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Review

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# Modifiable factors influencing relapses and disability in multiple sclerosis

**MB D'hooghe[1,2], G Nagels[1,3,4], V Bissay[5] and J De Keyser[5,6]**

**Abstract**

A growing body of literature indicates that the natural course of multiple sclerosis can be influenced by a number of factors. Strong evidence suggests that relapses can be triggered by infections, the postpartum period and stressful life events. Vaccinations against influenza, hepatitis B and tetanus appear to be safe. Surgery, general and epidural anaesthesia, and physical trauma are not associated with an increased risk of relapses. Factors that have been associated with a reduced relapse rate are pregnancy, exclusive breastfeeding, sunlight exposure and higher vitamin D levels. A number of medications, including hormonal fertility treatment, seem to be able to trigger relapses. Factors that may worsen progression of disability include stressful life events, radiotherapy to the head, low levels of physical activity and low vitamin D levels. Strong evidence suggests that smoking promotes disease progression, both clinically and on brain magnetic resonance imaging. There is no evidence for an increased progression of disability following childbirth in women with multiple sclerosis. Moderate alcohol intake and exercise might have a neuroprotective effect, but this needs to be confirmed.

**Keywords**

disability progression, infections, multiple sclerosis, pregnancy, relapse, smoking, stress, vitamin D

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## Introduction

Multiple sclerosis (MS), a multifocal inflammatory disease of the central nervous system (CNS) leading to progressive tissue injury, is characterized by a complex relationship between individual genetic susceptibility and environmental factors. The clinical course of the disease is heterogeneous. The majority of patients start with a relapsing–remitting disorder. Defined by clinical criteria, relapses are generally considered to reflect focal inflammatory events in the CNS. Their occurrence is for the most part unpredictable and the degree of recovery varies. With time and age the relapse rate decreases,[1] and many of the patients switch to a secondary progressive form. Patients with a primary progressive form of MS have progression of disability from onset of disease. Currently there are limited therapeutic options to prevent or slow disability in MS. Disease-modifying treatments suppress the inflammatory response on magnetic resonance imaging (MRI) and reduce the exacerbation rate. However, a variety of potentially modifiable factors may also influence the course of MS. A good understanding of these factors is important for proper management and counselling of MS patients.

The aim of this review article is to summarize the available data, based on a literature search for factors that have been investigated for their influence on exacerbation rate and progression of disability in MS.

## Methods

### *Search strategy and selection criteria*

References for this review were identified through searches of PubMed from 1969 to October 2009 using

[1]National Center For Multiple Sclerosis, Melsbroek, Belgium.
[2]Department of Neurophysiology, University Psychiatric Centre Catholic University Leuven campus Kortenberg, Kortenberg, Belgium.
[3]Department of Orthopedagogics, Faculty of Psychology and Education Sciences, University of Mons, Belgium.
[4]Department of Human Physiology, Vrije Universiteit Brussel, Brussels, Belgium.
[5]Department of Neurology UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium.
[6]Department of Neurology University Medical Center Groningen, Groningen, The Netherlands.

**Corresponding author:**
Marie B D'hooghe, MD, National Center for Multiple Sclerosis, Vanheylenstraat 16, 1820 Melsbroek, Belgium
Email: marie.dhooghe@ms-centrum.be

**Table 1.** Classification of studies[2]

| Classification of studies | |
|---|---|
| Class I and II High-quality Studies | Prospective data collection. Retrospective study of a broad spectrum of patients with the defined outcome compared with a broad spectrum of controls. |
| | Population-based study or representative population study. |
| | Low or moderate risk of bias. |
| | Masked or independent assessment of the outcome and prognostic factor. |
| Class III and IV Low-quality studies | Retrospective study of a narrow spectrum of patients with the defined outcome compared with a narrow spectrum of controls. |
| | Patients recruited from referral centres. |
| | Case series without controls. |
| | High or very high risk of bias. |

**Table 2.** Levels of evidence[3]

| Level of evidence | |
|---|---|
| Strong | Consistent findings (≥80%) in at least two high-quality cohorts |
| Moderate | One high-quality cohort and consistent findings in one or more low-quality cohorts |
| Limited | Findings of one cohort or consistent findings in one or more low-quality cohorts |
| Inconclusive | Inconsistent findings irrespective of study quality |

the terms 'multiple sclerosis' and 'relapses' or 'exacerbations' or 'disability' or 'progression' in combination with 'infections', 'vaccinations', 'menstruation', 'pregnancy', 'childbirth', 'oral contraception', 'breastfeeding', 'stress', 'stressful life events', 'trauma', 'surgery', 'anesthesia', 'radiotherapy', 'medication', 'vitamin D', 'sun exposure', 'smoking', 'diet', 'nutrition', 'alcohol', 'exercise' and 'fitness'. We largely selected publications from the past 10 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Only articles published in English were considered.

