# Multiple sclerosis: risk factors and therapies

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## Abstract

Multiple Sclerosis (MS) is a potentially progressive chronic autoimmune neurodegenerative disorder of the central nervous system, resulting from an autoimmune attack on the white matter. The main agents responsible for the development of MS involve exogenous, environmental, and genetic factors. The activation of the immune system triggers an inflammatory cascade at the level of nerve fibers and myelin. Regarding genetic predisposition, it is important to note that MS is not a hereditary disease. Infectious agents have also been studied as potential causes of the onset of MS. Several studies have shown that the Epstein-Barr Virus (EBV), responsible for mononucleosis, can influence the pathogenesis of MS, just as an altered mycobiome can play a role in triggering the pathology. Among the environmental factors, the prevalence of the disease observed as one moves away from the Equator is of particular etiopathogenetic relevance. This finding may be correlated with sun exposure and vitamin D (VD) levels. The aim of this article is to explore the complex risk factors and etiopathogenesis of MS, focusing on the interplay between genetic predisposition, environmental influences (such as VD deficiency and viral infections, particularly EBV), and the gut microbiome in the development and progression of the disease. This review was based on a comprehensive search of available medical and scientific literature, including observational studies (cohort, case-control, cross-sectional), meta-analyses, and systematic reviews, specifically addressing individuals with a confirmed MS diagnosis and studies related to genetic, environmental, or immunological risk factors. Studies that did not meet methodological standards, lacked relevant data, or were published in languages not understood by the authors were excluded.

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## Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease that affects the Central Nervous System (CNS), characterized by inflammation, demyelination, and axonal damage, which become apparent in the early stages of the disease. The course of the disease varies considerably from patient to patient, and despite recent therapeutic advances, MS remains one of the leading causes of neurological disability among young individuals.[1] Initially, demyelination slows down and reduces the effectiveness of nerve transmission. In the early stages, the body attempts to repair the damage through innate repair mechanisms, which can partially restore myelin and restore fairly normal nerve function. However, as the disease progresses and with repeated demyelinating events, this repair capacity decreases, leading to the onset of the disease.[2]

MS can present as Relapsing-Remitting (RR), with acute attacks followed by recovery and periods of stability. In the Primary-Progressive (PP) form, the disease progresses continuously without attacks. The Secondary-Progressive (SP) form begins as RR but becomes progressive over time. The Relapsing-Progressive (RP) form combines continuous progression and attacks, although its definition is still under discussion.[3] The prognosis depends on the individual response to treatment and the rate at which neurodegeneration occurs, with the hope that future research may provide more effective therapeutic strategies.[4] The common signs of MS are highly varied and can involve different areas of the CNS. Among the most frequent are vision loss, particularly unilateral optic neuritis, sensory disturbances, motor weakness, gait instability, and urinary, bowel, and sexual dysfunctions. Patients may also experience fatigue, heat intolerance, and cognitive changes. Numbness and loss of vibratory sensation are often among the first symptoms, while Lhermitte's phenomenon (an electric sensation along the spine with neck flexion) is a characteristic but not exclusive sign.[5]

The aetiology of MS is not yet fully understood, but it is

believed to result from an interaction between genetic predisposition and environmental factors. Research has suggested that certain viruses may play a role in the disease's genesis, acting through molecular mimicry.[1] Additionally, vitamin D (VD) deficiency has been identified as another important environmental factor, as low levels of this vitamin appear to be correlated with an increased risk of developing the disease. These factors, combined with genetic predisposition, may contribute to the onset of MS.[1]

The aim of this article is to explore the risk factors and etiopathogenesis of MS. It examines the interaction between genetic predisposition, environmental factors such as VD deficiency and viral infections, particularly by Epstein-Barr virus (EBV), and the gut microbiome in promoting the development and progression of the disease. The text also highlights future perspectives, including potential innovative treatments such as the use of probiotics, vitamins, and antiviral therapies.

This article was prepared by searching available medical and scientific literature.

The inclusion criteria were: observational studies (cohort, case-control, cross-sectional), meta-analyses, systematic reviews, studies including individuals with a confirmed diagnosis of MS, based on established diagnostic criteria, research addressing genetic, environmental, or immunological risk factors, as well as their interactions and mechanisms underlying the pathogenesis of MS.

The exclusion criteria were: abstracts without accompanying full texts, letters to the editor, opinion pieces, single case reports, studies including neurological conditions other than MS without clear differentiation, studies with inadequate methodology, unrepresentative samples or inconclusive results, articles published in languages not understood by the authors and without available translations, studies lacking quantitative or qualitative data relevant to MS risk factors or pathogenesis.

