HHS Public Access

Author manuscript

Semin Pediatr Neurol. Author manuscript; available in PMC 2024 July 01.

Published in final edited form as:

Semin Pediatr Neurol. 2023 July ; 46: 101049. doi:10.1016/j.spen.2023.101049.

Environmental Influences on Risk and Disease Course in Pediatric Multiple Sclerosis

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Abstract

Pediatric multiple sclerosis (MS) accounts for 3%−10% of all patients diagnosed with MS. Complex interplay between environmental factors impact the risk for MS and may also affect disease course. Many of these environmental factors are shared with adult-onset MS. However, children with MS are in closer temporal proximity to the biological onset of MS and have less confounding environmental exposures than their adult counterparts. Environmental factors that contribute to MS risk include: geographical latitude, viral exposures, obesity, vitamin deficiencies, smoking, air pollution, perinatal factors, gut microbiome, and diet. More recently, research efforts have shifted to studying the impact of these risk determinants on the clinical course of MS. In this article we will examine relevant environmental risk determinants of pediatric MS and review the current knowledge on how these factors may contribute to pediatric MS disease evolution.

Search Terms:

multiple sclerosis; pediatric; environment; risk

Introduction

Multiple sclerosis (MS) is an inflammatory disorder that affects the central nervous system. Though symptoms typically manifest in adulthood, MS can present prior to 18 years of age. Even though the clinical phenotype of pediatric-onset MS (POMS) has distinct differences from that of adult-onset MS, many of the environmental and genetic risk factors apply to both populations. Studying these risk determinants in POMS provides important insights into the pathobiology of MS, as children have fewer confounding features (e.g., shorter duration of environmental exposures and/or medical comorbidities) than adults. In this

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Declaration of interests

Dr. Dinov reports no financial interests/personal relationships.

Dr. Brenton has served as a consultant for Cycle Pharmaceuticals.

review we summarize known environmental influences linked with MS risk and their impact on the clinical course of MS in childhood.

Environmental Risk Determinants in Pediatric Multiple Sclerosis

I. Geography

MS increases in prevalence and incidence as latitude increases [1,2]. A study evaluating US nurses aged 20–50 from 1976 to 1994, found that the rate of MS diagnosis was 3.5 times greater in those living at a higher latitude (i.e., north of 41–42° latitude) compared to those living at a lower latitude (i.e., south of 37° latitude) [3]. A recent meta-analysis confirms a strong positive association of MS prevalence with increasing latitude (5.27/100,000 per degree of latitude) after adjustment for study prevalence year and method of ascertainment [1].

The impact of latitude on MS risk appears to be influenced by age. Migration studies indicate that the risk latitude poses is greatest prior to the age of 15 years. If an individual migrates from an area of high risk to an area of low risk prior to 15-years-old, they acquire the lower risk stratification of the place they migrated to [4]. Alternatively, individuals who migrate from an area of low risk to an area of high risk prior to the age of 15 will retain the lower risk stratification of their prior origin [4, 5]. European-descent population studies also show that latitude may impact the age of MS onset, such that every 10° increase in latitude has an associated 10-month earlier age of MS onset [6]. The relationship between latitude and MS risk is strongly related to sunlight exposure, which will be discussed further.

II. Vitamin Deficiencies

Vitamin D deficiency is associated with an increased risk of MS and other autoimmune conditions [7–9]. Vitamin D is largely obtained via skin exposure to sunlight and ultraviolet (UV) rays, while a lesser amount is derived from dietary intake. The vitamin D receptor (VDR) is expressed on immune cells, including B-, T-, and antigen presenting cells, and its effects have been linked with autocrine regulation of immune function [10–12]. Specifically, vitamin D suppresses T-cell proliferation, promotes a shift from Th1 to Th2 phenotype, facilitates the induction of T-regulatory cells, and inhibits B-cell proliferation [10].