To assess the methodological quality of the studies, we used the qualification of evidence scheme developed by the American Academy of Neurology for prognostic questions.[2] Based on these criteria all studies were classified into four classes. Class I and II studies were rated as high-quality studies, whereas Class III and Class IV studies were rated as low-quality studies (see Table 1). A well-conducted meta-analysis was rated a high-quality study. The strength of evidence was based upon criteria used in a systematic review of prognostic factors of whiplash-associated disorders (see Table 2).[3] Two reviewers (MBD and JDK) rated the evidence. In case of disagreement, consensus was achieved.

## Infections and vaccinations

### *Viral and bacterial infections*

A prospective study of common viral infections on exacerbations assessed 170 patients with MS monthly over a 5-year period. During cumulative periods designated 'at risk', defined as the period including 2 weeks before and 5 weeks after the onset of infection, the annual relapse rates were almost threefold greater than during periods not at risk.[4] In a cohort study with an 'at risk' period limited to 2 weeks after the onset of an upper respiratory tract infection, the relative risk of a clinical relapse increased from 2.1 for a serologically unconfirmed infection to 3.4 when the viral infection was serologically confirmed.[5] Based on these and other studies, definite evidence for an increased risk of exacerbations during the weeks around a potentially preventable infection was reported with a 'level A' recommendation.[6] Later on, a longitudinal study in 73 patients with relapsing–remitting MS suggested that exacerbations with onset around the time of a clinical infection lead to more sustained neurological damage than non-infection-associated exacerbations.[7] An association between bacterial infections and exacerbations has also been reported.[8,9]

To explain these findings, antigen-non-specific activation of the immune system during infection has been proposed.[10] Only a minority of infections varying, from 9% to 41%, appears to be associated with an exacerbation. Remarkably, MRI confirmation for the presence of new lesions has not been very consistent. It cannot fully be excluded that some of the clinical worsening around infections in MS may actually correspond to pseudorelapses instead of representing true relapses. Changes in neurological function might be due to physiological processes other than a new inflammatory process in the CNS.[10] From a clinical perspective the difference is not always immediately obvious.

In summary, there is substantial evidence for an increased risk of MS activity during the weeks around a viral, and probably also a bacterial, infectious episode. The mechanisms, however, remain incompletely understood.

### *Parasitic infections*

Parasitic infections may be associated with less inflammatory and clinical disease activity in MS, as reported

in 12 parasitic-infected MS patients with eosinophilia followed for more than 4 years. Cytokine responses in the infected MS patients were predominantly of an anti-parasitic Th2 type.[11] Given the lack of blinding, the small sample size and the observational design, caution is needed in interpreting these results.

### Vaccinations

A systematic review in 2002 analysed three randomized, placebo-controlled trials, one crossover and seven cohort studies to estimate the exacerbation rate during 6 months after influenza vaccination. Definite evidence against a substantially increased risk of MS exacerbation after influenza vaccine was found.[6]

The risk of triggering a relapse after vaccination in patients with MS has been addressed in the European multicenter study within the EDMUS network. Exposure to hepatitis B or tetanus vaccination did not increase the risk of relapse in a 2-month period in a large group of MS patients free of relapses for at least 12 months.[12] Most vaccinations, especially those against tetanus plus poliomyelitis or diphtheria, were actually associated with a lower risk of relapse, although the difference was not statistically significant. A more recent study reported the effects of vaccination against hepatitis B or tetanus after a first episode of CNS inflammatory demyelination in childhood. No increased risk of conversion to MS was found during a mean follow-up of 5.6 years, although the possibility of a small increase could not be excluded.[13] Insufficient information is available for vaccines against measles, polio, typhoid fever, hepatitis A, mumps, rubella or pneumococcus.[6] Nevertheless, it is recommended that people with MS who meet the Center of Disease Control criteria for any particular vaccination should be given it.[14]

## Menstruation, oral contraception, pregnancy, postpartum period and breastfeeding

### Menstruation and oral contraception

An association between the premenstrual periods, defined as a period of 6 days preceding the onset of menses, and exacerbations has been described in a subgroup of patients. Data from a structured MS database revealed that 42% of selected female patients had exacerbations starting in the premenstrual phase.[15] No protective effect of oral contraceptives was found. Since the premenstrual period can worsen MS symptoms as well, distinguishing between clinical relapses and pseudorelapses is not evident. A serial MRI study in eight women reported no difference in the activity between the follicular (from day 3 to day 9) and the luteal (from day 21 to day 28) phase of the menstrual cycle, but found enhancing lesions to be related to the actual progesterone/17-beta-estradiol ratio during the luteal phase.[16]

There is limited knowledge about the effect of oral contraceptives on the course of MS. In a recent questionnaire, few women reported changes in MS symptoms in relation to oral contraception.[17] Older data from 446 women with MS revealed no substantial influence of oral contraception on the degree of disability reached after a certain period.[18] From the available data, no conclusions can be drawn about the influence of oral contraceptives on the natural course of MS.