## Epidemiology

From an epidemiological perspective, MS can occur at any age, but it is most commonly diagnosed in individuals between the ages of 20 to 40; however, it can also manifest in children.[6] Several studies have highlighted a relationship between the prevalence of MS and latitude: the risk of developing the disease is lower in countries closer to the Equator, while it significantly increases in countries situated at higher latitudes, both in the North and the South. This phenomenon may be linked to VD levels, as equatorial countries have greater sun exposure, resulting in higher VD levels compared to populations in countries located farther from the Equator.[6]

Furthermore, the condition is more common in women, with a woman-to-man ratio of approximately 3:1; however, men experience a faster and more severe progression of the disease.[7,8]

The reasons for this prevalence are not yet fully understood, but various factors may be involved, including differences in hormonal and genetic structure, lifestyle, and environmental exposure.[9]

## Risk factors

Although the understanding of the causes and mechanisms underlying the disease is continually evolving, significant associations have already been identified with genetic predisposition, infectious agents, and environmental factors.[9]

Regarding genetic predisposition, it is important to note that MS is not an inherited disease; however, other epidemiological studies have highlighted a certain predisposition within the same family. Recent data, though, show that the risk of developing the condition is only slightly higher compared to individuals who are not genetically predisposed.[9]

The risk of developing MS is higher among the relatives of an affected individual compared to the general population, particularly among siblings, parents, and children.[10]

The familial recurrence rate of the disease is 20%.[11] In monozygotic twins, the concordance of MS occurs in approximately 35% of cases, while it drops to 5% in non-twin siblings, suggesting that the disease has a quantitative genetic component.[10,11]

In addition to family studies, specific genes associated with MS have been identified. In particular, alterations in the Human Leukocyte Antigen (HLA), a group of genes located on chromosome 6 that code for the Major Histocompatibility Complex (MHC), are linked to an increased risk of developing the disease.[11]

The most significant association concerns the HLA-DR15 and HLA-DQ6 alleles, which have been consistently linked to MS. In contrast, other loci, such as HLA-C554 and HLA-DRB1*11, appear to have a protective effect, reducing the likelihood of developing the disease. These findings highlight the genetic complexity of MS and suggest that the interaction between genetic variants may significantly influence the risk of disease onset.[11]

## Virus

Evidence that viruses may be triggering factors for diseases includes their observed presence in most patients who exhibit oligoclonal bands in cerebrospinal fluid.[12]

The Herpesviridae family of viruses may be associated with MS. Individuals who have never been infected with EBV exhibit a lower risk, while those who acquire the infection during adolescence have a higher risk compared to those who are infected at an earlier age.[11,13] In particular, a study conducted on 3 million individuals highlighted that EBV infection during young adulthood significantly increases the risk of developing MS with a relative risk of 3.0 (95% Confidence Interval 1.3–6.5).[14]

A molecular mimicry mechanism has been proposed between EBV and an autoimmune protein, where the immune response directed against the virus could mistakenly trigger an attack on the myelin, leading to demyelination.[15] In particular, four peptide-binding contacts of the T-cell receptor, restricted by the *DRB1* gene, have been identified, which are identical for both the myelin basic protein and EBV. Additionally, evidence suggests that a significant percentage of B cells present in chronic MS lesions are infected with EBV.[11]

It is believed that the subsequent reactivation of EBV within the CNS may trigger the development of MS. In fact, one study explored the possible role of EBV in the disease by examining post-mortem brain tissues from MS patients. Researchers found signs of EBV infection in a large proportion of infiltrating B cells and plasma cells in the brain (21 out of 22 cases). Specifically, in cases of secondary progressive MS, ectopic B follicles in the cerebral meninges were identified as the main sites of viral persistence. Expression of latent viral proteins was observed, while viral reactivation appeared to be confined to these follicles and acute lesions. Additionally, signs of activation of CD8+ T cells against infected plasma cells have been observed, suggesting an active role of the immune system. These findings indicate that the persistence and reactivation of EBV within the central nervous system may play a crucial role in the immunopathology of MS.[16]

Additionally, there are theories suggesting a possible association between MS and other infectious diseases, such as measles,

mumps, and rubella, although these correlations require further investigation.[11]

The growing evidence of the pathogenic involvement of EBV in MS offers new perspectives for the prevention and treatment of the disease, suggesting that it may be possible to effectively control EBV infection through vaccination, antiviral therapies, or interventions with EBV-specific cytotoxic CD8+ T cells.[17]

A study demonstrated that an experimental vaccine based on the EBV glycoprotein 350 (gp350) showed 78% efficacy in preventing infectious mononucleosis in EBV-seronegative individuals, though it did not protect against asymptomatic infections. Vaccinated participants maintained anti-gp350 antibodies for over 18 months, and the vaccine was found to be safe and well-tolerated.[18]

