THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

MEDICINE
Health and the Environment

THE MOST COMMON ENVIRONMENTAL RISK FACTORS ASSOCIATED WITH MULTIPLE SCLEROSIS – A 2019–2024 LITERATURE REVIEW

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Received March 19, 2025

Objective: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by demyelination and neurodegeneration, leading to varying levels of disability, especially present in younger individuals[1]. While the exact cause of MS is still unknown, the aim of this systematic literature review was to emphasize the most common environmental (modifiable) risk factors[2] while also mentioning genetic and less frequent risk factors in the hopes of better understanding and preventing MS onset and progression. **Methods**: To further this goal, we analyzed a total of 289 articles, after standardized selection criteria we were left with the final article count of 23 articles, left for complete text analysis. We have also freely added an additional 38 articles that provided additional relevant information. **Results**: The most common environmental risk factors for MS were: lower vitamin D levels and lower sunlight exposure – predominantly at higher, northern, latitudes (associated with increased risk of onset and relapses of MS[3]), which can also be influenced by seasonal and weather changes, smoking (as well as air pollution) (associated with increased risk of onset and progression acceleration)[4], EBV infection (especially if it manifests as infectious mononucleosis during adolescence, increases risk of MS[5]) – this is the most common infection cited, but other upper respiratory tract infections have also been cited as being commonly associated with MS relapses[3]; diet, obesity and gut microbiota also play an interesting role and have been a study of great debate regarding MS patients. **Conclusions:** While there still is a need to further understand these risk factors, future treatment strategies have to target these modifiable risk factors both in a theoretically healthy population that lives in a modern world that is evermore predisposed to autoimmune disease such as MS, but also at controlling these risk factors that may influence progression, relapse and complications for patients already diagnosed with MS.

Keywords: Multiple Sclerosis, environmental risk factors, smoking, air pollution, EBV, gut microbiota, diet, obesity.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by demyelination and neurodegeneration, leading to varying levels of disability (up to 60% of the affected individuals can no longer work in the later stages of disease – leading to marked quality of life reduction and important health and economic burdens to society[1]). It is the most common neurological disorder affecting young and middle-aged adults, especially women[6]. Demyelination affects the central nervous system – namely the brain and spinal cord[7]. It has a relapsing alternating with progressive pattern, with variation towards one of the two states based on the form. Most patients suffer episodic neurological dysfunction – the relapsing/remitting form of the disease (RRMS) with potential evolution towards the progressive phase of the disease (SPMS) or direct initiation with slow, progressive accumulation of neurological dysfunction – primary progressive multiple sclerosis (PPMS)[8,9].

Pathologically, the inflammatory process affecting MS is characterized by focal demyelination with activated microglia and peripheral inflammatory cell accumulation[8].

MS has a complicated **etiology**, with an unknown exact cause, but it is probably due to a dysregulation of the immunological system[8], involving both genetic (non-modifiable) and environmental (modifiable) risk

factors[2]. This literature review has aimed to analyze the key risk factors associated with the onset, relapses, and progression of MS based on recent research findings, hoping that highlighting them will lead to further study and prevention of this disabling pathology.

While there is no known cure for MS, stopping the inflammation, controlling the course of the disease through treatment and controlling the modifiable risk factors are important ways through which the individual can have an almost normal life[7].

In summary, we will discuss the following (**environmental) risk factors** extensively: lower **vitamin D** levels and lower **sunlight exposure** – predominantly at higher, northern, latitudes (associated with increased risk of onset and relapses of MS[3]), which can also be influenced by **seasonal and weather changes, smoking (as well as air pollution)** (associated with increased risk of onset and progression acceleration)[4], **EBV infection** (especially if it manifests as infectious mononucleosis during adolescence, increases risk of MS[5]) – this is the most common infection cited, but other upper respiratory tract infections have also been cited as being commonly associated with MS relapses[3]. **Diet, obesity and gut microbiota** also play an interesting role and have been a study of great debate regarding MS patients.