### Pregnancy and the postpartum period

Several, mostly retrospective, studies have suggested an increased relapse rate during the postpartum period.[19,20] The Pregnancy in MS (PRIMS) study, the first large prospective study of the natural history of MS in pregnant women, followed a total of 269 pregnancies in 254 women until 24 months after delivery. The annual relapse rate decreased dramatically during pregnancy. Compared with a mean relapse rate of $0.7 \pm 0.9$ in the pre-pregnancy year, a decrease by two thirds to $0.2 \pm 1.0$ was observed during the third trimester ($p < 0.001$). By contrast, the 3-month postpartum period was characterized by an increase in the rate up to $1.20 \pm 2.0$ ($p < 0.001$). Thereafter, the relapse rate stabilized towards the reference period rate.[21,22] Clinical predictors of a relapse during the postpartum period were an increased relapse rate in the year before or during pregnancy and a higher Expanded Disability Status Scale (EDSS) score at the onset of pregnancy. Still, 72% of the women did not experience a relapse during this period.[22] Serial MRI studies in 28 Finnish patients supported the finding of increased disease activity during the postpartum period.[23]

Several studies did not find an effect of pregnancy on the long-term outcome in MS.[20] A retrospective study of 185 women showed no association between disability and the number or timing of pregnancies relative to onset of MS.[24] A review of medical records in 178 patients with MS revealed no difference in the long-term disability of women with or without pregnancies.[25] Parity did not influence the risk of secondary progression in MS in a hospital-based cohort of Dutch patients.[26] However, other studies suggested a beneficial effect of pregnancy. In a Swedish population cohort study a lower conversion to progression in the 'pregnancy after onset' state compared with the state 'before pregnancy' was found ($p = 0.023$). Women who became pregnant after relapse onset of MS ($n = 28$) contributed to the 'before pregnancy' state until the

first pregnancy and then moved to the 'pregnancy after onset' state. Women without pregnancies ($n = 31$) also contributed to the state 'before pregnancy'. Women who had pregnancies before MS onset were not considered in this analysis. Matching groups were defined taking into account disability, age and disease duration. The risk of entering a progressive course was 3.2 times higher in the 'before pregnancy' state.[27] The interval between disease onset and wheelchair dependency was reported to be significantly longer in patients who had at least one pregnancy after the onset of MS compared with the other women, even after correction for age at onset ($p < 0.011$).[28] Recently, a reduced risk to reach EDSS 6 was found in 61 patients with children only after MS onset compared with 80 patients without children, using regression analysis correcting for age at onset (HR 0.61; 95%CI 0.37–0.99, $p = 0.049$). Furthermore, after correction for age at onset, all women who gave birth at any point in time did better than women without children (HR 0.66; 95% CI 0.47–0.95, $p = 0.023$).[29] Although a more aggressive disease in childless women could explain some of the findings, most women in this study first had children and later on developed symptoms of MS. As a consequence, the association of childbirth with a reduced risk to reach EDSS 6 suggests a favourable long-term effect of childbirth on the course of MS. The underlying mechanisms remain unclear. Sex hormones are obvious candidates because of their effects on inflammation, damage and repair. The hormonal changes associated with pregnancy and childbirth could result in a delay of progression in MS. Changes in lifestyle related to childbirth might also be involved.[29]

### *Breastfeeding*

Data from interviews found no altered risk or timing of relapses in the postpartum period during an average period of 6.3 months of breastfeeding.[30] Although the relapse risk after delivery was not affected by breastfeeding in the PRIMS study, women who breastfed had a lower relapse rate during the entire study period ($p = 0.02$), suggesting milder MS from the beginning of the study.[21,22] In the intravenous immunoglobulin study during pregnancy and postpartum, breastfeeding did not affect postpartum relapse rate.[31] In these studies, no data about supplemental feeding were provided. In a recent prospective cohort study, exclusive breastfeeding for at least 2 months postpartum was associated with a strongly reduced relapse rate compared with no breastfeeding or starting supplemental formula feedings within 2 months.[32] This association might indicate that patients who feel better and have a more benign course may be more inclined to give exclusive breastfeeding. Alternatively, these findings suggest a different biological effect of exclusive breastfeeding resulting in a significantly prolonged lactation amenorrhea compared with combined feeding.[32] Confirmation in a well-designed study is needed.