In an Australian study, higher vitamin D levels were associated with a reduced risk of an initial demyelinating event [13]. Vitamin D levels appear to influence the future risk of MS starting in the neonatal period and even prenatally. A Danish registry-based retrospective study evaluated vitamin D by quartiles, demonstrating that low vitamin D as a neonate was associated with an increased risk of future MS [14]. When comparing the lowest vitamin D quartile to the highest quartile, this study found that those in the highest quartile had the lowest risk for MS (OR: 0.53, 95% CI: 0.36–0.78, p=0.001) [14]. Contrastingly, in a population-based case-control study, there was no association between neonatal vitamin D and the future development of MS [15]. In this same study, pregnant females with low vitamin D levels (<31.5 nmol/L) in early pregnancy were associated with higher risk of MS in offspring compared to offspring of mothers with higher vitamin D levels (≥ 56.2 nmol/L) [16,17]. Timing of birth which has been related to exposure of UV exposure has also been

shown to be related to MS risk. People have a higher risk of MS when they are born in spring compared to autumn [10,14,18].

In terms of sunlight exposure, an indirect surrogate of vitamin D, an Australian study showed that hours of sunlight exposure are inversely correlated with prevalence of MS, particularly in childhood and adolescence [19,20]. A recent multi-center United States study, evaluating 332 children with MS and 534 controls, demonstrated that children with MS had less time spent outdoors and had less sunlight exposure compared to their peers [21]. Spending 1–2 hours a day outdoors was associated with an 81% reduction in MS odds (adjusted OR 0.19, 95% CI: 0.09–0.40; $p < 0.001$) [21].

The relationship between vitamin D with MS risk is heavily influenced by various genetic, epigenetic, and related environmental factors. For example, vitamin D helps to regulate HLA-DRB1*1501, an important MS genetic risk determinant [22]. Additionally, vitamin D supplementation alters the immune response to EBV by selectively reducing EBV nuclear antigen (EBNA)-1 IgG levels [23]. Finally, obesity increases the risk for vitamin D deficiency and is also a recognized independent risk factor for MS [24].

III. Gut Microbiome and Dietary Intake

There is growing evidence implicating the gut microbiome and its interactions with the host immune system on the pathogenesis of MS. There are recognized differences in the gut microbiome of MS patients compared to healthy controls [25–28]. Typically, this variability is found within the bacterial taxonomic groups and not in enzymatic function. Pediatric and adult MS patients exhibit elevations in Acinetobacter, Streptococcus, Akkermansia (which can induce pro-inflammatory responses in peripheral blood mononuclear cells) and reductions in Parabacteroides, Lachnospira, Prevotella (which stimulate anti-inflammatory T-cell responses) [29,30].

In addition to the gut microbiome, there is growing interest on how diet affects the risk for autoimmunity. Consumption of fatty fish may protect against MS and may be related to the higher vitamin D content of this food group [31]. A study of dietary intake in POMS cases (n=312) within a year of MS diagnosis demonstrated that POMS had lower dietary iron intake compared to controls (n=456), though there were no differences in consumption of major food groups (e.g. carbohydrates, fats, fruits/vegetables) [32]. The latter finding is supported by the NHS and NHSII studies evaluating female nurses, which found no correlation between dietary scores and risk of MS [33, 34]. In contrast, an Iranian study evaluated 547 MS cases and 1057 controls, finding that a higher inflammatory index diet was consumed more frequently in MS patients during adolescence when compared to controls, despite adjustment for covariates (OR: 1.86, 95% CI: 1.67–2.07, $p < 0.001$) [35].

IV. Metabolic Syndrome and Obesity

Metabolic syndrome is a condition that includes hypertension, hyperglycemia, elevated triglycerides, reduced high density lipoprotein (HDL), and increased waist circumference. The prevalence of metabolic syndrome is increasing across the world [36]. Metabolic syndrome induces systemic inflammation, increases permeability of the blood brain barrier, and heightens production/release of pro-inflammatory cytokines (TNF- and IL-6) and

adipokines (leptin) [36]. Evidence indicates that metabolic syndrome is more prevalent in adult MS patients (30–40%) compared to healthy controls (~25%) [37–40]. There is a lack of research evaluating metabolic syndrome in youth with MS.