Perhaps the least well studied, but arguably the most important factor regarding future study is **genetic predisposition** – particularly variations in the HLA-DRB1 gene, significantly increases the risk of MS[10]. Over 200 genetic risk variants have been identified[11], many of which are involved in immune response regulation[12].

METHODS

Risk factors	Initial number of articles	Final Article Count	Article Name	Doi
Vitamin D	93	4	1: Gombash SE, Lee PW, Sawdai E, Lovett-Racke AE. Vitamin D as a Risk Factor for Multiple Sclerosis: Immunoregulatory or Neuroprotective? Front Neurol. 2022 May 16;13:796933.	doi: 10.3389/fneur.2022.796933. PMID: 35651353; PMCID: PMC9149265.
			2: Rodney C, Rodney S, Millis RM. Vitamin D and Demyelinating Diseases: Neuromyelitis Optica (NMO) and Multiple Sclerosis (MS). Autoimmune Dis. 2020 Jan	doi: 10.1155/2020/8718736. PMID: 32373353; PMCID: PMC7187724.
			3: Jasper EA, Nidey NL, Schweizer ML, Ryckman KK. Gestational vitamin D and offspring risk of multiple sclerosis: a systematic review and meta-analysis. Ann Epidemiol. 2020 Mar;43:11-17.	doi: 10.1016/j.annepidem.2019.12.010. Epub 2020 Jan 3. PMID: 32014337.
			: Ismailova K, Poudel P, Parlesak A, Frederiksen P, Heitmann BL. Vitamin D in early life and later risk of multiple sclerosis-A systematic review, meta-analysis. PLoS One. 2019 Aug 27;14(8):e0221645.	doi:10.1371/journal.pone.0221645. PMID: 31454391; PMCID: PMC6711523.
Air pollution	7	5	1: Lotfi F, Mansourian M, Mirmoayyeb O, Najdaghi S, Shaygannejad V, Esmaeil N. Association of Exposure to Particulate Matters and Multiple Sclerosis: A Systematic Review and Meta-Analysis. Neuroimmunomodulation. 2022;29(1):21-27.	doi: 10.1159/000516559. Epub 2021 Jun 16. PMID: 34134109.
			2: Tang C, Li QR, Mao YM, Xia YR, Guo HS, Wang JP, Shuai ZW, Ye DQ. Association between ambient air pollution and multiple sclerosis: a systemic review and meta-analysis. Environ Sci Pollut Res Int. 2021 Nov;28(41):58142-58153.	doi: 10.1007/s11356-021-14577-z. Epub 2021 Jun 9. PMID: 34109523.
			3: Noorimotlagh Z, Azizi M, Pan HF, Mami S, Mirzaee SA. Association between air pollution and Multiple Sclerosis: A systematic review. Environ Res. 2021 May;196:110386.	doi: 10.1016/j.envres.2020.110386. Epub 2020 Oct 28. PMID:33129851.
			4: Farahmandfard MA, Naghibzadeh-Tahami A, Khanjani N. Ambient air pollution and multiple sclerosis: a systematic review. Rev Environ Health. 2021 Jan 4;36(4):535-544.	doi: 10.1515/reveh-2020-0079. PMID: 34821118.
			5. Abbaszadeh S, Tabary M, Aryannejad A, Abolhasani R, Araghi F, Khaheshi I, Azimi A. Air pollution and multiple sclerosis: a comprehensive review. Neurol Sci. 2021 Oct;42(10):4063-4072.	doi: 10.1007/s10072-021-05508-4. Epub 2021 Aug 3. PMID: 34341860.
Smoking	51	4	1: Arneth B. Multiple Sclerosis and Smoking. Am J Med. 2020 Jul;133(7):783-788	doi: 10.1016/j.amjmed.2020.03.008. Epub 2020 Apr 5. PMID: 32259516.
			2: Rosso M, Chitnis T. Association Between Cigarette Smoking and Multiple Sclerosis: A Review. JAMA Neurol. 2020 Feb 1;77(2):245-253.	doi: 10.1001/jamaneurol.2019.4271. PMID: 31841592.