## Non-traumatic stress

The belief that stress causes exacerbation is widespread among people with MS. However, the nature of the relationship between stress and MS disease activity is complex. Different types of stressors may have different effects, and the impact of stressful life events may depend upon the balance of positive and negative events. A bidirectional relationship between stress and disease progression has been reported, independent of baseline disability.[33]

A meta-analysis of 14 studies found a modest but clinically meaningful association between non-traumatic stressful life events and an increased risk of exacerbation.[34] The findings were statistically homogenous, except for one study reporting a decrease of exacerbations during the first Gulf war.[35] This was not the case during the 2006 war in northern Israel, when an increased relapse rate occurred during compared with before and after the war.[36] No MRI data were available.

Although no relationship with clinical exacerbations was evident, conflict and disrupted daily routine were found to be associated with an increased risk of new gadolinium-enhancing lesions.[37] Patients with MS who more frequently used emotional preoccupation as coping strategy were more likely to show this relationship.[38]

A 2-year prospective study in Australia related relapses to the number and not the severity of reported stressful life events.[39] Similarly, in Greek women with relapsing–remitting MS, experiencing three or more stressful events during a 4-week period was associated with a fivefold increase in relapse rate.[40]A prospective study found high levels of anxiety to be related to the report of stressful events during the preceding period and a relapse in the following period. A common underlying emotional factor is suggested to play a role in triggering MS relapses.[41] ''Two studies reported the effect of infections to be independent of stress'' has to be changed into ''Two studies reported the effect of stress to be independent of infections''.[41,42]

Although most clinical studies suggest a modest association between stressful life events and exacerbations in MS, it is not straightforward to link these events to increased inflammatory disease activity in MS. The activation of the sympathetic system and hypothalamic–pituitary–adrenal axis following stress is thought to suppress the immune system. At present, difficulties in defining and measuring stress in MS do not allow establishing a causal link between non-traumatic stressful events and aggravation of multiple sclerosis, but the reported association needs further clarification.

## Physical trauma

It has been suggested that physical trauma involving the cervical spinal cord or the brain may influence the disease course in MS. A prospective, 8-year follow-up of 170 patients with MS did not find a correlation between disease activity and all traumas, including surgery and dental procedures. Although patients with MS had two to three times more trauma than controls, no association between the frequency of trauma and progression of disability has been found.[43] In 1999, based on strong and consistent Class II evidence, including the study mentioned above, any association of trauma, especially head trauma, with more than a small effect on either MS onset or MS exacerbation has been excluded.[44]

Acute cervical cord hyperextension–hyperflexion injury has been related to worsening in 15 MS cases. New symptoms began between 1 and 12 weeks post trauma and did not correlate with the severity of injury. No further follow-up was reported.[45]

Based on the available data, there is no convincing evidence that physical trauma alters the natural progression of disability.

## Anaesthesia and surgery

All anaesthetic techniques have been implicated in the exacerbation of symptoms in MS but no controlled studies exist. Many anaesthetists still believe that general anaesthesia causes fewer exacerbations than neuraxial blocks, most particular spinal anaesthesia.[46] General anaesthesia and epidural anaesthesia with low concentration local anaesthetics are considered to be relatively safe.[47]

The relapse incidence in women who received epidural anaesthesia for vaginal delivery did not significantly differ from that in women who received local infiltration.[48] However, all women with postpartum relapses in this study had received epidural concentrations of bupivacaine greater than 0.25%. This suggests that higher concentrations administered for longer periods of time might adversely influence the relapse rate. In the PRIMS and intravenous immunoglobulin studies, women with or without epidural analgesia did not differ in their risk of postpartum relapses.[21,22] Also, no effect on disability progression has been found.[22]

## Radiotherapy

External beam radiotherapy of the brain in patients with MS may be associated with an increased risk of neurotoxicity compared with patients without demyelinating illness.[49] Four patients received radiation therapy in full tumoricidal doses for suspected intracerebral neoplasms subsequently found to be demyelinating lesions. All had an unexpectedly poor clinical outcome, suggesting that conventional doses of radiation may result in enhanced toxicity.[50] A patient with MS treated for a parotid malignancy with surgery and radiotherapy developed new neurological symptoms 6 weeks after completion of radiotherapy. MRI demonstrated new hyperintense lesions within the 50% isodose radiation field.[51] An older report described a clinicopathological study of a women with a glomus jugulare tumour treated with radiotherapy. Activation of silent MS lesions was confined to the radiation fields.[52]

