The Role of Environment and Lifestyle in Determining the Risk of Multiple Sclerosis

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Abstract MS is a complex disease where both genetic and environmental factors contribute to disease susceptibility. The substantially increased risk of developing MS in relatives of affected individuals gives solid evidence for a genetic base for susceptibility, whereas the modest familial risk, most strikingly demonstrated in the twin studies, is a very strong argument for an important role of lifestyle/environmental factors in determining the risk of MS, sometimes interacting with MS risk genes. Lifestyle factors and environmental exposures are harder to accurately study and quantify than genetic factors. However, it is important to identify these factors since they, as opposed to risk genes, are potentially preventable. We have reviewed the evidence for environmental factors that have been repeatedly shown to influence the risk of MS: Epstein–Barr virus (EBV) infection, ultraviolet radiation (UVR) exposure habits/vitamin D status, and smoking. We have also reviewed a number of additional environmental factors, published in the past 5 years, that have been described to influence MS risk. Independent replication, preferably by a variety of methods, may give still more firm evidence for their involvement.

Keywords Multiple sclerosis · Gene–environment interactions · Smoking · Epstein–Barr virus · Vitamin D · Obesity

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1 Introduction

Numerous epidemiological studies have shown that MS is a complex disease where both genetic and environmental factors contribute to disease susceptibility. For monozygotic twins, the concordance rate is around 30 %, whereas it is approximately 7 % for dizygotic twins (Ebers 2008). Recent population-based studies give more certain and even lower figures, with age-adjusted concordance rates of ~17 % for monozygotic twins, as opposed to ~2 % for dizygotic twins and siblings in general (Westerlind et al. 2014). The substantially increased risk of developing MS in relatives of affected individuals gives solid evidence for a genetic base for susceptibility, whereas the modest familial risk, most strikingly demonstrated in the twin studies, is a very strong argument for an important role of lifestyle/environmental factors in determining the risk of MS, sometimes interacting with MS risk genes.

Migration studies have shown that when people move from a high to a low risk area in childhood, this reduces the risk of MS to an intermediate between that of their birth country and that of their final residence. Migration in the opposite direction does not consistently increase the risk of MS until the next generation whose risk is close to that of their birthplace (Ascherio and Munger 2007a; Gale and Martyn 1995). These data suggest that environmental exposures during childhood and adolescence are of essential importance for disease risk.

Lifestyle factors and environmental exposures are harder to accurately study and quantify than genetic factors. However, it is important to identify these factors since they, as opposed to risk genes, are potentially preventable. We have reviewed the evidence for environmental factors that have been repeatedly shown to influence the risk of MS: Epstein–Barr virus (EBV) infection, ultraviolet radiation (UVR) exposure habits/vitamin D status, and smoking. We have also reviewed a number of additional environmental factors, published in the past 5 years, that have been described to influence MS risk. Independent replication, preferably by a variety of methods, may give still more firm evidence for their involvement.

Since we believe that environmental factors should not be studied in isolation from genetics, we here give a short summary of the current status of the MS

genetics. As in most autoimmune/inflammatory disorders, the strongest genetic associations with MS are located within the human leukocyte antigen (HLA) complex. The class II allele HLA-DRB1*15 increases the risk of developing MS in almost all populations, with an odds ratio (OR) around 3 (Lincoln et al. 2005), whereas the class I allele HLA-A*02 has a protective effect with an OR of approximately 0.7 (Bergamaschi et al. 2010; Brynedal et al. 2007; Burfoot et al. 2008). Over recent years, genome-wide association studies (GWAS) have identified a large number of genetic regions outside the HLA complex that influence disease susceptibility. These studies have at this moment unequivocally associated over a 100 susceptibility loci (International Multiple Sclerosis Genetics Consortium 2013; International Multiple Sclerosis Genetics Consortium and Wellcome Trust Case Control Consortium 2 2011). The non-HLA loci have a smaller impact on MS risk with ORs in the order of 1.2. A main motif for finding all these loci is to provide a basis for defining central pathogenic pathways, in turn giving a basis for definition of new therapeutic targets, as well as biomarkers. Despite the large numbers of gene loci now reported, they only explain a fraction of the heritability. One out of several potential reasons for the missing heritability is interactions between risk genes and lifestyle/environmental factors, giving a further motif for the study of the latter as accurately as possible.

