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A Systematic Review of Several Potential Non-Genetic Risk Factors for Multiple Sclerosis

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Key Words
Multiple sclerosis · Review · Sunlight · Sex hormones · Dietary fats

Abstract
We reviewed the literature published in the English language to determine the weight of evidence for several potential non-genetic risk factors for multiple sclerosis, including solar ultraviolet radiation (UVR), sex hormones and dietary fat/fatty acids. We ranked the plausibility of each factor and graded the methodological rigour of case-control and cohort studies to determine whether there was a sufficient number of high-quality studies to weigh the evidence. Based on our criteria, the plausibility for solar UVR and sex hormones is good and fair for dietary fat/fatty acids. However, the body of epidemiologic evidence is insufficient for these three sets of risk factors. We did not find a sufficient number of methodologically rigorous studies to weigh the evidence for any of the potential risk factors we examined.

Introduction

The first systematic studies of multiple sclerosis (MS) in populations were conducted in the early decades of the 20th century, but information on the epidemiology of MS did not increase substantially until the 1950s. At that time, epidemiologists began to use surveys to explore aetiological hypotheses related to environmental factors such as residence, climate and soil conditions [1]. Despite decades of epidemiologic, clinical and laboratory research, however, the causes of MS remain unknown. Although it seems clear that there is a genetic component, the fairly low concordance rate among identical twins indicates that non-genetic factors play a strong role in influencing risk [2].

We conducted a review of the literature to rank the plausibility, body of epidemiologic evidence and weight of evidence for several potential non-genetic risk factors for MS, using the criteria described in table 1 and in Methods. We also describe some issues related to measuring exposure to each potential risk factor. Our goal was to provide an overview of the most plausible hypotheses that can be tested in a precise manner, since we believe that these should be given priority for research.

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Methods

Plausibility

Potential risk factors should be reconcilable with at least some aspects of the epidemiology of MS. For the purposes of this paper, we considered the primary epidemiologic features of MS to be: (1) MS affects more females than males, in a ratio approaching 2:1 [3, 4]; (2) in general, the prevalence and incidence of MS increase with latitude [5, 6], although exceptions to this latitude gradient exist [7–9]; (3) migration studies suggest that individuals who move from an area where the risk of MS is high to an area where the risk is lower show a decrease in risk. Although it is difficult to establish a critical age at which migration affects risk since few studies have collected information on age at migration, it does appear that the younger the age the greater the reduction in risk. In contrast, individuals who move from an area of lower risk to an area of higher risk appear to demonstrate little change in risk [10], and (4) the risk of MS onset peaks at age 30, with initial symptoms in people younger than age 10 or older than age 50 accounting for less than 5% of cases [11].

Support for a cause-and-effect relationship is strengthened if there is a known or postulated biologic mechanism through which an exposure could affect the risk of disease [12]. However, as it is beyond the scope of this paper to comprehensively review experimental evidence, we have chosen to include examples of experimental studies that support a *potential* aetiologic contribution, without assessing the quality or range of evidence to determine whether it is a *probable* aetiologic contribution. The ranking of plausibility is described in table 1.

Table 1. Ranking system for plausibility, body of epidemiologic evidence and weight of evidence for several potential non-genetic risk factors for MS

	Ranking criteria used	Ranking system
Plausibility	1 Does the factor conform to one or more epidemiologic features of MS[1]? 2 Has a biologic mechanism been postulated by which the factor may affect the risk of MS, with supporting experimental evidence? 3 Does experimental evidence support a role for this factor in the onset of animal models of MS?	*Good* Conforms to at least one epidemiologic feature of MS AND biologic mechanism has been postulated for which experimental evidence exists AND experimental evidence exists for role in onset of animal models of MS *Fair* Meets two of the above criteria but not all three; OR meets one of the above criteria AND experimental evidence exists for role in affecting disease activity in MS or animal models of MS *Poor* None of the above
Body of epidemiologic evidence	Is the number of methodologically rigourous published studies sufficient to examine the weight of evidence?	*Good* Three or more case-control or cohort studies graded as 'a'[2] *Fair* Two case-control or cohort studies graded as 'a'[2] *Insufficient* None of the above
Weight of evidence	If the body of epidemiologic evidence is good, does the evidence support an association with MS?	*Good support* Good or fair plausibility AND good consistency[3] *Fair support* Good or fair plausibility AND fair consistency[4]; OR poor plausibility BUT good consistency[3] *No clear support* None of the above *Not applicable* Cannot be determined at this time due to insufficient body of epidemiologic evidence

1 Sex ratio; latitude gradient; migration data; age-incidence curve.
2 Method score (derived from criteria listed in Conclusion) > 75%.
3 Conclusions of ≥ 67% of 'a' studies support an association.
4 Conclusions of 50–66% of 'a' studies support an association.

