cholecalciferol is synthesized in the skin from 7-dehydrocholesterol under ultraviolet (UV) radiation exposure. Vitamin D3 is then converted in the liver and kidneys into its main active form – 1,25-dihydroxycholecalciferol [1,25$(OH)_2$D], also known as calcitriol. In contrast, ergocalciferol is produced from ergosterol under UV radiation and is found primarily in fungi and plants. [19] [Fig. 1] Vitamin D has a wide range of effects in the human body, primarily through the regulation of transcription of many genes essential for cellular homeostasis. Its active form, 1,25$(OH)_2$D, binds to vitamin D nuclear receptors (VDRs), which are expressed in multiple types of cells [19,20]. Although the main function of vitamin D is the regulation of calcium homeostasis, increasing attention has been directed toward its effects on the immune system and the central nervous system (CNS), including both functional regulation and development. The immunomodulatory properties of 1,25$(OH)_2$D have been described by Gombash et al., demonstrating its influence on both innate and adaptive immunity. Vitamin D is one of the main regulators of inflammatory cells, and may therefore affect the course of infection [20]. Moreover, 1,25-dihydroxycholecalciferol inhibits autoimmune processes by promoting anti-inflammatory cytokines production and reducing pro-inflammatory cytokines expression [21]. Within the CNS, vitamin D has been shown to stimulate the synthesis of neurotrophic factors, synaptic structural proteins, and neurotransmitters, as well as to reduce oxidative stress [1,15,20].

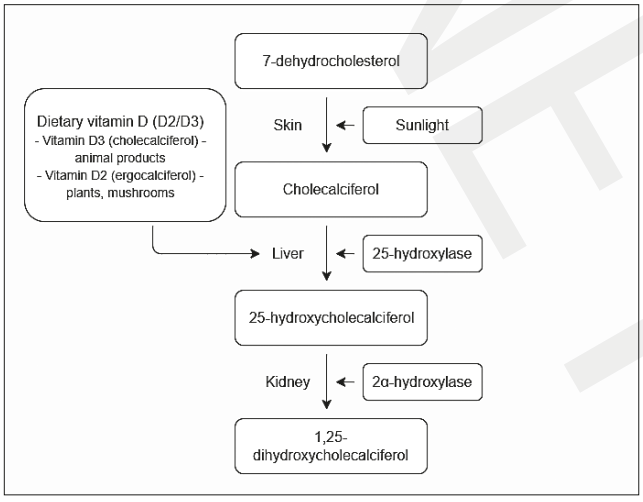

Figure 1. Synthesis of 1,25-dihydroxycholecalciferol.
Source: own elaboration based on [19]

Vitamin D deficiency is common worldwide and, due to its neuroprotective properties, it has been associated with numerous neurological diseases, including MS, Alzheimer's disease, and Parkinson's disease [19]. According to the Endocrine Society, serum vitamin D levels below 20 ng/ml (50 nmol/L) are considered deficient [22].

Many studies have identified a relationship between vitamin D levels and the risk of MS. Lower levels of 1,25$(OH)_2$D are associated with an increased risk of MS, supporting the protective effect of the vitamin [21, 23]. A large-scale cohort study conducted by Yu XH et al. confirmed an inversely proportional relationship between circulating 1,25$(OH)_2$D levels and MS risk. In addition, they demonstrated a genetic correlation between vitamin D levels and susceptibility to MS [24]. Mendelian randomization analyses have further supported a causal relationship, indicating that genetically determined lower vitamin D levels are associated with an increased risk of MS [21, 25].

Additionally, the occurrence of MS has been associated with geographic latitude, with a higher incidence observed at greater distances from the equator, as demonstrated in a meta-analysis conducted by Ehtesham et al. [24, 26]. This phenomenon is likely related to differences in sunlight exposure, which is considerably lower in northern regions of the globe. Reduced sunlight exposure may influence the risk of MS through decreased ultraviolet radiation, which stimulates the synthesis of vitamin D – a factor that has been suggested to exert a protective effect against the development of MS [23].