## Medication

### *Monoclonal antibodies against tumour necrosis factor alpha*

A phase I trial with monoclonal antibodies against tumour necrosis factor alpha led to intrathecal immune activation and increased inflammatory disease activity on MRI in two patients.[53] An increased number of exacerbations were found in lenercept-treated patients compared with placebo during a phase II trial involving 168 patients, most with relapsing–remitting MS.[54]

### *Granulocyte colony-stimulating factor*

Neurological worsening was evident in 4 of 10 patients treated with granulocyte colony-stimulating factor to mobilize factor progenitor and stem cells from bone marrow.[55] The enhanced adhesion of encephalitogenic T cells to extracellular matrix components has been proposed as a possible mechanism.[56]

### *Statins*

Following preliminary data suggesting a beneficial effect of statins in experimental autoimmune encephalomyelitis (EAE) and MS, the combination of 40 or 80 mg atorvastatin with thrice-weekly 44 μg interferon beta-1a was studied in 26 patients with clinically stable, relapsing–remitting MS. Patients on atorvastatin had a greater risk of either clinical or MRI disease activity compared with the placebo group. Since interferon beta and statins exert different effects on the immune system, some of these may be antagonistic.[57] Whether these findings were coincidental, related to dose and/or product is currently not known. Well-designed studies in a larger patient group are needed to answer these questions. Ongoing clinical trials are further examining the effects of statins as monotherapy and add-on therapy (http://clinicaltrials.gov/).

### *Assisted reproduction technology*

An increased relapse rate has been found following assisted reproduction technology (ART) in MS patients. This technique involves administration of gonadotropin-releasing hormone analogues, agonists or antagonists, to down regulate the endogenous gonadotropin release and to achieve a superovulation. Progesterone supplementation is usually accomplished during the luteal phase, following replacement in utero of in vitro-produced embryos. One treatment cycle lasts approximately 4–6 weeks. An increased incidence of MS relapses was first described within 3 months following administration of gonadotropin-releasing hormone agonists.[58] Then either luteinizing hormone releasing hormone (LHRH) agonists (9 cycles) or LHRH antagonists (5 cycles) were associated with a single relapse within 3 months after ART in five of six MS patients.[59] The same authors confirmed these findings in 23 MS patients who underwent 78 hormonal stimulations. Whereas no patient had a relapse 3 months before treatment, 12 patients suffered from a single relapse within 3 months after ART. The relapse rate increased significantly from $0.62 \pm 0.1$ before to $0.95 \pm 0.12$, independent of the hormonal approach or the time interval between the stimulations. None of the patients who became pregnant had a relapse. Reduced oestrogen levels, temporary cessation of immunomodulatory treatment or ART as stressful life event might be involved. The authors conclude that women with MS should be informed about a possible risk of relapse after ART.[60]

## Vitamin D and sun exposure

An exploratory study in the USA found mortality from MS reduced with increased residential exposure to sunlight (odds ratio = 0.53, 95% CI 0.48–0.57). Possible protective effects of sunlight exposure might be directly immunological or mediated by melatonin or vitamin D.[61]

Vitamin D is best known as a calcium homeostasis modulator. The serum concentration of 25(OH) vitamin D predominantly reflects its synthesis from provitamins in the skin under the influence of ultraviolet light, and the contribution of dietary vitamin D is rather low. In northern regions, a relative vitamin D deficiency during winter months is common.

Lower serum levels of 25(OH) vitamin D have been reported in relapsing–remitting MS patients compared with healthy controls.[62,63] Both in cross-sectional and longitudinal studies, slightly lower serum levels of 25(OH) vitamin D were found in MS patients during a relapse compared with remission.[62–64] Higher serum levels have been associated with low relapse activity.[65]

A study of ambient environmental variables in 142 relapsing–remitting MS patients in Southern Tasmania, Australia, found prior erythemal ultraviolet radiation, lagged 1.5 months, to exhibit a significant, inverse correlation with the monthly relapse rate. Serum 25(OH) vitamin D levels, taken from a previous study, seemed to correlate with the monthly relapse rate when no lag was applied. Linear regression found either prior sun exposure or serum vitamin D level to account for one tenth of the variation in relapses.[66] Upper respiratory tract infections were also associated with relapses, but not independently of prior sun exposure. The combination of prior sun exposure and upper respiratory tract infections explained 18.1% of the relapse rate.[66]