2 Epstein–Barr virus infection

There is a strong association between EBV and MS risk, but whether this demonstrates a causal relationship is being debated. EBV infection is usually asymptomatic in childhood, and in countries where MS is rare, early infection with EBV is almost universal. However, in countries where primary infection is delayed beyond the early years of childhood and the infection more commonly results in infectious mononucleosis (IM), the prevalence of MS is high. Several studies have examined the association between IM and MS, with consistent results. People who have had IM have a 2.3-fold increased risk of developing MS compared to those who were infected during childhood, whereas people who remain uninfected with EBV have an extremely low risk of developing the disease (Handel et al. 2010; Levin et al. 2010; Thacker et al. 2006). A meta-analysis of eight published studies found that the overall OR for MS was 13.5 (95 % 6.3–31.4) when comparing EBV-seropositive and EBV-seronegative people (Ascherio et al. 2001).

By measuring anti-EBV titers before and after MS onset in 305 cases, Levin et al. (2010) demonstrated that 100 % of MS cases who were initially EBV seronegative had seroconverted prior to MS onset. Several studies have observed a significant increase in antibody titers many years prior to MS onset (Ascherio et al. 2001; DeLorenze et al. 2006; Sundström et al. 2004). Nielsen et al. (2007) found that the increased risk following IM is independent of age, gender, and infection severity and may persist for decades. The consistent findings that EBV infection and elevation of

anti-EBNA (Epstein–Barr virus nuclear antigen) antibody titers precedes MS onset suggest that EBV is likely to be a causal factor of MS development.

In similarity to MS, IM has a latitudinal gradient seen across developed countries. Furthermore, a meta-analysis found a significant latitudinal gradient of EBV seroprevalence that was independent of age, gender, and MS status (Disanto et al. 2013a, b). The variation in the occurrence of IM suggests that UVB radiation/vitamin D status or other factors with a similar latitudinal and seasonal variation influence the risk of primary EBV infection or the subsequent immune response leading to IM. However, IM at any season is associated with MS and the association is not stronger among those reporting a history of IM in spring when vitamin D levels reach nadir (Lossius et al. 2014). It is currently unclear whether EBV is independently associated to MS or whether some other factor predisposes to both EBV infection and MS. Neither can it be completely ruled out that a dysregulated immunological response to EBV infection may be a consequence of the underlying pathophysiology of MS.

3 UVB Exposure/Vitamin D Status

Both the incidence and prevalence of MS increase with the distance from the equator. Latitudinal gradients have been identified throughout the world including Europe, North America, Australia, and New Zealand (Koch-Henriksen and Sorensen 2010). It has been suggested that this latitude-dependent gradient in MS occurrence is caused by less exposure to sunlight/decreased levels of vitamin D (Simpson et al. 2011).

There is evidence suggesting that frequent exposure to UVR confers a protective effect against developing MS (Islam et al. 2007; Kampman et al. 2007; van der Mei et al. 2003), and vitamin D has been proposed to be the major mediator of this protective effect (Ascherio and Munger 2007b; Smolders et al. 2008). The intensity of UVR exposure varies with latitude and season, and lower intensity of UVR in winter may be insufficient to support vitamin D synthesis in some locations (O'Gorman et al. 2012). Vitamin D is involved in the regulation of the immune system by binding to vitamin D response elements in the regulatory region of immune genes (Disanto et al. 2012; Ramagopalan et al. 2010). Furthermore, in several GWAS and candidate studies, an association has been observed between MS risk and markers in the CYP27B1 and CYP24A1 regions (Australia and New Zealand Multiple Sclerosis Genetics Consortium 2012; Sundqvist et al. 2010), the latter coding for an enzyme involved in vitamin D metabolism.