Regarding antiviral therapies, in patients with relapsing-remitting MS, treatment with acyclovir reduced the annual relapse rate by 34% compared to placebo.[19] Although the overall result was not statistically significant (P = 0.083), further analysis revealed a significant reduction in relapses in subgroups of patients with high disease activity.[19]

Another study assessed the effectiveness of valacyclovir in reducing active lesions identified by MRI in MS patients. While the treatment did not significantly reduce new lesions overall, in patients with high disease activity there was a reduction in active lesions and an increase in scans free of new lesions.[20]

## Vitamin D

VD is a fat-soluble vitamin that requires two conversion phases to become active. Initially, it is converted into calcidiol (25(OH)D) in the liver, and then it is further converted into calcitriol (1,25(OH)D2), primarily in the kidneys. Calcitriol represents the active form of VD, a steroid hormone that interacts with the VD receptor (VDR).[21]

Cholecalciferol, a precursor of VD, can be taken as a dietary supplement to prevent or treat VD deficiency.[22]

Numerous studies have shown an association between MS and VD deficiency, suggesting that VD may play a significant role in modulating the immune response.[23] Additionally, studies conducted on *in vitro* models and animal models of toxin-induced demyelination have provided evidence that VD may positively influence the process of myelination.[23]

In particular, one study evaluated the efficacy of cholecalciferol (D3) and ergocalciferol (D2) in promoting nerve lesion recovery in rats, using doses of 100 or 500 IU/kg/day.[22] Although it was unclear which form was more effective, the results showed that D3, at a dose of 500 IU/kg/day, induced significant recovery compared to ergocalciferol and the control group. Specifically, cholecalciferol increased: i) the number of preserved or newly formed axons at the proximal end; ii) the average axon diameter at the distal end; iii) myelination of neurites at both ends.

In parallel, to identify the genes regulated by VD in the dorsal root ganglia and/or Schwann cells, an *in vitro* transcriptome study was conducted. This revealed that cholecalciferol activates several genes associated with axonogenesis and myelination.[22]

Specifically, genes such as *Cdw92*, *Kras*, *Metrn*, *Myc, Ppp3cb, Rtn4rl2, Spp1, Trim2, Tspan2*, and *Vegfa* contain a Vitamin D-Responsive Element (VDRE) in their promoter regions and are known for their role in axonal growth. For instance, *Igf1* promotes neurite elongation, while *Metrn* regulates glial cell differentiation and axonal extension.[22]

However, it is important to emphasize that, despite the demonstrated benefits, the use of high doses of VD, especially in chronic therapy, must be carefully monitored. VD toxicity can cause serious side effects, including renal failure, cardiac arrhythmias, and epileptic seizures, and its symptoms, such as fatigue and muscle weakness, may mask the signs of MS progression.[23]

## Intestinal microbiota

The composition of the intestinal microbiota and the gut-brain axis are increasingly relevant factors in the development of diseases. Alterations in the microbiota, such as dysbiosis, may be implicated in the pathogenesis and progression of autoimmune diseases, particularly in Western societies.[24]

A comparison between 34 pairs of monozygotic twins discordant for the disease revealed an increase in *Akkermansia muciniphila* in untreated twins. Furthermore, fecal microbiota transplantation from twins with MS into a mouse model increased the incidence of brain autoimmunity. Although 16S sequencing and shotgun metagenomics did not detect significant global differences, *Akkermansia muciniphila* was more abundant in the untreated twins. When the microbiota of MS-afflicted twins was transplanted into mice, it led to higher autoimmunity compared to that from healthy twins. Mice colonized with the microbiota from MS twins produced less IL-10, a regulatory cytokine, than mice with healthy microbiota. These findings suggest that the microbiota in MS patients contains factors that promote disease development in animal models, paving the way for new research into microbial components in human MS.[25]

A recent meta-analysis conducted on patients with relapsing-remitting MS examined four studies that included a total of 213 patients, with 106 treated with probiotics. The results suggested that the use of probiotics led to improvements in disability, depression, and overall health of the patients.[24] However, it is important to emphasize that these findings should be interpreted with caution. The included studies were relatively small, had limited duration, and did not provide sufficient information on potentially influencing factors, such as dietary habits and other elements that may affect disease activity. Furthermore, the overall impact of these factors on clinical outcomes was not adequately explored. The use of probiotics had a positive effect on the composition of the intestinal microbiome in nine patients, and induced a shift toward an anti-inflammatory cytokine profile in the blood during the weeks of treatment. These results, although promising, require further confirmation through larger and longer-term studies to fully assess the therapeutic potential of probiotics in MS.[24]