			3: Jasielski P, Piędel F, Rocka A, Petit V, Rejdak K. Smoking as a risk factor of onset and relapse of Multiple Sclerosis - a review. Neurol Neurochir Pol. 2020;54(3):243-251. 32285433.	doi: 10.5603/PJNNS.a2020.0032. Epub 2020 Apr 14. PMID:
			4: Schlindwein MAM, de Moura Campos MH, Breis LC, Chara BS, Scherer CS, Caminski VAP, Matta A, Gonçalves MVM. Impacts of environmental tobacco smoke on the onset and progression of multiple sclerosis: a systematic review. Arq Neuropsiquiatr.	doi: 10.1055/s-0044-1779271. Epub 2024 Mar 15. PMID: 38490261; PMCID: PMC10942830.
Diet/gut microbiota/obesity	61	5	1: Samara A, Cantoni C, Piccio L, Cross AH, Chahin S. Obesity, gut microbiota, and multiple sclerosis: Unraveling the connection. Mult Scler Relat Disord. 2023 Aug;76:104768.	doi: 10.1016/j.msard.2023.104768. Epub 2023 May 18. PMID:37269641.
			2: Qu X, Walsh EI, Cherbuin N, Black LJ. Mapping the Literature on Diet and Multiple Sclerosis: A Data-Driven Approach. Nutrients. 2022 Nov 14;14(22):4820.	doi: 10.3390/nu14224820. PMID: 36432507; PMCID: PMC9696310.
			3: Brockhoff JD, Bereswill S, Heimesaat MM. The impact of ketogenic diet on the onset and progression of multiple sclerosis. Eur J Microbiol Immunol (Bp). 2023 Sep 4;13(2):29-36.	doi: 10.1556/1886.2023.00020. PMID: 37665667; PMCID: PMC10578139.
			4: Fotros D, Noormohammadi M, Razeghi Jahromi S, Abdolkarimi M. Fruits and vegetables intake may be associated with a reduced odds of multiple sclerosis: a systematic review and dose-response meta-analysis of observational studies. Nutr Neurosci. 2023 Oct 18:1-12.	doi: 10.1080/1028415X.2023.2268390. Epub ahead of print. PMID: 37851580.
			5: Sato W, Yamamura T. Multiple sclerosis: Possibility of a gut environment-induced disease. Neurochem Int. 2019 Nov;130:104475.	doi:10.1016/j.neuint.2019.104475. Epub 2019 May 30. PMID: 31152766.
Measles/EBV infection	77	5	1. Soldan SS, Lieberman PM. Epstein-Barr virus and multiple sclerosis. Nat Rev Microbiol. 2023 Jan;21(1):51-64.	doi: 10.1038/s41579-022-00770-5. Epub 2022 Aug 5. PMID: 35931816; PMCID: P
			Houen G, Trier NH, Frederiksen JL. Epstein-Barr Virus and Multiple Sclerosis. Front Immunol. 2020 Dec 17;11:587078.	doi: 10.3389/fimmu.2020.587078. PMID: 33391262; PMCID: PMC7773893.
			Thomas OG, Rickinson A, Palendira U. Epstein-Barr virus and multiple sclerosis: moving from questions of association to questions of mechanism. Clin Transl Immunology. 2023 May 17;12(5):e1451.	doi: 10.1002/cti2.1451. PMID: 37206956; PMCID: PMC10191779.
			Hedström AK. Risk factors for multiple sclerosis in the context of Epstein-Barr virus infection. Front Immunol. 2023 Jul 24;14:1212676.	doi: 10.3389/fimmu.2023.1212676. PMID: 37554326; PMCID: PMC10406387.
			Ruprecht K. The role of Epstein-Barr virus in the etiology of multiple sclerosis: a current review. Expert Rev Clin Immunol. 2020 Dec;16(12):1143-1157.	doi: 10.1080/1744666X.2021.1847642. Epub 2020 Dec 17. PMID: 33152255.