In a population-based study in Tasmania, disability in MS cases was strongly associated with lower serum levels of 25(OH) D and lower levels of recent sun exposure. Nearly half of this association appeared to be due to less recent sun exposure in cases with higher disability. Whether the low vitamin D level among the higher disability cases reflects a different disease-related outdoor behaviour or suggests an effect of low vitamin D on disability is presently unknown.[67] An association between lighter skin types and lower disability scores has been reported in a subgroup of female patients with MS for longer than 10 years. No data about recent sun exposure were provided.[68] Recent Dutch studies found circulating levels of 25(OH) vitamin D to be inversely associated with MS-related disability.[65,69] The available data suggest some protective effect of vitamin D levels on exacerbations and disability in MS. The possible mechanisms are not well understood, although important gene–environment interactions probably exist. Recently a single major histocompatibility complex (MHC) vitamin D response element has been localized to the promoter region of HLA-DRB1, suggesting direct functional interaction with the major locus determining genetic susceptibility.[70] Direct effects of 1,25 $(OH)^2$ vitamin D on ex vivo T cells suggest a role in T-cell homeostasis.[63] Further studies are warranted.

## Smoking

Smokers with a clinically isolated syndrome were 1.8 times more likely to develop clinically definite MS than non-smokers during a follow-up of 36 months.[71]

A more than threefold increased risk of conversion from relapsing–remitting to progressive MS has been reported in smokers.[72] No effect on progression was shown in a retrospective study of 364 patients with disease duration of 17 years. In women, the number of total smoked-pack-years correlated weakly with the Multiple Sclerosis Severity Score (MSSS) and EDSS.[73] Higher disability, as measured by the MSSS, was found in ever smokers compared with never

smokers in a study of 122 MS cases with disease duration of 6 years. This was most pronounced in 29 individuals who started smoking early (≤15 years of age).[74] In a prospective cohort study of 198 cases followed for 909 days, cumulative pack-years smoked after entry was associated with increase in longitudinal MSSS, not with relapses.[75] In a recent study in 1465 patients, current smokers were more likely to have primary progressive MS and had worse disease at baseline in terms of EDDS, MSSS and brain parenchymal fraction as measured by MRI. In a longitudinal analysis, an accelerated conversion from relapsing–remitting to secondary progressive MS was found in current smokers (HR 2.5; 95% CI 1.42–4.41). Also, T2-weighted lesion volume increased faster and brain parenchymal fraction decreased faster in smokers.[76] Smoking was associated with increased blood-brain barrier disruption, higher lesion volumes and greater atrophy in a MRI study of 368 consecutive MS patients.[77] Overall, several well-designed studies now support the hypothesis that cigarette smoking modifies the clinical course of MS and promotes progression. Although confounding factors cannot be excluded, the adverse effect is in line with studies indicating neurotoxic and immunomodulatory effects of cigarette smoke. A dose–response effect may be present, and the period of influence may extend from the period preceding the clinical onset of MS. The different conversion rates in current and ex-smokers suggest that some adverse effects may be partially reversible.[76] These findings should encourage neurologists to advice patients with MS to quit smoking.

## Dietary habits and nutritional status

Mortality rates from MS for the period 1983–1989, obtained from the World Health Organization for 36 countries, and consumption levels of the different types of fat, provided by the United Nations Food and Agriculture Organization for the period 1979–1981, indicated a significant and positive correlation between MS mortality and consumption of saturated fatty acids (FA), animal fat or animal minus fish fat, supporting a link between dietary fat intake and MS mortality.[78]

The literature on dietary interventions in MS is extensive but the quality of the studies appears to be low. According to a recent systematic review, slight decreases in relapse rate and relapse severity have been associated with omega-6 FA in some small studies. Omega-3 FA had no benefit on progression. The authors conclude that available data are insufficient to assess the real benefit or harm that might result from polyunsaturated FA supplementation.[79]

Not included in this review is the publication of Swank and Goodwin, who reported an increased survival among 70 MS patients who strictly followed a low saturated fat diet for 34 years. Vitamins were added to guard against deficiencies.[80]

Whether the nutritional status has an effect on the course of MS is unknown. With increasing disability, weight loss, malnutrition and vitamin deficiency are frequently found. On the other hand, obesity is a frequent finding in MS due to immobility, subsequent low energy expenditure, steroids, antidepressants and an inactive daily life.[81]

## Alcohol, exercise and fitness

A questionnaire from Northern California revealed a dose–response association between alcohol consumption and lower EDSS scores, in both relapsing and progressive patients. Patients with lower disability may have a better tolerance for alcohol. On the other hand, alcohol might have a protective effect in MS.[82] In the context of experimental traumatic brain injury, neuroprotective effects of ethanol have been found probably related to effects on cerebral glucose metabolism and blood flow.[83] Further research is needed to determine if and how alcohol might influence disability in MS.