However, low levels of UVR exposure may have an independent effect on MS risk (Becklund et al. 2010), suggesting that the association between UVR exposure and MS risk cannot be fully explained by vitamin D-mediated mechanisms. A population-based case–control study further supports the hypothesis that UVR exposure contributes to decreasing MS risk independently of its effects on vitamin D levels (Bäärnhielm et al. 2012). Adjusting for 25(OH)D regarded as a mediator of the

protective effect of UVR only marginally changed the estimated association between UVR exposure and MS. There are a number of pathways whereby UVR may affect immune functions that are independent of vitamin D production (Mehta 2010). UVB appears to upregulate the secretion of TNF-a, IL-10, and regulatory T cells (Lucas and Ponsonby 2006), and UVA radiation has a complex dose-related immunomodulating effect where the underlying mechanism is not fully investigated. In EAE studies, UVB exposure influenced systemic immune reactions and attenuated systemic autoimmunity via the induction of skin-derived tolerogenic dendritic cells and regulatory T cells (Breuer et al. 2014). Vitamin D status may thus not be the only mediator of a latitude effect related to exposure to UV radiation.

An additional item discussed in the context of UVR/vitamin D is when insufficient exposure exerts its effect on the risk for MS, and if there is an interaction with MS predisposing genes. There are observations of a "month of birth effect." Several reports claim that children born in the spring on the Northern Hemisphere would run an increased MS risk later in life (Burrell et al. 2011; Willer et al. 2005), perhaps through epigenetic mechanisms, refuted by others (Fiddes et al. 2013). In our own studies of vitamin D in newborns later developing MS, there was no difference in vitamin D levels in individuals later developing MS compared to matched controls (Ueda et al. 2014). An action during adolescence might be more probable. In an experimental model for MS, there were striking effects in adolescent rats, but not during pregnancy or in adult rats (Adzemovic et al. 2013). An interaction with the HLA locus has been suggested (Handunnetthi et al. 2010). However, we found no such interaction in our case–control cohort (Bäärnhielm et al. 2012).

4 Smoking

The first detected association between smoking and MS risk was reported in the 1960s (Antonovsky et al. 1965). However, other studies found no impact of smoking on MS risk (Simpson et al. 1966). In the 1990s, smoking was found to be associated with MS risk in two prospective cohort studies (Villard-Mackintosh and Vessey 1993). Several studies investigating the link between smoking and MS susceptibility have been published during the last decade and almost all have detected a significant detrimental effect (Ghadirian et al. 2001; Hedström et al. 2009; Hernan et al. 2001; Pekmezovic et al. 2006; Riise et al. 2003). A pooled analysis of previous studies on smoking and MS risk rendered an OR of 1.5 (95 % CI 1.3–1.7). In a study using banked blood samples, Sundström et al. (2008) found that cotinine levels, indicating recent exposure to tobacco smoke, were increased in MS cases compared with controls. There is also evidence of a dose–response correlation between cumulative dose of smoking and the risk of developing the disease (Ghadirian et al. 2001; Hedström et al. 2009). Both duration and intensity of smoking seem to contribute independently to the risk of MS (Hedström et al. 2013a).

Both family studies and migration studies suggest that the influence of environmental factors contributes to MS at different age periods. Some aspects of

adolescence thus seem to be critical regarding the impact of several environmental factors on MS risk. Smoking, on the contrary, seems to affect MS risk regardless of age at exposure, and the detrimental effect abates a decade after smoking cessation regardless of the timing of smoking and regardless of the cumulative dose of smoking (Hedström et al. 2013a).