Body of Epidemiologic Evidence

For each potential risk factor, we evaluated the methodological rigour of case-control and cohort studies only. As the purpose of this review was not to duplicate previous efforts, we first searched MEDLINE (1966 to January week 2, 2002) for meta-analyses or other quantitative reviews of the evidence published in English. Reviews were found for organic solvents [13], physical trauma [14] and Epstein-Barr viral infections [15]. Accordingly, we chose not to review these factors. We then did a subject heading and key word search of MEDLINE (1966 to January week 2, 2002) for studies examining an association between MS and solar ultraviolet radiation (UVR), several hormonal exposures and dietary fat/fatty acids. We limited our search to articles in English. We also searched the reference lists of articles located through our MEDLINE search. Summaries of the studies we reviewed are presented in tables 2 and 3.

The study design of the individual studies was assessed using a set of criteria to examine how the roles of chance, bias and confounding were minimized, elements that may affect the validity of a study's findings (see Conclusion for details) [12]. The scoring system was adapted from one developed by the National Kidney Foundation-Dialysis Outcomes Quality Initiative to assess the methodological rigour of published evidence [16]. A method score was derived by summing responses, divided by the applicable number of criteria and multiplied by 100%. We then graded individual studies as follows:

Table 2. Summary of case-control studies reviewed

Reference (grading of methodological rigour)	Cases		Comparison group and effective sample size	Exposures relevant to this review	Exposure measurement	Potential confounders controlled for	Results
	source(s)	case definition and effective sample size					
Antonovsky et al. [36] (c)	All known cases in Israel identified through nationwide survey of MS in 1961	241 prevalent cases of probable or possible MS (clinical criteria)	917 randomly selected from population (47 served as duplicate controls; analysis based on 964 controls)	Average number of hours spent outdoors in summer from school age until age 15, and from age 15 to onset; frequency outdoors without being fully clothed; age at menarche; parity	Interview [unknown whether interviewer(s) blinded to study hypotheses and/or case/control status]	Age, sex, region of birth	No association between age at menarche or parity and MS 2+ h/day spent outdoors in summer was significantly associated with MS ($p = 0.02$)
Berr et al. [72] (c)	General practitioners and neurologists in Hautes-Pyrénées, France	63 prevalent cases of definite or probable MS (Poser et al. criteria)	63 unrelated controls (source not reported)	Age at menarche	Interview (conducted by one of the investigators)	Age, parish of residence	Older age at menarche significantly associated with MS ($p < 0.002$)
Cendrowski et al. [37] (c)	All known cases identified through neurological in- and outpatient departments, sanatorial centers and care homes for the chronically disabled in Poznán District, Poland	300 cases of probable or possible MS (clinical criteria)	300 patients with sciatica residing in same district as cases	Average number of hours spent outdoors in summer from school age until age 15	Interview (unknown whether interviewer blinded to study hypotheses and/or case/control status)	Not reported, although controls had a 'similar demographic pattern'	No significant association between time spent outdoors and MS
Freedman et al. [33] (b)	National Cancer Institute, National Institute for Occupational Safety and Health, and National Center for Health Statistics database of all deaths in 24 US States	5,701 deaths from MS (ICD-9 code 340)	2 control groups: 6,565 deaths from non-melanoma skin cancer and 153,502 deaths from other causes	Level of solar radiation (low/medium/high) of residence at death and occupational exposure to sunlight based on usual occupation	Residential exposure classified as annual mean daily solar radiation based on United States Weather Bureau data; occupational exposure classified by industrial hygienist (unknown whether blinded to study hypotheses and/or case/control status)	Age, sex, race, SES	Group with highest residential and occupational exposure to sunlight were significantly less likely to have MS (OR = 0.24; 95% CI 0.15–0.38)
Ghadirian et al. [94] (b)	MS Association of Montreal East, neurologists, general physicians, media announcements in Montreal	197 incident cases (diagnosis and diagnostic criteria not reported)	202 randomly selected from population	Daily vegetable fat intake; daily animal fat intake; daily total fat intake; daily saturated fat intake; daily oleic acid intake; daily linoleic acid intake (all during year prior to diagnosis, not onset)	Interview (unknown whether interviewers blinded to study hypotheses and/or case/control status)	Age (± 5 years), sex, 1st 3 digits of phone number	Increased animal fat intake significantly associated with MS (OR = 2.0; 95% CI 1.1–3.5)