We analyzed a total of approximately 289 articles, after selection 23 articles were left for complete text analysis – which we have linked in the table below, for ease of use. The selection was based on the following keywords, which were added in the PubMed search engine – "multiple sclerosis" and "environmental risk factors" – with additions of each frequent risk factors as well "vitamin D", "sunlight", "air pollution", "smoking", "diet", "gut microbiota", "obesity", "measles", "EBV", "infection". We selected articles dating from the last 5 years, opting for meta-analysis, randomized clinical trials, literature reviews and systematic reviews.

RESULTS

The bulk of our work targeted the most common risk factors in MS. The following paragraphs will summarize our findings.

Vitamin D deficiency

There has been a continual rise in global (regardless of climate or geographical location) autoimmune disease incidence, which has corresponded with the population's vitamin D level fall[13]. Researchers have demonstrated evidence that women are predisposed towards autoimmune disease diagnoses, MS included– most likely due to the complex synergic relationship between estrogens and vitamin D[14].

Physiology of vitamin D: Potential sources include: **sunlight** (the main source) – through UVB photolysis 7-dehydrocholesterol becomes pre-vitamin D3 in the epidermis, which then isomerizes to vitamin D3; **diet** – ingesting vitamin D2 derived from plants/ cholecalciferol supplements and oily fish (a study even mentioned the surprising discrepancy in rural populations with MS in Norway based on the consumption / lack of consumption of large quantities of oily fish, in similar geographical locations)[15]. After hydroxylation, first in the liver as 25(OH)D3 – the main circulation form, and second in the kidney as biologically active hormone 1,25(OH)2D3[16]. This active hormone has both genomic (gene transcription in many cell types)[17] and non-genomic effects: namely modulating calcium physiology, but interestingly also the development and function of the CNS. Study shows that the active hormone has the ability to regulate certain neurotrophic factors (such as GDNF and NGF[18]) and as such researchers have expressed the hypothesis that vitamin D could be considered neuroprotective, with proven benefits of reduction in ROS induced cell death and promoting anti-oxidant species in glia cell[19].

Normal levels of vitamin D vary from 20–40 ng/ mL, with levels between 20–29 ng/ml being insufficient, and below 20 ng/ mL considered to be deficient, with an estimation that 30–50% of Americans may be vitamin D deficient according to certain studies[20].

Vitamin D deficiency during childhood has been cited as being linked to adult onset MS – the mechanism seems to be based on the immunoregulatory properties of Vitamin D innate and adaptive immunity, with low levels resulting in abnormal immune responses. Moreover, vitamin D receptors are located in various cells that govern the structural and functional properties of the CNS (central nervous system) – neurons, but also oligodendrocytes, astrocytes, and microglia. As such, low vitamin D levels affect the vulnerable CNS through inflammation and developmental blockages[8]. Vitamin D deficiency has been associated with the process of demyelination[13]. Even if the association between vitamin D deficiency in early life and later life MS seems extremely likely, more thorough research is needed to conclude this statement[6].

Moreover, vitamin D deficiency has been demonstrated to be associated with other neurological disorders besides MS, such as Parkinson's disease, schizophrenia, depression, and cognitive decline[21].

There are multiple studies which show that MS has a direct proportional relation with **latitude** – with the lowest prevalence at the equator and highest in northern regions[22]. Several studies have also studied this north-south gradient, sometimes even within the same country[23]. This is partly due to inversely correlated exposure to the sun's light, but genetics and the different lifestyles of individuals also play a factor[24]. When talking about migration, the moment of changing one's country seems to play an important role – when migrating from high to low-MS-risk areas[6], persons younger than 15 years old adopting the new country's (lower) risk frequency of developing MS and persons older than 15 maintaining the old country's (higher) risk pattern[22]. This relationship seems to be reversed when migrating from low to high-MS-risk areas[6]. Another study proved that second-generation migrants from low to high-MS-risk areas still show increased MS risk[25]. Overall,

the risk of devolving MS is determined mainly around the age of 15 years, which proves the important role of environmental factors (such as sunlight and vitamin D exposure) during childhood and teenage years[26].