Obesity, one component of metabolic syndrome, reflects a state of abnormal adipose tissue accumulation in the body. Adipocyte-derived cytokines (adipokines) directly modulate the immune system to promote a pro-inflammatory serologic state and may thereby mediate MS risk. Several studies show that obesity is strongly associated with an increased risk of POMS [41–45]. The first of these studies evaluated 75 children diagnosed with MS and clinically isolated syndrome (CIS) and found that obesity was associated with an increased risk for MS or CIS in girls but not in boys [42]. This relationship was dose-dependent: overweight (OR: 1.58, CI: 0.71–3.50), obese (OR: 1.78, CI: 0.70–4.49), and extremely obese (OR: 3.76, CI: 1.54–9.16) [42].

A Danish prospective study evaluating over 300,000 school aged children reinforced the dose-dependent effect of obesity. Authors showed that for every one-unit increase in BMI, children had a higher risk of MS (hazard ratio (HR): 1.15–1.18) [41]. In evaluating solely female patients, those with a BMI at $\geq 95^{th}$ percentile exhibited a 1.6 to 1.9-fold increased risk of POMS when compared to those with a BMI of $\leq 85^{th}$ percentile [41]. While reverse causation is a possibility when considering BMI in the context of MS risk, a single study has assessed BMI trajectories of pediatric MS patients in the years prior to their first clinical symptoms [46]. This study evaluated 40 consecutive pediatric MS patients matched 3:1 to controls on age-, sex-, race/ethnicity-, and socioeconomic status [46]. Compared to controls, pediatric MS subjects exhibited significantly higher BMI Z-scores up to 10 years prior to their first clinical manifestations of MS [46]. To better elucidate a the relationship of obesity on risk of MS, Mendelian randomization studies have shown that obesity is an independent risk factor for MS [47–49], despite adjusting for age, sex, vitamin D status, human leukocyte antigens (HLA), and ancestry.

Hypertension occurs more frequently in MS and is associated with worsening neurologic disability [50–52]. MS patients have up to a 50% higher chance than the general population for developing hypertension [50]. Hypertension plays a role in B-cell activation, subsequent production of autoantibodies, and diminishing T-regulatory lymphocyte activity [53]. The incidence of hypertension in pediatric MS has not been studied.

V. Tobacco Smoke Exposure

Smoking is a dose-dependent risk factor for MS [54,55]. A Danish case-control study found that the odds for POMS increased 4.6% for each additional year of secondhand smoke exposure between the ages of 10–19 years [56]. Children with secondhand smoke exposure at home were twice as likely to develop MS compared to children without exposure [55]. Cigarette smoking contributes to a pro-inflammatory cascade, potentially driven macrophage-driven release of pro-inflammatory cytokines and free radicals and also via antigen cross-reactivity between lung antigens and myelin antigens [55].

Cotinine is a metabolite from nicotine and a biomarker of tobacco use [57]. There is inconsistent data on serum cotinine values in relation to the development of MS. In a

Canadian pediatric study, there was no difference in serum cotinine levels between MS patients and controls [55]. However, another study found elevated levels of serum cotinine were associated with a 50% increased risk for MS in participants aged less than 26 years [57]. This metabolite is not studied frequently in the pediatric population due to a reduced prevalence of smoking. As such, there is a paucity of data on serum cotinine in relation to secondhand smoking.

VI. Air Pollution

A multi-center study demonstrated that air pollution increases the risk of pediatric MS – specifically, carbon monoxide (CO), particulate matter ($PM_{2.5}$), and sulfur dioxide (SO_2) [58]. This is supported by adult studies that show associations between MS and air pollution with these specific constituents in addition to ozone (O_3) and nitrous oxide (NO) [59,60]. However, a Canadian population-based adult cohort study did not find a relationship between air pollution and MS risk [61].