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Table 2 (continued)

Reference (grading of methodological rigour)	Cases		Comparison group and effective sample size	Exposures relevant to this review	Exposure measurement	Potential confounders controlled for	Results
	source(s)	case definition and effective sample size					
Hopkins et al. [73] (b/c)	All known cases in Galion, Ohio identified through Galion City Health Department, MS support group, local physicians, media announcements	16 prevalent cases of definite or probable MS (Poser et al. criteria)	61 randomly selected from population	Age at menarche	Interview [unknown whether interviewer(s) blinded to study hypotheses and/or case/control status]	Age (±5 years), race	No association with age at menarche
Kurtzke et al. [71] (c)	Known cases on Faroe Islands	15 prevalent cases of possible MS and 8 deceased cases (criteria not reported)	127 total: 69 siblings of cases; 37 neighbours and their spouses/siblings and case spouses; 21 distant controls, their spouses and other relatives	Age at menarche	Interview of prevalent cases/controls, and relatives of deceased [unknown whether interviewer blinded to study hypotheses and/or case/control status]	Age	No association with age at menarche
Leibowitz et al. [74] (c)	All known cases in Israel identified through nationwide survey of MS in 1961	208 prevalent and 13 incident cases of probable or possible MS (clinical criteria)	416 randomly selected from population registry	Pregnancy (never/ever prior to onset)	Interview [unknown whether interviewer(s) blinded to study hypotheses and/or case/control status]	Age, region of birth	No association with pregnancy
Neutel et al. [34] (b)	Canadian death certificates from 1963 to 1972	Coding of MS as primary cause of death (number not reported)	Randomly selected from list of non-violent deaths in 1969	Annual hours of sunshine	Report No. 3 of the Canada Land Inventory (Dept of Forestry and Rural Development) and climatic maps (Meteorological Branch of Dept of Transport) used to assign ecologic measure of exposure based on province of birth	Age, sex, province of death, Canadian- or foreign-born (frequency matched)	Excess of MS cases in areas with increased exposure to sunshine and degree days (but only statistically significant in Quebec)
Norman et al. [35] (b)	United States military veterans of World War II and Korean conflict	4,371 cases granted disability compensation for MS	4,371 selected from National Service Life Insurance policyholders and persons who left military service between 1950 and 1970	Annual solar radiation; mean annual sunshine	National atlas of USA used to assign an ecologic exposure value for 3,012 United States counties of birthplace	Restricted to white males; matched on year of birth, date of entry into service, branch of military and survival of wars; adjusted for latitude of county of birth	No association between climatic variables and MS
Operskalski et al. [70] (c)	All known cases in Los Angeles County, California and King and Pierce Counties, Washington identified through prevalence study in 1970	145 prevalent cases of definite or probable MS (diagnostic criteria not reported)	145 friends of cases	Age at menarche; parity	Self-administered questionnaire	Age (±5 years), race, birthplace, residence	No association between parity and MS; age at menarche in cases significantly lower than in controls ($p = 0.01$)
Runmarker and Andersen [44] (b)	Incidence cohort of patients with onset of MS from 1950 to 1964 resident in Göteborg, Sweden	153 prevalent cases of definite or probable MS (Poser et al. criteria)	Swedish general population	Pregnancy (ever/never before onset)	Not reported for cases; National Central Bureau of Statistics for comparison group	Year of birth	Nulliparity significantly increases risk of MS

SES = Socioeconomic status.