A strong argument favoring the correlation between MS and latitude and sunlight exposure (and subsequent vitamin D deficiency) is that of the **seasonal fluctuations** of MS flares. In addition, researchers have demonstrated seasonal fluctuations of vitamin D levels, resulting in lower in-utero exposure, which may contribute to individuals born in Spring at a higher risk of developing MS compared to those born in the fall[27]. This risk continues to fluctuate in early infancy, childhood and then adolescence – with higher sun exposure[28] and time spent outdoor activities[29] (especially in warm seasons) reducing MS risks.

There were no relevant statistical data to link **EBV antibody titers and vitamin D levels**, but there has been evidence that both are higher and lower, respectively, in MS patients[30] and together with smoking and genetic predisposition, may work interactively to determine MS susceptibility[31].

Vitamin D also acts as a **modulator of MS clinical evolution** – with lower blood levels during relapses than during remissions[32], with an inverse proportional relation with EDSS and frequency of relapse[33].

What is interesting is that researchers have demonstrated the potential of vitamin D receptor-activating drugs that enhance remyelination in patients with demyelinating diseases such as MS and neuromyelitis optica (NMO)[13].

Cigarette Smoking and MS

Cigarette smoking is a common environmental risk factor and addiction, with pathological health repercussions, such as that being associated with disease activity and negative prognosis in patients with MS[34]. Smoking may be a key modifiable risk factor in MS, according to most researchers[17]. In addition, smoking promotes a faster brain atrophy rate and a greater disability burden[35]. Researchers have also studied the effect that environmental tobacco smoking (ETS) (aka "passive smoking") has had on the development and evolution of MS – with two meta-analyses, and two extensive systematic reviews mostly showing articles with a positive association between ETS exposure and higher risk of developing MS, but could not establish a strong association with MS progression[36].

Pathology: acting as an irritative agent on the respiratory tract, it unleashes a proinflammatory cascade that may end up in autoimmunity; disease activity association is explained by the antigen cross-reactivity between lung antigens and myelin antigens, in patients with MS chronic inflammation; there may also be a genetic component, with certain individuals being more predisposed towards this process; cigarette smoke may also contain free radicals, cyanates, carbon monoxide – these components can be directly neurotoxic. While these are possible venues of exploration regarding the mechanism of smoking linked to the progression of MS, more thorough research is needed to understand the underlying mechanism[37]. While it may not be the only cause of MS, it appears to be an important aggravating factor, influencing both MS onset and progression.

While smoking does have a long-term toll on an individual's health, some of the neurological outcomes of smoking can be reversible – making counseling in stopping the addiction key[38].

Smoke Pollution and MS

What we call ``air pollution`` is actually a mixture of PM (particulate matter), gasses (ozone, carbon monoxide, sulfur, nitrogen oxides), heavy metals (lead, manganese, copper) and organic compounds (bacterial endotoxins, aromatic polycilic hydrocarbons)[39].

PMs can range from 10 to 2.5 μm (PM10 and PM2.5, respectively) and ultra-fine particles. PMs are thoracic and breathable air particles, capable of deeply penetrating into the bloodstream, upper respiratory tract and nervous system itself[40,41].

PMs can originate from different sources – but most importantly we mention living in proximity to major roads, big cities with poor air quality control, working in toxic environments.

The **mechanism** through which these air particles chronically induce inflammation seems to be explained by the promotion of proinflammatory markers in the human brain, leading to neuroinflammation, neurodegeneration, and alteration in the blood-brain barrier – all processes that can elevate the risk of MS development and relapse[42]. The pulmonary tissue affected by PMs also has an indirect effect that leads to systemic inflammation and autoimmunity[43]. The effect that

PMs have may also produce epigenetic changes, promoting the production of proinflammatory cytokines.

While the association between air pollution and MS is unclear, preliminary data demonstrated by multiple studies show that exposure to particulate matter (PM) is associated with increased MS relapse and incidence[39].

MS is not the only autoimmune disease known to be correlated with limited air quality, but the frequent association of MS in highly developed and technologized countries, marked by abundant air pollution, makes this risk factor worth studying[39].