A later study compared 334 POMS cases and 565 healthy controls in relation to ozone pollution [62]. Investigators found that patients who lived in higher ozone tertiles had twice the risk of MS (adjusted OR 2.47, 95% CI: 1.69–3.59 for tertile 2 and OR 1.95, 95% CI: 1.32–2.88 for tertile 3) [62]. The exact pathogenic mechanism remains unclear. However, it is likely related to secondary oxidative stress and/or cellular damage leading to the release of pro-inflammatory cytokines [59].

VII. Infection

Infections can act as triggers that induce autoimmunity, resulting in the clinical manifestations of MS in people who are genetically and environmentally predisposed. Molecular mimicry is a process where similarities between pathogen-derived peptides and self-peptides result in activation of autoreactive T- or B-cell responses in susceptible individuals [63]. Ultimately this induces an autoimmune process that could promote the development of MS.

For years, EBV has been implicated as the cause and/or trigger of MS [64–67]. Recent research tested the hypothesis that EBV triggers MS by studying the serial EBV infection status in a cohort of 801 US military members who developed MS while in service and 1,566 age-, sex-, and race-matched control members that did not develop MS [64]. Of these, 35 subjects (who eventually developed MS) and 107 controls (i.e., subjects who never developed MS) were EBV-negative at baseline testing [64]. Out of the subjects who were eventually diagnosed with MS, 97% had become infected with EBV, with the first EBV-positive sample noted at a median of 5 years prior to MS onset. Concurrently, only 57% of controls were infected with EBV at follow-up, denoting a 32-fold increased risk of MS after EBV infection (95% confidence interval (CI): 4.3 to 245.3, $P < 0.001$) [64]. This relationship was not seen with cytomegalovirus (CMV), a herpesvirus that is also transmitted via saliva, supporting the hypothesis that EBV specifically triggers a response leading to heightened risk for MS.

Pediatric MS offers a unique window to study infectious triggers, as these patients have had fewer confounding exposures to certain pathogens and environmental triggers. In childhood,

the prevalence of EBV exposure is approximately 50–70% while in adults it reaches >90% [68,69]. Yet, pediatric MS patients demonstrate markedly higher rates of remote EBV infection (83%) compared to age-matched controls (42%) [70]. With the more recent advent of autoantibody testing for disorders that mimic MS (e.g. myelin oligodendrocyte glycoprotein (MOG) antibody disease), the rates of EBV positivity in definitive pediatric MS cases are likely higher than previously recognized [71].

Several properties of EBV infection in humans contribute to its candidacy as a trigger for MS. Firstly, EBV exposure results in persistent B-cell infection with continued antibody production against EBV viral antigens and lifelong T-cell surveillance of these infected B-cells. Secondly, there is cross-reactivity between self-antigens (including myelin basic protein and alpha-crystallin) and EBV antigens, which results in the production of autoreactive T-cells and humoral immune responses. Thirdly, the presence of EBV within the brain tissue of MS patients has been demonstrated in numerous studies – including the detection of EBV-infected B cells, PCR-detected EBV, and evidence of EBV-related gene expression from infected cells [124]. Despite this, there is conflicting pathobiological evidence which likely stems from methodologic differences between various studies [125].

Separate from EBV, other viruses have been linked with MS risk. Early infection with CMV may be protective against future MS diagnosis. In a study comparing CMV prevalence in POMS (n=189) compared to controls (n=66), evidence of prior CMV infection resulted in a lower risk of developing MS (OR: 0.27; 95% CI 0.11– 0.67, p=0.004) [72]. This is supported by a meta-analysis evaluating adult MS patients with CMV seropositivity, finding that those who were positive had an overall decreased risk of MS [73]. The seroprevalence of other viruses (herpes simplex virus, parvovirus B19, and varicella zoster virus) is not different between pediatric MS subjects and healthy controls [129].