The molecular pathways responsible for the association between smoking and MS are not yet known, but several plausible hypotheses regarding the mechanism have been put forward. Both humoral and cell-mediated immunity are affected by smoking (Moszczynski et al. 2001), and smokers have increased levels of important markers of inflammation in autoimmune disease such as C-reactive protein and Interleukin-6 (Bermudez et al. 2002). Serum concentrations of cyanide are strongly correlated with the level of tobacco consumption, and chronic cyanide intoxication may lead to widespread demyelination (Freeman 1988; van Houten and Friede 1961). Some evidence points to a potential role of the free radical nitric oxide. Exposure to nitric oxide has been shown to cause axonal degeneration or block axonal conduction (Redford et al. 1997; Smith et al. 2001). Another possible mechanism linking smoking to MS susceptibility involves irritative events in the lungs creating autoimmunity against proteins with posttranslational modifications that are cross-reactive with CNS antigens with activation of CNS autoaggressive T cells. The absence of risk increase, rather than the opposite, by oral tobacco use (see below) argues that the main effect of tobacco is mediated in the lungs. Exposure to tobacco smoke results in increased pro-inflammatory cell activation in the lungs and posttranslational modifications of proteins (Makrygiannakis et al. 2008), which may break self-tolerance (Cloos and Christgau 2004; Doyle and Mamula 2002). Autoimmune memory cells are present and available for triggering in the lungs. In EAE studies, these cells strongly proliferate after local stimulation of the lungs and, after assuming migratory properties, reach the CNS with inflammation as a consequence (Odoardi et al. 2012). Finally, smoking or long-term exposure to smoke may increase the risk of MS by increasing the frequency and persistence of respiratory infections.

5 Passive Smoking

Data have been inconsistent regarding the influence of passive smoking. A French case–control study found an association between exposure to parental smoking at home and early onset MS (Mikaeloff et al. 2007). The risk increased with longer duration of exposure. However, no effect of maternal smoking during pregnancy on MS risk in offspring has been observed (Montgomery et al. 2008; Ramagopalan et al. 2013). In the study by Montgomery et al. (2008), information regarding maternal smoking during pregnancy was recorded prospectively, thus eliminating the problems associated with differential reporting bias. However, many women who smoke during pregnancy incorrectly report themselves as non-smokers (Lawrence et al. 2003; Lindqvist et al. 2002). Furthermore, maternal smoking during pregnancy may not be a sufficiently sensitive measure of later parental smoking at home.

In a Swedish case–control study, the incidence of MS among never-smokers who had been exposed to passive smoking was higher than among those who had never been exposed (OR 1.3, 95 % CI 1.1–1.6) (Hedström et al. 2011b). The risk increased with longer duration of exposure. The association between passive smoking and MS risk suggests that also lower degrees of lung irritation may contribute to the triggering of MS. Further studies would be valuable in order to investigate the impact of other forms of lung irritation, such as air pollution, in the etiology of MS.

6 Snuff Use

The use of moist snuff often leads to exposure to high doses of nicotine. Only two studies, both from Sweden, have investigated the effect of moist snuff on the incidence of MS with disparate results (Carlens et al. 2010; Hedström et al. 2009). One of them is a recently published cohort study of male construction workers, no overall effect was observed with respect to use of moist snuff (Carlens et al. 2010). However, the study had a long follow-up period which means that observed relative risks may be biased toward the null value. The other Swedish study found a decreased risk of developing MS among snuff users compared with those who have never used moist snuff, and there was evidence of an inverse dose–response relationship between cumulative dose of snuff use and the risk of developing the disease (Hedström et al. 2009).

Moist snuff contains a number of different substances apart from nicotine, and any of them could theoretically be involved in the protective effect. However, nicotine stands out as the main candidate in view of numerous studies on its immunomodulatory effects. Nicotine may exert systemic effects on the immune system by inhibiting the production of pro-inflammatory cytokines from immune cells, such as macrophages, via the alpha7 subunit of the acetylcholine nicotinic receptor (Nizri et al. 2009; Ulloa 2005). Since MS is most likely driven by systemic immune responses targeted at the CNS, there is a theoretical possibility that nicotine dampens this response by acting immunomodulatory, consistent with the apparent lower incidence in long-term snuff-takers.