Another factor associated with lower EDSS scores was exercise, suggesting a better tolerance for exercise in patients with less disability.[82] In a cross-sectional study in patients with MS, lower fitness levels were associated with slower behavioural performance and lesser recruitment in the right inferior and middle frontal gyrus of the cerebral cortex. This region's recruitment seems to play a role in compensating for cognitive deterioration in MS.[84] In view of these and findings from a descriptive longitudinal study,[85] a beneficial effect of exercise and aerobic fitness cannot fully be excluded.

Although these observations need to be interpreted very cautiously, they might be in line with the effects of physical activity on the aging brain[86] and the association of physical fitness with cognitive reserve in older people.[87]

## Conclusion

Review of the factors influencing disease activity in MS reveals a variety of associations with exacerbations and progression of disability. Increasing evidence indicates that some of these associations may be relevant. The strength of evidence for each of these factors, based on careful assessment of the quality of the studies, is summarized in Table 3. Strong evidence for the presence of an effect was found for infections, childbirth, stressful life events and smoking.

There are, however, a number of limitations. First of all, distinguishing true relapses from pseudorelapses

**Table 3.** The strength of evidence on modifiable factors influencing relapses and disability in multiple sclerosis

| | Finding | Rating of studies | Evidence classification |
|---|---|---|---|
| Infections | Two to threefold increased risk of relapse in the period 'at risk' (–2 weeks to + 3 to 5 weeks around infection). | At least two high-quality studies.[6] | **Strong evidence** for an increased risk of exacerbations around an infectious episode. |
| Vaccinations | No increased short-term risk of relapse following vaccinations. | For influenza: at least two high-quality and several low-quality studies.[6,13] | *Influenza:* **strong evidence** against a substantial increased risk of multiple sclerosis relapse. |
| | | For tetanus and hepatitis B: one high-quality study[13] and one case crossover study.[12] | *Tetanus and hepatitis B:* **moderate evidence** against a substantial increased risk of multiple sclerosis relapse. |
| | | For others: low-quality studies.[6] | *Other:* unknown. |
| Pregnancy | Decreased risk of relapse, especially in third trimester. | One high-quality cohort[21] and several low-quality studies.[19] One prospective cohort did not find a decreased relapse rate during pregnancy.[20] | **Moderate evidence** for a decreased risk of exacerbations during pregnancy. |
| Postpartum period | Two to threefold increased risk of relapse in the period 'at risk'. | At least two high-quality cohorts[20,21] and several low-quality studies.[19] | **Strong evidence** for an increased risk of exacerbations in the postpartum period. |
| Long-term effects of childbirth | No increased progression of disability following childbirth. | At least two high-quality[20,27] and several low-quality studies.[24–26,28,29] Some of the studies suggested a reduced risk to progression or EDSS 6.[27–29] | **Strong evidence** against an increased progression of disability following childbirth. |
| Breastfeeding | No increased short-term risk of relapse. | Several low-quality studies.[21,22,30,31] One cohort study found exclusive breastfeeding to be associated with reduced risk of relapse compared with non-exclusive breast feeding.[32] | **Limited evidence** against an increased risk of MS relapse during breastfeeding. |
| Stressful life events | Twofold increased risk of relapse. | Two high-quality cohorts[34,42] and consistent findings in several low-quality cohorts.[36,39,40] | **Strong evidence** for an increased relapse risk following self-reported stressful life events. |
| Physical trauma | No obvious effect. | One high-quality report[43] and consistent findings in several low-quality cohorts.[44] | **Moderate evidence** that physical trauma does not increase the relapse risk. |
| Epidural analgesia | No obvious effect. | Several consistent low-quality cohorts.[21,22,31,47,48] | **Limited evidence** that epidural analgesia does not increase the relapse risk. |
| Radiotherapy | Associated with activation of MS. | Several consistent low-quality studies.[49–52] | **Limited evidence** for increased activation of disease following radiotherapy. |

(continued)