Another herpesvirus implicated in MS risk is HHV-6. However, unlike EBV, the serological tests for HHV-6 are less reliable [74]. The majority of studies show higher rates of latent HHV-6 titers in MS patients compared to controls [74]. Additionally, when comparing MS brain plaques to healthy control white matter, those with MS have higher rates of HHV-6 DNA detection [74].

VIII. Perinatal Factors

Various perinatal factors have been associated with autoimmunity. However, these particular factors are highly susceptible to recall bias as they often occur long before retrospective assessment. Breastfeeding is thought to enhance immune function through IgA transmission, innate immunity enhancement and maturation, in addition to its direct impacts on the gut microbiota [75]. Information on the protective effect of breastfeeding against MS risk has been inconsistent. A case-control study found that absence of infant breastfeeding was associated with increased odds of future POMS diagnosis (OR: 4.43; 95% CI: 1.68 to 11.71; p = 0.003) [76]. In this study, POMS subjects had lower rates of being breastfed compared to controls (36% vs 71%, p=0.001) and, if breastfed, had shorter average durations (5±10 weeks vs 30±43 weeks; p=0.001) [76]. In a German retrospective study, adults that had been breastfed >4 months had a protective effect against MS with an adjusted odds ratio of 0.51 (95% CI: 0.29–0.88, p= 0.016) compared to the group that had been breastfed <4

months [77]. In contrast, an Iranian adult study demonstrated that patients with MS (n=660) were breastfed more compared to healthy controls (n= 421), OR: 2.90, 95% CI: 1.49–5.65, p=0.002 [78]. Similarly, a Norwegian national adult cohort study found no association between breastfeeding and MS risk [79].

Birthweight has been studied in an Argentinian population, showing that POMS patients had a higher birth weight compared to the general population [80]. Prematurity is not associated with POMS risk [81], though there is some evidence that birth order might be a contributing factor. This is thought to be related to the hygiene hypothesis, which states that less infectious exposures early on in life lead to higher risk of future autoimmunity [82]. In a Saudi Arabian study, authors found that patients with MS tend to be higher in birth order [83], findings which are supported by multiple other studies [77,83,84].

Birth seasonality may also impact the risk of MS [85–88]. In a United Kingdom study, investigators found that those born in winter had a lower risk of MS while individuals born in the spring had a higher risk of MS [88]. While the pathobiology behind this association is unclear, one study shows that individuals born in spring had more CD4+ and CD8+ cells and lower vitamin D levels as compared to those born in winter [89]. Both of these factors can contribute to MS pathobiology through altered function of the immune system.

Environmental Association with Pediatric Multiple Sclerosis Disease Progression

I. Vitamin D

Higher vitamin D levels associate with reduced disease activity on neuroimaging and potentially improved clinical outcomes [90–93]. A prospective longitudinal study from the Netherlands found that relapsing MS patients with moderate or high levels of vitamin D (> 20 ng/mL) had lower risk for relapse [10]. The BEYOND study was an international, randomized double-blind phase 3 trial evaluating adult MS patients that showed higher vitamin D levels correlate with a 31% lower rate of new T2-hyperintense lesions on MRI [123. However, there were no differences for relapse rate or neurologic disability [10]. These findings are supported by the BENEFIT trial, which evaluated early *versus* delayed interferon beta-1b treatment in adult MS patients. In this study, vitamin D levels were measured for 5 years. Patients who had 20 ng/mL higher serum vitamin D levels exhibited a lower relapse rate and lower rate of new, active lesions [22]. In a study evaluating vitamin D levels with concurrent interferon β-1b therapy, authors found that those who had lower vitamin D levels had a higher Expanded Disability Status Scale (EDSS) scores ($p < 0.001$) [94]. A French study has similarly showed that slower EDSS progression is noted in those who are receiving vitamin D compared to those who are not (95% CI: −0.61 to −0.4, p=0.03) [94]. The CHOLINE study was a double-blind, placebo-controlled study evaluating vitamin D supplementation (100,000 IU every other week vs placebo) in patients taking interferon-β 1a therapy. This study did not meet its primary end point (change in annualized relapse rate) but did find that relapse rate reduction and slower EDSS progression were noted in the vitamin D cohort [127].