Table 3. Summary of cohort studies reviewed

Reference (grading of methodological rigour)	Cohort	Follow-up	Cases	Case ascertainment	Exposure measurement	Potential confounders controlled for	Results
Hernán et al. [75] (b)	238,371 participants in NHS I and II	18 years for NHS I and 8 years for NHS II	315 cases of definite or probable MS according to treating physician	Self-report on biennial questionnaire; case status then confirmed by contacting physician	Baseline and biennial questionnaire asking about oral contraceptive use (current/past/never) and duration of use and number of pregnancies	Age, latitude tier at age 15, ancestry, smoking status at baseline	OC use or parity not significantly associated with MS
Thorogood and Hannaford [77] (b/c)	46,000 married women recruited in late 1960s for General Practitioners' Oral Contraception Study (UK)	564,000 person-years of observation	114 cases with ICD-8 diagnosis of MS (code 340)	Diagnosis supplied by general practitioners as part of study	Information collected at baseline on combined oral contraceptive use (never/former/current) and dose of oestrogen in oral contraceptives for current users and parity; information updated throughout study period by general practitioners	Age, parity at diagnosis, social class at baseline, smoking status at baseline	OC use not significantly associated with MS
Villard-Mackintosh and Vessey [76] (b)	17,032 white married women aged 25–39 attending 17 clinics in Britain and recruited for Oxford Family Planning Association Contraceptive Study	275,867 person-years of observation	63 cases with ICD-8 diagnosis of MS (code 340)	Diagnosed while in study by a hospital consultant	Baseline and annual follow-ups to determine duration of oral contraceptive use and parity	Age, smoking, parity	OC use not significantly associated with MS; parity (3+ vs. 0) protective against MS (RR = 0.4; 95% CI 0.2–1.4)
Zhang et al. [95] (b)	187,811 participants in NHS I and II	14 years of follow-up for NHS I and 4 years of follow-up for NHS II	195 cases of definite or probable MS according to treating physician	Self-report on biennial questionnaire; case status then confirmed by contacting physician	Consumption of total fat; animal fat; vegetable fat; saturated fat; monounsaturated fat; n–6 polyunsaturated fat; *trans*-unsaturated fat; oleic acid; linolenic acid; arachidonic acid; fish omega-3 fatty acids; eicosapentaenoic acid; docosahexaenoic acid	Age, sex (study population restricted to women), geographic tier at birth, pack-years of smoking, total energy intake	Increased n–6 polyunsaturated fat associated with MS (RR = 1.7; 95% CI 1.0–2.8); increased linoleic acid protective against MS (RR = 0.3; 95% CI 0.1–1.1); no significant association between total fat or other major specific types of fat and MS

NHS = Nurses' Health Study; OC = oral contraceptive; RR = relative risk.

(a) method score greater than 75%; (b) method score between 51 and 75%; (c) method score between 26 and 50%, and (d) method score less than or equal to 25%. Studies with a method score of 25, 50 or 75% were graded as c/d, b/c or a/b, respectively. We then ranked the body of epidemiologic evidence for each potential risk factor as good, fair or insufficient (see table 1 for details).

Weight of Evidence

If the body of epidemiologic evidence was good, then an assessment of the weight of evidence was made, using the criteria of plausibility and consistency of results with other investigations (table 1). We gave higher priority to the criterion of consistency of results, since what is considered plausible according to our criteria requires the existence of a postulated biologic mechanism. This depends on the current state of knowledge, and a lack of a postulated mechanism does not mean that none exists [12]. Although the magnitude of the association is often included as a factor in determining causality [12], the presumed multifactorial nature of MS may decrease the relevance of this criterion, and therefore we did not include it when weighing the evidence. All references to significance in the following text refer to statistical significance using an alpha of 0.05.

Results

Solar UVR

The latitude gradient in MS has prompted a number of studies of geoclimatic factors. Several ecologic studies have reported an inverse correlation between solar UVR and MS risk [17–19]. Solar UVR dose decreases with increasing distance from the equator. For example, annual UVB radiation – the component of UVR that is

believed to be mainly responsible for health effects in humans – expressed in minimal erythema dose is 6,000 in Hawaii at latitude 20 degrees North, compared with 2,500 in Spain at latitude 40 degrees North and 1,500 in Belgium at latitude 50 degrees North. Maps of annual UVR exposure compiled for epidemiologic studies of skin cancer and other diseases clearly show the inverse relationship between UVR dose and latitude [20]. Thus, the hypothesis that solar UVR exerts a protective effect against MS conforms to the latitude gradient seen in MS.