7 Alcohol Consumption

The impact of alcohol, which may directly suppress various immune responses (Romeo et al. 2007), on the risk of developing MS, has been investigated in several case–control studies (Brosseau et al. 1993; Hedström et al. 2014a; Pekmezovic et al. 2006,) and one prospective study (Massa et al. 2013). The results were inconsistent. However, frequently, case numbers have been small (Brosseau et al. 1993; Massa et al. 2013; Pekmezovic et al. 2006) and some of the studies were subject to methodological limitations (Brosseau et al. 1993; Pekmezovic et al. 2006).

According to observations in two Swedish population-based case–control studies, alcohol consumption exhibits a dose-dependent inverse association with MS (Hedström et al. 2014a). The findings differ from those based on the prospective Nurses' Health Study (NHS) (Massa et al. 2013). However, in the NHS, the power to identify an OR in the order of 0.8, as observed by the Swedish studies, was low. It is thus possible that a protective effect of alcohol on MS risk went unnoticed in the NHS due to limited case numbers. This effect would not be unique for MS, but is well established in other inflammatory diseases, such as rheumatoid arthritis (Källberg et al. 2009).

While the exact mechanisms by which alcohol affects the risk of autoimmunity remain to be discovered, experimental and clinical data suggest that alcohol has significant dose-dependent immunomodulatory properties (Goral et al. 2008).

8 Adolescent Body Mass Index

The relationship between obesity during adolescence and MS risk has been investigated using two large cohorts of American women in which obese female adolescents displayed an increased risk of developing MS (Munger et al. 2009). Adult obesity was not associated with MS risk. The findings were replicated in a Swedish population-based case–control study and the association was extended to include males (Hedström et al. 2012). A higher BMI during childhood has also been associated with increased MS risk later in life (Munger et al. 2013). However, body size has been reported to be correlated over the life course (Munger et al. 2009) and when the most critical period occurs is currently unknown.

The molecular pathways behind the association between adolescent obesity and MS may involve fat-related chronic inflammation. By increasing the production and release of pro-inflammatory cytokines and promoting Th1 responses, and decreasing the number of regulatory T cells (Lumeng et al. 2007; Matarese et al. 2008; Subramanian and Ferrante 2009), obesity may increase the risk of recruitment of autoimmune CD4+ cells that target CNS autoantigens. Furthermore, obese people have lower levels of vitamin D metabolites as compared to those of normal weight and decreased levels of serum 25-hydroxyvitamin D appear to increase MS risk (Worstman et al. 2000).

9 Shift Work

Shift work results in circadian disruption (Arendt 2010) and sleep restriction (Bollinger et al. 2010), and mounting evidence indicates that shift work is associated with a wide variety of adverse health consequences. The impact of shift work on MS risk has been investigated in one incident and one prevalent case–control study (Hedström et al. 2011a). In both studies, a statistically significant association between working shift at a young age and occurrence of MS was observed (OR 1.6,

95 % CI 1.2–2.1 in the incidence study, and OR 1.3, 95 % CI 1.0–1.6 in the prevalence study). Circadian disruption and sleep restriction are associated with disturbed melatonin secretion and enhanced pro-inflammatory responses and may be part of the mechanism behind the association.

10 Exposure to Organic Solvents

Exposure to organic solvents has been observed to be associated with increased risk of MS in some studies, but not in others. A recent review and meta-analysis concluded that exposure to organic solvents is a risk factor for developing autoimmune disease in general (Barragán-Martínez et al. 2012). Each autoimmune disease was also considered separately and a significant association was observed between exposure to organic solvents and increased MS risk. Based on 15 studies published between 1994 and 2012, the OR of developing MS was 1.53 (95 % CI 1.03–2.29) among subjects exposed to organic solvents. Several biological models could explain how organic solvents affect susceptibility to MS, such as altering the impermeability of the blood–brain barrier (Kim et al. 2011). Accumulating evidence also suggests that chronic exposure to organic solvents can induce oxidative stress-mediated inflammatory responses (Feltens et al. 2010; Mögel et al. 2011). Furthermore, organic solvents, such as trichloroethene, induce lipid peroxidation which is implicated in the pathogenesis of various autoimmune diseases. Trichloroethene-reactive metabolites bind to endogenous proteins to form protein adducts (Cai et al. 2008) and the modified self-proteins may become immunogenic and induce autoimmune responses (Odoardi et al. 2012; Wang et al. 2008).