Tobacco exposure. Exposure to tobacco smoke, both active and passive, is a recognized risk factor for numerous diseases, including MS. Tobacco smoke contains a wide range of harmful and toxic substances that promote the accumulation of inflammatory cells and mediators, thus initiating inflammatory processes in the lungs [1, 10, 27]. In smokers, increased activity and dysregulated function of T-cells, excessive production of pro-inflammatory cytokines, and disturbances in the immune response, have been observed [18, 27]. Persistent, non-specific pulmonary irritation further activates inflammatory pathways, which may contribute to the development of autoimmunity. According to this hypothesis, tobacco smoke exposure may act as a trigger for various autoimmune diseases, including MS [1, 4, 10]. Neurotoxin compounds present in tobacco smoke, such as hydrogen cyanide, carbon monoxide, and nitric oxide, can also directly affect the nervous system by increasing oxidative stress, promoting inflammation, and inducing immunosuppression [15, 27]. In addition, chronic inflammation and the direct toxic effects may impair the integrity of the blood-brain barrier, thereby disrupting central nervous system (CNS) homeostasis and potentially lead to MS development [15]. Despite these proposed mechanisms, the precise causal pathway linking tobacco exposure to MS remains incompletely understood. Nevertheless, substantial epidemiological evidence supports an association between smoking – both active and passive – and increased MS risk. Observational studies and meta-analyses consistently report an odds ratio (OR) of approximately 1.6 for smokers compared with non-smokers. Importantly, a dose-response relationship has been demonstrated, which means that higher cumulative cigarette exposure is associated with greater disease risk. Furthermore, smoking has been shown to accelerate disease progression, leading to faster disability [10, 15].

Manouchehrinia et al. conducted a large case-control study using data from two Swedish cohorts – the Epidemiological

Investigation of Multiple Sclerosis (EIMS) and the Genes and Environment in Multiple Sclerosis (GEMS) studies, to estimate the population attributable fraction (AF) of MS caused by smoking, and, based on this, to assess the impact of smoking on the risk of developing MS. The analysis included 9,419 patients with MS and 9,419 controls. The total AF was estimated at 13%, indicating that approximately 13% of MS cases in Sweden could be due to active smoking [28]. A recent meta-analysis conducted by Vitturi et al. further confirmed smoking as a risk factor for MS in both current and former smokers. Their analysis demonstrated that active smokers had nearly a 50% higher likelihood of receiving an MS diagnosis compared with non-smokers [15] (Fig. 2). Another previously cited meta-analysis focusing on risk factors operating during childhood and adolescence identified exposure to tobacco smoke during these critical developmental periods as a significant risk factor for developing MS in later life [18].

In addition to conventional cigarette smoking, alternative forms of nicotine consumption are becoming increasingly popular. Waterpipe (hookah) smoking has also been evaluated in relation to MS risk. A 2024 meta-analysis including five studies and 3,087 participants (1,135 patients with MS) demonstrated that active waterpipe smoking was significantly associated with MS risk (OR = 1.73), and that smoking in the past also increased the risk of developing the disease [29].

Obesity. Obesity is a chronic disease that affects an increasing number of people globally over time. It is characterized by a state of low-grade systemic inflammation that affects multiple organs. Adipose tissue functions as a metabolically active, pro-inflammatory organ, producing inflammatory mediators such as interleukin-6 and interleukin-8, which induce a generalized inflammatory response [30]. The inflammatory activity associated with excess adipose tissue may also involve the central nervous system (CNS), which can potentially lead to pathological changes in the white matter of the brain [18].

Body mass index (BMI), calculated based on an individual's height and weight, is commonly used to assess body weight status [31]. According to the World Health Organization (WHO), a BMI between 25.0 – 29.9 kg/m^2 in adults is classified as overweight, while a BMI greater than or equal to 30.0 kg/m^2 is defined as obesity. The normal weight for an adult is indicated by a BMI between 18.5 – 24.9 kg/m^2 [32].

Accumulating evidence suggests that obesity, particularly BMI > 27 kg/m^2, and even overweight status, are associated with an increased risk of developing MS [10]. This association was confirmed, among others, in the previously mentioned observational study conducted within the German National Cohort (NAKO), which reported an odds ratio (OR) of 1.14 for elevated BMI and MS risk. The study also identified childhood and adolescence as critical periods, indicating that excessive weight gain during these stages may exert the strongest influence on MS development in later life [4]. These results are further supported by a 2025 meta-analysis, which shows that obesity in childhood or adolescence increases the risk of MS, while maintaining a normal BMI appears to have a protective effect. However, this analysis did not identify a significant association between overweight status during these periods and risk of developing MS [18]. Additionally, Mendelian randomization analysis conducted by Jacobs et al. provided evidence that genetically determined higher BMI in childhood is associated with increased MS risk, thus strengthening the argument for a potential causal relationship [25].