## Conclusions

MS represents a complex condition, with its causes and mechanisms largely still to be fully understood, despite significant progress in scientific research. The disease involves interactions between genetic predisposition, environmental factors, and infectious agents, with EBV and VD deficiency appearing to play crucial roles in the development and progression of the disease. Furthermore, the growing awareness of the intestinal microbiome opens new perspectives for the treatment and prevention of MS, suggesting the possibility of modulating the immune system through the use of probiotics or other targeted therapies. Current therapies offer improvements in disease management, but it is clear that a deeper understanding of the underlying mechanisms of MS and its interactions with external factors could pave the way for more effective and personalized treatments. The exploration of innovative approaches, such as targeted

antiviral therapies, the use of VD, and modulation of the intestinal microbiome, could further enhance the quality of life for patients and potentially alter the course of the disease. However, continued rigorous and long-term clinical studies are necessary to confirm the efficacy of these approaches and ensure that no unwanted side effects occur.

In summary, research on MS is making significant strides, but it remains essential to continue deepening our knowledge of the disease to develop more effective and personalized treatments, to reach the objective of reducing the impact of MS on patients' life and improving their long-term health prospects.

## References


1. Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: clinical aspects. Curr Opin Neurol 2018;31:752-9.
2. Buzzard K, Chan WH, Kilpatrick T, Murray S. Multiple sclerosis: basic and clinical. In: Multiple Sclerosis: Advances in Clinical and Basic Research. Springer; 2017. p. 149-73.
3. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996;46:907-11.
4. Weinshenker BG. The evolution of multiple sclerosis: natural history of multiple sclerosis. Ann Neurol 1994;36:S6-11.
5. Deangelis TM, Miller A. Diagnosis of multiple sclerosis. In: Multiple Sclerosis: A Comprehensive Textbook. 2nd ed. Elsevier; 2015. p. 159-68.
6. Dobson R, Giovannoni G. Multiple sclerosis - a review. Eur J Neurol 2019;26:27-40.
7. Alwan S, Sadovnick AD. Multiple sclerosis and pregnancy: maternal considerations. Expert Rev Obstet Gynecol 2012;7: 489-97.
8. Jobin C, Larochelle C, Parpal H, et al. Gender issues in multiple sclerosis: an update. Women's Health 2010;6:797-820.
9. Nourbakhsh B, Mowry EM. Multiple sclerosis risk factors and pathogenesis. Curr Opin Neurol 2019;32:264-70.
10. Compston A, Coles A. Multiple sclerosis. Lancet 2002;359: 1221-31.
11. Compston A, Coles A. Multiple sclerosis. Lancet 2008;372: 1502-17.
12. Gilden DH. Infectious causes of multiple sclerosis. Lancet Neurol 2005;4:278-85.
13. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol 2007;61:288-99.
14. Levin LI, Munger KL, Rubertone MV, et al. Temporal relationship between elevation of Epstein-Barr virus antibody titers and initial onset of neurological symptoms in multiple sclerosis. JAMA 2005;293:2496-501.
15. Lang HL, Jacobsen H, Ikemizu S, et al. A functional and structural basis for TCR cross-reactivity in multiple sclerosis. Nat Immunol 2002;3:920-7.
16. Serafini B, Rosicarelli B, Franciotta D, et al. Dysregulated Epstein-Barr virus infection in the multiple sclerosis brain. J Exp Med 2007;204:1595-604.
17. Pender MP, Burrows SR. Epstein-Barr virus and multiple sclerosis: potential opportunities for immunotherapy. Clin Transl Immunol 2014;3:e25.
18. Sokal EM, Hoppenbrouwers K, Vandermeulen C, et al. Recombinant gp350 vaccine for infectious mononucleosis: a phase 2, randomized, double-blind, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of an Epstein-Barr virus vaccine in healthy young adults. J Infect Dis 2008;197:73-81.
19. Thacker EL, Mirzaei F, Ascherio A. Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis. Ann Neurol 2006;59:499–503.
20. Lycke J, Svennerholm B, Hjelmquist E, et al. Acyclovir treatment of relapsing-remitting multiple sclerosis. A randomized, placebo-controlled, double-blind study. J Neurol 1996;243: 214–24.
21. Jeon SM, Shin EA. Exploring vitamin D metabolism and function in cancer. Exp Mol Med 2018;50:1-14.
22. Chabas JF, Stephan D, Marqueste T, et al. Cholecalciferol (Vitamin D3) improves myelination and recovery after nerve injury. PLoS One 2013;8:e65034.
23. Feige J, Moser T, Bieler L,et al. Vitamin D supplementation in multiple sclerosis: A critical analysis of potentials and threats. Neurol Res Pract 2020;2:14.
24. Preiningerova JL, Zakostelska ZJ, Srinivasan A, et al. Multiple sclerosis and microbiome. Biomolecules 2022;12:433.
25. Berer K, Gerdes LA, Cekanaviciute E, et al. Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proc Natl Acad Sci U S A 2017;114:10719-24.