Further studies are needed, but it seems that exposure to PMs and heavy metals has been associated with the risk of MS onset and a direct correlation with its severity[42]. Another systematic review has also put forth the importance of nitrogen oxides (and other gasses) in relation to the prevalence and relapse of MS[44].

Diet, gut microbiota and obesity and MS

The ketogenic diet (KD) is a popular non-pharmacological option in treating various medical conditions dating back to more than a century ago (including epilepsy, but also Parkinson's disease and Alzheimer's disease). Based on the proven anti-convulsive, anti-inflammatory and potentially neuroprotective effects properties of said diet, researchers have screened the literature for reports of potential benefits towards MS patients. While the existing literature supports the safety and feasibility of KD in MS patients, with positive impacts on cellular metabolism and disease outcome and animal trials that confirmed the application of the properties mentioned above for MS, larger human clinical trials are needed to confirm these initial encouraging findings[45].

MS and nutrition – an extensive search: The cited researchers conducted a thorough literature analysis of the last 50 years of MS publications related to diet and have defined 4 clusters of research[46] – risk and symptom management, mouse models of MS, gluten sensitivity; and dysphagia. They remarked an emphasis on MS onset and risk factors in the detriment of MS progression, and also a lack of evidence of specific foods' and nutrients' effects in relation to MS – with a need to fill these gaps in knowledge with future study. According to this analysis, the most commonly researched food items in relation to MS seem to be (in order of citations) salt, milk and dairy, olive oil, fish, and meat. Nutrients were even more frequently researched – with vitamin D being the top search result, followed by fat, protein, vitamin B, gluten, sodium, iron, cholesterol, and alcohol.

Some researchers have pointed out that **fruit and vegetable intake** may reduce the odds of multiple sclerosis based on the high levels of vitamins, minerals, fiber, and active molecules that contribute to the body's health and immunity and physiological function – with no statistical relevant data to press this statement further[47].

Risk-associated diet choices may include foods or nutrients affecting neurodegeneration – in a similar fashion, predisposing the patient to MS and Alzheimer's disease. But in studying this, researchers caution in taking account of other factors that promote neurodegeneration – such as oxidative stress, neuroinflammation and apoptosis[46].

Another "hot topic" discussion was that regarding **gut microbiota in relation to MS** – with various theories but no hard evidence. One such theory is based on the fact that gut microbiota constitutes an important part of our body, that plays critical roles in various neurological diseases, that were not initially thought to be linked to any intestinal pathology. This is supported by numerous reports from Japan, North America, and Europe that confirm that dysbiosis of the gut microbiota is frequently found in MS patients[48]. Japan, in particular, has seen a rise in cases of MS (and Crohn's disease, in a similar pattern) that has pushed research towards identifying MS environmental risk factors, to further enhance the development of prevention and treatment of MS for future generations[47]. In studying the potential explanations for this rise of autoimmune diseases, the leading theory is that of dietary changes in a population that traditionally consumes a lot more fiber (rice) and fish, much less rice. Changing from a mostly vegetarian to a meat-centric regime leads to significant alterations of the gut microbiota as well, with new bacteria species more suited to the task at hand[49].

Dysphagia-related articles referred mostly to the advanced neurological disability that can occur in MS patients – and discussed management issues permitted and recommended dietary choices[50].

Gluten sensitivity was also mentioned frequently as a possible contributor to neurological disease – with a gluten-free diet being proposed as a beneficiary[51].

Obesity is associated with chronic, if mild, systemic inflammation – including neuroinflammation. Researchers have pointed out that obesity in early life can contribute as a significant risk factor for MS development – without current exact knowledge in understanding the underlying mechanism between the two. There seems to be a consensus that obesity and high-calorie diets can alter gut microbiota, leading to further autoimmune dysregulation. The researchers propose a further study emphasizing dietary interventions, microbiota-derived products, exogenous antibiotics, and probiotics, and, of course, controlling obesity, a risk factor for many other neurological pathologies, stroke included[52].