An Australian prospective study, evaluating 170 MS patients, found that those with greater sun exposure after their first relapse had a lower relapse rate and a longer time to second attack [95]. The effect of sunlight exposure upon disease progression is supported by a second study that demonstrated higher relapse rates in patients receiving lower UV radiation levels [96].

Supplementation is also a key factor to consider in MS disease progression. In a Finnish study evaluating vitamin D as an addition to interferon-β, patients who took 20,000 IU/week of vitamin D3 showed fewer T2-hyperintense lesions and contrast-enhancing lesions compared to placebo [97]. However, this study was not powered to assess clinical outcomes. This is in contrast to the SOLAR study, a randomized double-blind placebo-controlled study that evaluated relapsing MS patients on interferon-β treatment plus placebo vs 14,007 IU of vitamin D daily. There was no significant difference between groups for the primary outcome – no evidence of disease activity (NEDA) [126]. Similarly, the EVIDIMS study comparing high-dose to low-dose vitamin D did not show a difference in clinical outcomes [130].

Despite vitamin D's potential effects on neuroimaging and relapse rates, a meta-analysis evaluating 6 trials does not support an effect of vitamin D on neurologic disability [98]. However, there are multiple points to be considered for this meta-analysis: the supplementation of vitamin D was not standardized and although data was pooled, confounding factors such as age, sex, lifestyle habits, and ethnicity were not able to be adequately evaluated [98].

II. Dietary Intake and Gut Microbiota

More recently, dietary intake and interventions have been studied in patients living with MS. There is evidence that various, structured interventions – including a ketogenic diet, a low-fat diet, intermittent fasting, paleolithic diet, and Mediterranean diet - are beneficial in improving MS-related fatigue, depression/anxiety, and disability [99]. There are trials underway evaluating how structured diets may affect more objective MS outcomes, such as lesion burden and brain volume loss. There are currently no dietary interventions that have been shown to definitively impact disease course in MS. A single cross-sectional study found that in adults with relapsing MS, dietary intake that is more closely aligned with a Mediterranean diet correlated with higher thalamic volumes [128]. This data is limited due to the study's cross-sectional design and reliance on patient-completed diet surveys.

A multi-centered, longitudinal relapse study assessed dietary intake in a large cohort of POMS cases over a median of 1.8 years. Using a dietary questionnaire to assess nutritional intake, this study found that POMS patients with higher energy intake from fat (particularly saturated fats) exhibited an increased risk for relapse (HR: 1.58, 95% 1.06–2.36, p=0.026), whereas higher vegetable intake was associated with a reduced relapse risk (HR 0.5, 95% CI: 0.27–0.91, p=0.024) [100].

There is some early evidence that gut microbiota associate with MS disease activity. For example, pediatric MS patients with a higher abundance of *Firmicutes* and the presence of Archaea *Euryarchaeota* associated with higher risk of relapse [101]. A single study showed

that absence of *Fusobacteria* in pediatric MS patients associates with an increased risk of relapse (HR: 3.2; 95% CI: 1.2–9.0, p=0.024) [101]. As with many of the environmental prognostic factors this needs to be studied more to truly evaluate the effects.

III. Metabolic Syndrome and Obesity

There is a paucity of data regarding the impact of metabolic syndrome and hypertension on MS progression. A few studies have looked at obesity's impact on MS disease progression and relapse risk in children and adults [102–108]. Although the most specific marker for obesity is visceral fat (waist-to-height ratio), most studies use body mass index (BMI) as a marker for obesity despite its potential limitations [108].