It has also been hypothesized that exposure to anesthetic agents, some of which are chemically related to organic solvents, may affect the risk of developing MS. The relationship between anesthetic agents and risk of developing MS has been investigated in several studies (Flodin et al. 2003; Hedström et al. 2013b; Landtblom et al. 2006; Stenager et al. 2003). However, frequently, case numbers have been limited (Flodin et al. 2003; Landtblom et al. 2006; Stenager et al. 2003), and two of the studies were subject to methodological limitations (Flodin et al. 2003; Landtblom et al. 2006). In 2013, two large Swedish population-based case–control studies found that occupational exposure to anesthetic agents has no impact on MS risk (Hedström et al. 2013b).

11 Cytomegalovirus

Cytomegalovirus from the Herpesviridae family is a common virus with a seroprevalence ranging from 45 to 100 % worldwide (Cannon et al. 2010). Several studies on the association between CMV and MS risk have been carried out, most of which have rendered nonsignificant results (Banwell et al. 2007; Mowry et al. 2011; Zivadinov et al. 2006). Recently, a negative association between CMV

seropositivity and pediatric MS was demonstrated (Waubant et al. 2011). This finding was confirmed in a meta-analysis of previous studies on CMV serostatus and MS risk, and replicated in a large cohort of adult MS cases and controls (Sundqvist et al. 2014). The exact mechanisms by which different viruses affect MS etiology are still unknown, but the observed associations are interesting pieces in the puzzle to understand the disease.

12 Pregnancy and Reproductive History

The complex alteration of the immune system that takes place during pregnancy in order to avoid maternal rejection of the fetus seems to have a favorable effect on MS in terms of relapse rate. The risk of relapse is decreased during the third trimester, but increased in the postpartum period (Confavreux et al. 1998). However, possible long-term effects of childbearing patterns on MS risk have been discussed for a long time, with conflicting results (Hernán et al. 2000; Hedström et al. 2014b; Nielsen et al. 2011; Posonby et al. 2012; Runmarker and Andersen 1995; Villard-Mackintosh and Vessey 1993).

A register-based Danish cohort study, comprising 4.4 million Danish men and women, showed that parity, number of children, age at first childbirth, and time since birth of the most recent child affected the risk of developing MS. However, the observed differences in childbearing patterns were restricted to the 5 years before MS diagnosis, and almost identical results were observed for men and women (Nielsen et al. 2011). This speaks in favor of reversed causality being a possible explanation to an inverse association between parity and MS risk. The findings were replicated in a large population-based case–control study in Sweden (Hedström et al. 2014b). A reduced reproductive activity in people with yet-undiagnosed MS would render results similar to those observed in these studies. There is evidence that autoimmune mechanisms may influence the reproductive life and fertility of both sexes (Carp et al. 2012; Ballester et al. 2004; Geva et al. 2004; Kay and Bash 1965; Nelson et al. 1993; Silman and Black 1988). Similarly, subtle symptoms or depressive symptoms that can precede the onset of neurological symptoms could affect the desire to become a parent (Gout et al. 2011; Vattakatuchery et al. 2011).

13 Gene–Environment Interactions

MS is a complex disorder in which environmental exposures operating at different time points trigger disease onset in genetically susceptible individuals. Genetic susceptibility to MS is mainly located within the MHC region (Ascherio and Munger 2007a; Brynedal et al. 2007; Gale and Martyn 1995; Lincoln et al. 2005), but several other non-MHC genetic loci have been observed to confer a less pronounced influence on MS risk (Bergamaschi et al. 2010; Burfoot et al. 2008).