Epstein-Barr virus infection and MS

Epstein-Barr virus (EBV), a B lymphotropic human gamma herpesvirus[53], is arguably one of the most successful pathogens to infect humans – leading to almost 90% of the global population being infected with mostly asymptomatic forms[54]. Studies show that almost all (99.5%) of patients with MS are seropositive for antibodies directed against EBV[55]. EBV has an established causal role in multiple types of cancer as well. How a mostly benign infection can lead to autoimmunity and cancer in certain individuals is still in discussion, but environmental risk factors seem to be the answer[53].

What's more, seronegative EBV, although rare, has virtually no risk for developing MS, while a history of infectious mononucleosis (acute symptomatic primary infection with EBV) significantly heightens the risk considerably. This has led to postulating that EBV produces persistent changes that are most likely required for the development of MS[56].

In a most interesting way, the pattern of MS and its different types of evolution (RRMS, PPMS, SPMS) can be explained by chronic/ recurrent EBV infection with repeated entry/ persistence of EBV-transformed B cells in the CNS, with superimposability regarding seasonal and weather variations between the two[57]. This may be possible through reprogramming of latently infected B lymphocytes and the chronic presentation of viral antigens as a potential source of auto-reactivity through molecular mimicry[53].

We still do not possess knowledge related to the intricacies that involve the interplay between MS and EBV – theories include an EBV-induced immune dysregulation as a trigger/ promoter of MS in susceptible (genetically prone) individuals. Potential research targets have included the study of virological and immunological events during the first infection with EBV, emphasizing understanding long-term effects of seric persistence of B cells[54]. As such, new treatments based on monoclonal antibodies targeting B cells have proven to be efficient for both RRMS and PPMS, while options that inhibit B cell mobilization and entry in the CNS show great promise in RRMS. According to some researchers, the mechanism of actions of said treatments may be hypothesized to function by counteracting this exact chronic EBV infection[57].

We will also briefly mention **other viral infections** apart from EBV that may be implicated in MS, such as human endogenous retroviruses (HERVs), human herpesvirus 6 (HHV-6), and cytomegalovirus (CMV), which, in a similar fashion, may induce chronic, sometimes life-long infections[58].

Genetic risk factors

Research shows a close association between EBV – MS and genetic predisposition, perhaps explaining why, out of an almost global asymptomatic EBV infection, certain individuals develop MS/ other autoimmune disorders. We have found multiple articles pointing out evidence of gene-environment interactions and epigenetic modifications triggered by environmental factors we've already covered in genetically susceptible individuals[59].

The strongest and most frequently discussed link is between HLA class I and II allelles and MS, namely the genetic factor DRB1*15:01 allele in the class II region, which increases the risk of MS approximately 3 times, while the HLA class I allele A*02:01confers a protective effect[60].

In addition, our current literature survey has offered a few **other potential risk factors** which we will mention without extensively covering: other environmental factors – such as **organic solvents**, stressful job environments, and working hours (long shifts). We also found a few potential **protective factors** in our study, namely, high coffee consumption and high nicotine and alcohol intake, which are associated with reduced risk[4]. **Pregnancy** has been cited as having an ambivalent effect regarding MS – with a marked drop of relapse episodes during pregnancy, but without altering the risk of MS or long-term

progression[3]. Vitamin D levels seem to dwindle during and shortly after pregnancy, which is why close monitoring of both mother and child is necessary peripartum. Moreover, sufficient vitamin D levels during pregnancy may protect against the offspring's development of multiple sclerosis later in life[61].

CONCLUSION

While there still is a need to further understand these risk factors, future treatment strategies have to target these modifiable risk factors both in a theoretically healthy population that lives in a modern world that is evermore predisposed to autoimmune diseases such as MS, but also at controlling these risk factors that may influence progression, relapse and complication for patients diagnosed with MS. We would like to emphasize that these modifiable risk factors are environmental, commonly found on a global scale, even in a benign form, affecting non-MS patients. Future research is needed to determine the genetic predisposition of certain individuals to develop MS and how to prevent onset and progression.

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