A German pediatric MS study evaluating 453 patients on injectable disease modifying therapies (i.e., interferon beta, glatiramer acetate) noted a higher frequency of relapse in obese patients (95% CI: 1.1–1.6, $p < 0.001$) [104]. It is important to note that the injectable DMTs are highly lipophilic, thus it is possible that obese patients exhibited lower DMT bioavailability leading to a higher relapse risk [105].

Although not directly measuring obesity, adipokines are secreted from adipose tissue and represent a potential biomarker linking obesity and the immune system [103]. At least one study (32 POMS, 67 controls) has shown that pro-inflammatory adipokine levels are higher in pediatric MS patients compared to controls, though this study did not account for important differences in BMI. In this same study, the authors paradoxically found that increased levels of leptin (a pro-inflammatory adipokine), adjusted for age and vitamin D, were associated with longer time to next relapse in males (95% CI: 0.05–0.96, p=0.044) [103].

Obesity has been linked with risk for greater disability in adult MS patients. In a German study evaluating 1066 adult MS patients, authors found that the median time to achieve an EDSS of 3 was 0.99 years for those with a BMI of ≥ 30 kg/m^2 (compared to 1.46 years for those who had a BMI ≤ 30 kg/m^2) (HR 1.47, 95% CI: 0.34–0.66, $p < 0.001$) [106]. This remained statistically significant after adjusting for age, sex, smoking, and co-morbidities (e.g., type 2 diabetes and hypertension) [106]. In this study, obesity was not associated with relapse rates or T2-lesion burden [106,109]. Obesity has been associated with greater rates of brain atrophy. From 469 participants with MS, each 1 kg/m higher BMI associated with reductions in normalized gray matter volume (−1.1 mL, 95% CI: −1.8 to −0.5, p=0.001) and normalized brain parenchymal volume (−1.1 mL, 95% CI: −2.1 to −0.05, p=0.039). BMI was not associated with white matter volume loss [110].

Lastly, at least one study has noted a relationship between BMI and relapse severity. This study assessed adults with acute optic neuritis (AON) relapses [102], finding that male patients with moderate/severe AON relapses exhibited higher BMI compared to those with mild AON relapses after adjusting for disease duration and age (OR: 1.33, 95% CI: 1.06–1.66, p=0.03) [102]. As we continue to learn about lifestyle factors with disease progression it is imperative as providers address them to improve our patient outcomes.

IV. Tobacco Smoke Exposure

There is currently no literature on smoking as it relates to pediatric MS disease course. However, data from adult populations provide valuable insights. A prospective study of 1,465 patients, followed over a mean of 3 years, found that MS patients with either a history of smoking or current smoking were more likely to transition to a secondary progressive course [111]. Potential reasons for this may be secondary to the increased levels of NO or NO metabolites, which can contribute to axonal degeneration, block nerve conduction, and inhibit the mitochondrial respiratory chain pathway [112]. Other studies in adults have corroborated an increased risk of secondary progressive MS in smokers [113–117]. Smoking can also impact important co-morbidities, such as infection and risk for neoplastic disease. MS smokers also demonstrate greater degrees of whole brain atrophy [115,118] and an increase in T2-hyperintense and contrast-enhancing demyelinating lesions in MS smokers compared to non-smokers [29].

V. Air Pollution

A small (n=52) cohort study found that adult relapsing MS patients with higher PM_{10} levels had more inflammatory activity on MRI and higher disability levels than their counterparts with lower PM_{10} levels [29]. Similarly, an Italian study found that higher levels of PM_{10} are associated with an increase in hospital admissions for MS [119]. No significant evidence has been found associated with NO_2, and O_3 [29].

VI. Infectious

The impact of infectious etiologies on MS course remains limited. In a study evaluating 54 adult MS patients, authors evaluated both the viral capsid antigen (VCA) IgM and early antigen (EA) IgG for EBV reactivation, yet found no change in titers during clinical relapses [120]. This is supported by a study evaluating EBV nuclear antigen and VCA IgG levels in MS patients over 5 years, finding no correlation with MS activity and progression [121].