A large number of studies have investigated the presence of interactions between genes and environmental factors in MS development.

Data from several studies suggest that HLA status and either IM or high anti-EBV titers synergistically increase the risk of MS (Disanto et al. 2013a, b; Sundqvist et al. 2011). In the largest study on this topic, individuals who were positive for HLA-DRB1*15, negative for HLA-A*02, and with high EBNA:385-420 titers had a 16-fold higher risk for MS than those who did not carry any of these factors (Disanto et al. 2013a, b). Similar findings have been found when smoking rather than EBV titers are considered, with a 13-fold increased risk among HLA-DRB1*15 positive, HLA-A*02 negative smokers as compared to those who did not carry any of these factors (Hedström et al. 2011c) (Table 1). This concept is supported by the finding of an interaction between smoking, HLA-DRB1*01, and autoimmunity to posttranslationally modified proteins with regard to rheumatoid arthritis (Klareskog et al. 2006). CD4+ T cells are activated after seeing its antigen presented by class II molecules. The spectrum of peptides presented by class II

Table 1 Lifestyle/environmental factors in MS development

Lifestyle/ environmental factor	Odds ratio	Interaction with HLA genes	Odds ratio combined	References
EBV serology	~13.5	+	~16	Ascherio et al. (2001)
Mononucleosis	~2.3	+	~7	Thacker et al. (2006), Levin et al. (2010), Handel et al. (2010)
Lack of sun exposure	~2	−	No effect	Islam et al. (2007), Kampman et al. (2007), van der Mei et al. (2003), Bäärnhielm et al. (2012)
Vitamin D < 50	~1.4	−	No effect	Ascherio and Munger (2007a, b), Smolders et al. (2008)
Active smoking	~1.6	+	~14	Pekmezovic at al. (2006), Hernan et al. (2001), Riise et al. (2003), Ghadirian et al. (2001), Hedström et al. (2009), Hedström et al. (2013a, b)
Passive smoking	1.3–1.6	+	~6	Hedström et al. (2011a, b, c)
Snuff use	0.5–0.9	−	−	Hedström et al. (2014a, b)
Alcohol	0.6	−	−	Mehta (2010)
Adolescent obesity	~2	+	~15	Munger et al. (2009), Hedström et al. (2012)
Shift work before age 20	~1.7	−	No effect	Hedström et al. (2011a, b, c)
Organic solvents	~1.5	Unknown		Barragán-Martínez et al. (2012)
CMV serology	0.7	−	No effect	Waubant et al. (2011), Sundqvist et al. (2014)

molecules is determined by the shape of the antigen binding cleft, in turn determined by the genetic sequence as reflected by the HLA allele nomenclature. With the two different autoimmune conditions triggered by smoking, but with different class II molecules, it points to T-cell activation as being critical, in turn leading to activation of T cells with different organ specificities.

14 Conclusions

Studies on how environmental factors influence MS risk are associated with several methodological and practical problems. The two major methods, population-based case–control studies and cohort studies, have provided the majority of our current knowledge on environmental factors in MS. Case–control studies in MS are generally better powered and can provide quantification of the magnitude of effect of the environmental exposures. The drawback is the risk of bias in recruitment of cases and recall bias in responses from cases with MS compared with controls. Thus, the best case–control studies are those that are carried out in newly diagnosed patients and in which both cases and controls are recruited from the same defined study population. Cohort studies are usually less subject to both these biases but often have a low power in uncommon diseases such as MS, particularly when there is a long follow-up period. In these cases, the associations between environmental exposures and MS often are underestimated, unless environmental conditions have been repeatedly measured. Optimally, results from the two approaches should be combined.

Advances in our understanding of environmental risk factors can lead to avenues of research exploring how these factors may play a role in the pathogenesis of the disease. It has become increasingly clear that the risk conveyed by an environmental factor may substantially differ depending on genetic background. In future studies, it is necessary not to study environmental risk factors for MS in isolation since interactions with both other environmental influences and an individual's genetic background are likely to contribute to MS development.

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