**Table 3.** Continued

| | Finding | Rating of studies | Evidence classification |
|---|---|---|---|
| Assisted reproductive technology | Increased risk of relapse. | Several low quality studies.[58–60] | **Limited evidence** for an increased risk of relapses following assisted reproductive technology. |
| Sun exposure | Inverse correlation with relapse rate. | One high-quality cohort.[66] | **Limited evidence** that sun exposure is associated with a decreased relapse rate. |
| | Less sun exposure in cases with higher MS disability. | One study.[67] Not confirmed.[69] | **Inconclusive evidence** that less sun exposure is associated with higher disability. |
| Vitamin D levels | Inverse correlation with relapse rate. | Two studies with consistent findings.[65,66] | **Limited evidence** that lower vitamin D levels are associated with a higher relapse rate and higher EDSS scores. |
| | Association of lower levels of 25 (OH) vitamin D with higher EDSS scores. | Low quality-studies with consistent findings.[65,67,69] | |
| Smoking | Increased progression in smokers. | Two high-quality cohorts found increased conversion from relapsing–remitting to secondary progressive MS.[72,76] Three high-quality cohorts found increased progression in smokers.[75,76,77] One study did not find increased progression.[73] | **Strong evidence** that smoking is associated with an increased risk of progression. |
| Dietary habits | Slight decrease in relapse rate and severity of relapses associated with omega-6 fatty acids. | Several low-quality cohort studies suggest an effect of supplements with omega-6 fatty acids.[79] A low saturated fat diet has been suggested in one low-quality cohort.[80] | **Limited evidence** for supplements with omega-6-fatty acids and low saturated fat to affect disease activity. |
| Alcohol | Alcohol consumption is associated with lower EDSS scores. | One survey study.[82] | **Limited evidence** for alcohol consumption to be associated with lower EDSS scores. |
| Exercise | Higher exercise levels are associated with lower functional disability. | Two survey studies.[82,85] | **Limited evidence** for exercise to be associated with lower functional disability. |
| Fitness | Higher fitness is associated with faster behavioural performance. | One study.[84] | **Limited evidence** for fitness to be associated with faster behavioural performance. |

EDSS, Expanded Disability Status Scale.

remains a difficult issue. Despite efforts to create objective criteria, relapses are highly subjective, both for the patients and for the examiner. Supportive MRI data are often not available. Even strong evidence cannot be considered definitive. Secondly, the association of self-reported stressful life events with disease activity in MS remains controversial. It cannot be excluded that a relapse occurring in this context reflects high anxiety levels instead of an inflammatory event. Nevertheless, effective coping strategies to deal with concerns and anxiety may be helpful. It has been shown that increasing autonomous decision making in patients with relapsing MS leads to a reduced number of relapses, changes in relapse management and an improved subjective rating of disease course, compared with standard information leaflets.[88] Thirdly, some of the lifestyle factors may be linked to each other. For example, the inverse association between sun exposure, serum 25(OH) vitamin D levels and MS disease activity does not seem to be independent from the association between respiratory infections and relapses.[66] Vitamin D levels can be increased through fish intake and regular exercise, as was reported in a study in healthy, middle-aged Asian men.[89] Although little is known about the effects of higher vitamin D metabolite levels on sex hormone levels, supplements in young women not using hormonal contraceptives resulted in higher serum 25(OH) vitamin D levels and lower luteal progesterone levels, suggesting an interaction.[90]

Since infections are associated with a two to threefold increase in the risk of an exacerbation, reducing the risk of infections, for example by yearly vaccinating MS patients against influenza, continues to be a relevant health care issue. Vaccinations do not increase the short-term risk of relapse in MS, but reliable information is only available for influenza, tetanus and hepatitis B.

Some women have relapses related to the premenstrual period. It has not been investigated whether extended use of oral contraception to prevent menstruation might be beneficial. When considering fertility treatment, women with MS should be informed about the increased relapse risk after ART. A reduction of the relapse rate during pregnancy, especially in the last trimester, is counteracted by an increased risk in the postpartum period. In most studies, breastfeeding did not appear to influence the occurrence of postpartum relapses. A recent prospective study reported a decreased relapse risk during exclusive breastfeeding with lactation amenorrhea. This finding remains to be confirmed. A favourable long-term effect of childbirth on the course of MS has been proposed, independent of the timing of childbirth. Overall, the role of sex hormones in MS seems to be more important than previously estimated, but further studies are needed.

No increased relapse risk has been found following trauma, surgery and anaesthesia. Epidural anaesthesia with low concentrations of anaesthetics appears to be safe. Publications on the effects of cranial radiotherapy are limited but indicate a worsening of MS lesions in the radiation fields, suggesting enhanced neurotoxicity.

Granulocyte colony-stimulating factor, monoclonal antibodies against tumour necrosis factor alpha, and perhaps atorvastatin given in combination with interferon beta, may enhance disease activity.

Smoking appears to affect the risk of progression, with some arguments for a partial reversible effect. Data about diets in MS are limited. Possible beneficial effects of moderate alcohol intake and physical activity on disability in MS are of interest, but need to be confirmed.

Despite some uncertainties, a number of lifestyle changes with varying degrees of confidence to modify disease activity can now be proposed to MS patients.

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## Conflict of interest

The authors report no conflicts of interest.

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