Psychological stress. In recent years, psychological stress has been increasingly considered a potential risk factor for the development of MS. Stress is defined as a state of disturbed physiological homeostasis triggered by an external or internal stimulus, referred to as a stressor. During a stress response, adrenaline is released and the hypothalamic-pituitary-adrenal (HPA) axis is activated, leading to the secretion of hormones that induce systematic physiological changes. Acute stress responses are physiological, generally adaptive and may even be beneficial to the human body. In contrast, chronic and prolonged stress can lead to pathological changes affecting multiple organ systems, including the immune system and the central nervous system (CNS). [33, 34]. Persistent activation of stress pathways may promote immune dysregulation and neuroinflammatory processes, which are considered relevant mechanisms in autoimmune diseases. Consequently, chronic stress has been implicated in the development of various non-communicable disorders, both somatic and psychiatric [4].

Several studies have evaluated the association between stress and the risk of developing MS. A 2025 meta-analysis conducted by von Drathen et al., which included 30 studies identified through a PubMed search, concluded that exposure to stressors was associated with a small to moderate increase in MS risk [35]. Similarly, in the previously mentioned analysis of the German National Cohort (NAKO), the cumulative burden of stressful life events (SLEs) was associated with a higher likelihood of developing MS (odds ratio [OR] 1.25) [4].

Despite these findings, the overall body of evidence remains limited, and the magnitude of the association appears modest compared with other established environmental risk factors. Therefore, further well-designed longitudinal studies are required to clarify the role of stress in MS pathogenesis, and to determine whether the observed associations reflect a causal relationship or are influenced by confounding factors.

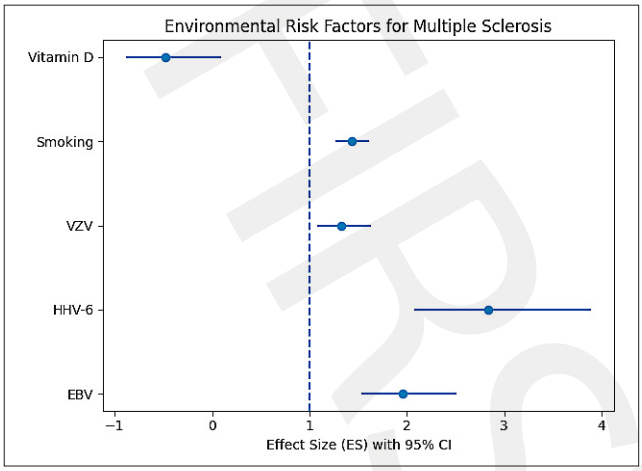

Figure 2. Pooled effect sizes (ES) with 95% confidence intervals for selected environmental risk factors associated with MS, based on meta-analysis by Vitturi et al. 'Environmental risk factors for multiple sclerosis: a comprehensive systematic review and meta-analysis' [15].
Positive ES indicates an increased likelihood of MS, whereas negative values suggest a potential protective effect. The strongest positive association was observed for HHV-6 (ES = 2.84, 95% CI = 2.08–3.89), then for EBV (ES = 1.96, 95% CI = 1.53–2.51). Significant associations were also found for VZV (ES = 1.33, 95% CI = 1.08–1.63) and smoking (ES = 1.43, 95% CI = 1.27–1.61). Vitamin D levels were inversely associated with MS risk (ES = -0.48, 95% CI = -0.88–0.09); however, the confidence interval crossed the null value, indicating a lack of statistical significance in the pooled analysis.
VZV – varicella zoster virus; HHV-6 – Human herpes virus 6; EBV – Epstein-Barr

SUMMARY

Available evidence indicates that environmental factors play a significant role in the pathogenesis and risk of MS, although their individual impact varies. The strongest association has been observed for EBV infection, supported by high odds ratios and a clear temporal relationship with disease onset. However, due to the high prevalence of EBV in the general population, infection alone is insufficient to cause MS, suggesting the importance of interactions between multiple environmental factors and genetic susceptibility. Vitamin D deficiency, tobacco smoking, and obesity show moderate but consistent associations with increased MS risk. The timing of exposure appears particularly important, especially during childhood and adolescence. In the case of tobacco smoking, an additional argument is the dose-response relationship and the impact on disease progression.

A major limitation of the available literature is the predominance of observational studies, which are prone to confounding factors and do not allow for definitive causal inference. Methodological heterogeneity and inconsistent results regarding less well-established factors, such as psychological stress and other infections, further complicate data interpretation.

The pathogenesis of MS appears to involve the cumulative impact of multiple environmental risk factors that act through both immune and neuroinflammatory mechanisms. Despite significant progress in understanding these associations, the exact causal pathways remain incompletely defined. Continued research focusing on the environmental determinants of MS may improve our understanding of the etiology of the disease, and support the development of effective preventive strategies.

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