At least two biologic mechanisms have been postulated by which solar UVR may decrease the risk of MS. First, UVR may exert a protective effect due to its suppressive effects on the immune system. Suppression of local and systemic immune function by UVR has been documented in rodents [21], and in humans, sunlight exposure increases suppressor T cell activity [22] and inhibits the recruitment of autoreactive T cells [23].

A second possible mechanism is through the involvement of solar UVR in the biosynthesis of vitamin D. Through a chemical photolysis reaction in the skin, humans produce vitamin D. UVR acts as a catalyst in the first step of this reaction [24]. The most potent metabolite of vitamin D is 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$] [25]. Receptors for this compound have been found on peripheral blood monocytes and activated T lymphocytes [25, 26], suggesting a role for 1,25-$(OH)_2D_3$ in inflammation [24, 27]. In vivo, 1,25-$(OH)_2D_3$ inhibits interleukin (IL)-2, a cytokine that promotes the growth of T cells [25]. In a series of experiments, investigators studied the effects of 1,25-$(OH)_2D_3$ on experimental allergic (autoimmune) encephalomyelitis (EAE) [28–30], a demyelinating disease of the central nervous system (CNS) with a similar pathological and clinical profile to MS [31] that serves as an animal model for MS. In brief, mice or rats treated with 1,25-$(OH)_2D_3$ prior to induction of EAE showed significant signs of reduced EAE severity and CNS inflammation [28] and improved inhibition of EAE relapses [29, 30]. Further experimental evidence of a protective role of UVR, regardless of the mechanism, comes from another study done in mice. Only 9% of mice irradiated with whole-body UVR prior to immunization with mouse spinal cord homogenate to induce EAE developed clinical signs of acute EAE in contrast to 86% of mice who were not irradiated [32].

In the epidemiologic literature, 5 case-control studies that assessed the association between exposure to solar UVR and MS risk were identified. Three were graded as 'b' [33–35] and 2 were graded as 'c' [36, 37]. Accordingly, the body of epidemiologic evidence was ranked as 'insufficient'. Three of the studies assigned an ecologic measure of residential exposure: either annual hours of sunshine [34, 35] or annual solar radiation [35] of place of birth, or the level of solar UVR based on the residence at death [33]. The 2 studies that examined individual levels of residential exposure asked about the time spent outdoors in summer from school age until age 15 [37], and in summer and winter from school age to age 15 and from school age to onset, as well as the amount of time spent outdoors 'not fully clothed' [36]. Individual-level occupational exposure was classified according to one's usual occupation as indoor work, combined indoor and outdoor work or outdoor work [33].

We could not weight the evidence as the body of epidemiologic evidence was insufficient. More precise measures of UVR exposure are needed to investigate whether there is any association with MS [33]. For example, a number of factors influence ambient UVR, including cloud cover, altitude and air pollution [20]. Furthermore, although measures of ambient UVR provide upper limits of human exposure, actual exposure is dependent on individual behaviours related to clothing, sunscreen use, the number of hours spent in the sun and exposure to artificial sources of UVR, such as sun lamps. Estimates of individual exposure could thus combine data on ambient UVR with a behavioural model of exposure [20]. Guidelines for the measurement of sun-related behaviours have been published [38].

Sex Hormones

A skewed sex distribution is a common factor in many autoimmune diseases [39]. The hypothesis that sex hormones may influence susceptibility to MS therefore accords well with the sex ratio in MS. This hypothesis also accords with the age-incidence curve in MS, as a number of sex hormones have similar age curves, including androstenedione [40], oestrone, oestradiol and 17-OH progesterone in females [41], and dehydroepiandrosterone sulphate in males and females [42].

There is evidence that sex hormones affect disease activity in MS and EAE. For example, pregnancy has been associated with a lower relapse rate in MS, with a subsequent increase in disease activity in the postpartum period in some studies [43, 44], but not in others [45]. Worsening of MS symptoms immediately prior to or at the beginning of menstruation has also been reported in women with relapsing-remitting MS [46]. Further evidence that sex hormones are associated with disease activity in MS comes from a magnetic resonance imaging (MRI) study. When serum oestradiol and progesterone levels

were correlated with gadolinium-enhancing lesions (an indicator of disease activity) on MRI, women with high oestradiol and low progesterone levels demonstrated a significantly higher level of disease activity than women with low levels of both hormones. Furthermore, women with a high oestrogen-to-progesterone ratio demonstrated a significantly greater number of gadolinium-enhancing lesions than women with a low ratio of these hormones [47].