Although these studies do not demonstrate a correlation between EBV and disease progression, current research is evaluating the role of EBV vaccination in the prevention of MS [122]. These vaccines primarily target glycoprotein-350, an EBV envelope protein that is necessary for viral attachment to B lymphocytes [122]. Clinical trials are ongoing to assess the role of these vaccines in eliminating EBV infection and/or reducing EBV-associated diseases, like MS. A second potential avenue is a therapeutic EBV vaccine that would treat those with established MS, though current data does not strongly support the effectiveness of such a strategy. In addition to EBV vaccination studies, there are also trials assessing immunotherapies and cell-based therapies that target EBV-infected B cells and plasma cells. Other proof-of-concept studies are evaluating the effect of antivirals on EBV shedding in the saliva of patients with MS.

Conclusion

Latitudinal exposure, infections, cigarette smoking, obesity, hypertension, diet, gut microbiota, and pollution may all contribute to the overall risk of MS in childhood. Data strongly suggest-that cigarette smoking (active or passive) influences the course of MS.

Recent data regarding EBV, obesity, diet/gut microbiota, and air pollution suggest that these environmental factors may also impact the course of MS, but require more targeted, longitudinal study.

In order to provide the best care for our pediatric patients, it is imperative that we provide comprehensive treatment. Patients and their parents must be counseled on modifiable risk factors, assessed for development or worsening of these risk factors, and monitored for comorbid conditions in an effort to treat comprehensively. In particular, counseling should include promoting, maintaining and advancing physical activity levels, establishing a healthy weight and well-balanced diet, eliminating tobacco exposure, and a critical assessment of the obstacles to achieving these goals. Addressing these critical behaviors will impact MS course and its common comorbidities while promoting patient wellness – all equally critical cornerstones of comprehensive treatment in pediatric MS.

Acknowledgements:

J.N. Brenton's research time and effort is funded through NIH/National Institute of Neurological Disorders and Stroke grant number K23NS116225.

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Table 1:

Environmental Factors for MS Risk and Disease Course

Environmental Factor	Risk for POMS	Impact on MS Disease Course
Geography	• Higher latitude correlates to a higher risk of POMS, greatest impact when < 15 years old [1]	• No current evidence
Vitamin Deficiencies	• Low levels of vitamin D are associated with a higher risk for POMS [16,17] • More sunlight exposure is associated with reduced risk for POMS [19,20]	• Higher vitamin D level is associated with a decreased risk for relapse, decreased risk of new T2 lesions, and decreased risk of disability [10,94]
Diet and Gut Microbiome	• Gut microbiota varies in POMS compared to healthy controls [25–28]	• Increased fat intake is associated with a higher risk for relapse [100] • Increased vegetable intake is associated with lower risk for relapse [100] • Certain microbiota are associated with an increased relapse risk [101]
Metabolic Syndrome and Obesity	• Metabolic syndrome is more frequent in adult MS versus controls [37–39] • Obesity is associated with an increased risk of POMS [41]	• Obesity correlates with higher rates of depression and fatigue • Obesity is linked with greater degrees of normalized gray matter and brain parenchymal volume loss [110]
Smoking Exposure	• Smoking and secondhand exposure are associated with an increased risk of POMS [56]	• Smokers develop greater degrees of brain atrophy, higher T2 lesion volume, and hastened progression of disability [29]
Air Pollution	• Higher ozone concentrations are associated with a higher risk for MS [62]	• Higher PM_{10} levels are associated with greater inflammatory activity on MRI and higher disability [29]
Infection	• A remote history of EBV infection is associated with an increased MS risk [70]	• Trials are currently underway assessing EBV vaccines, antivirals, and immunotherapy
Perinatal Factors	• Breastfeeding may reduce the risk of MS in children [77]	• No current evidence

Abbreviations: EBV = Epstein Barr virus; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; MS = multiple sclerosis; POMS = pediatric-onset multiple sclerosis