The role of sex hormones has also been studied in EAE. Some of the laboratory studies suggest that the gender difference observed in EAE susceptibility is due primarily to the protective effect of testosterone [4, 48]. Nonetheless, other experimental studies have shown a decrease in disease severity following induction of EAE in both mice and rats after administration of oestriol pellets [49] or synthetic oestrogen 17α-ethinyloestradiol [50]. Similarly, the decrease in disease severity during pregnancy is thought to be due, in part, to high levels of oestriol observed during this time period [49, 51]. Experimental evidence also exists for a protective role of sex hormones produced in the ovaries against the onset of EAE [52] and the relapse of EAE [51].

Although the precise mechanisms by which sex hormones may influence susceptibility to MS are not known, in vivo and in vitro studies have demonstrated that sex hormones affect immunoreactivity [39, 53, 54]. In general, oestrogens tend to stimulate humoral and cell-mediated immune responses, while androgens tend to be immunosuppressive [55]. Therefore, if sex hormones do play an aetiological role, they may do so through their effects on the immune system. One hypothesis is that sex hormones may be involved in one or more stages of lymphocyte maturation, whereby inappropriate regulation during lymphocyte development leads to the breakdown of self-tolerance [56]. Another hypothesis is that oestrogens may affect expression of the proto-oncogenes and oncosuppressor genes involved in programmed cell death, which may be relevant to human autoimmune disease [53].

A third hypothesis relates to cytokines. Cytokines are secreted by immune cells, including T cells, and act on other cells of the immune system to regulate their function [57]. Cellular immunity is promoted and regulated by Th1, or pro-inflammatory cytokines, including IL-2, IL-12, interferon (INF)-γ and tumour necrosis factor (TNF)-β. Humoral immunity is promoted and regulated by Th2, or anti-inflammatory cytokines, such as IL-4, IL-5 and IL-6 [58]. In EAE, a predominance of Th1-cytokine-secreting cells has been found in clinical disease, whereas a predominance of Th2-cytokine-secreting cells has been found in the recovery phase [59, 60]. Furthermore, the clinical course of EAE can be altered or prevented by the administration of certain cytokines [61, 62]. It has therefore been postulated that MS may be associated with a dysregulation in the balance between Th1 and Th2 cytokines [58, 63].

Experimental evidence has shown that sex hormones affect cytokine secretion. The administration of male hormones such as synthetic androstene derivatives and androstenetriol in mice is thought to limit the production of certain Th1 cytokines and can significantly delay the onset and severity of EAE [31]. Conversely, oestradiol has been found to enhance the secretion of the Th1 cytokine IFN-γ, when administered at a concentration found during the pre-ovulatory phase. Oestrone, oestriol and progesterone were also found to affect the secretion of cytokines IL-10, IFN-γ and TNF-β by human CD4+ T cell clones [64, 65]. Thus, by modulating cytokine secretion, sex hormones may influence susceptibility to MS. This hypothesis accords with the observations mentioned earlier regarding pregnancy and MS. Pregnancy causes a shift towards a Th2 cytokine profile. There is a radical shift postpartum in hormone levels, and lower levels of hormones that inhibit Th1 cytokines may allow inflammatory diseases such as rheumatoid arthritis and MS to flare up or to develop [66].

A few studies have examined serum hormone levels in MS. Grinsted et al. [67] measured serum hormone levels in 14 premenopausal women and 14 controls, and found that compared with the control group, the MS group had significantly higher mean serum concentrations of prolactin, luteinizing hormone, follicle-stimulating hormone, total and free testosterone, dihydrotestosterone and androstenedione, and a significantly lower serum concentration of oestrone sulphate. They did not appear to control for the possible confounding influences of age and body mass index. Another small study measured serum testosterone in 20 men with MS and found that 4 men had abnormally low levels. No control group was used [68].

The findings of these studies must be interpreted with caution since MS lesions may disrupt CNS pathways controlling endocrine output [69], and thus differences in hormone levels may be secondary to the disease. Accordingly, we limited our search to potential hormonal risk factors for which exposure was known to have occurred prior to disease onset.

In examining the epidemiologic data on sex hormones and MS, we focused on 4 hormonal risk factors: (1) age at menarche: we found 5 case-control studies, 4 of which we

graded as 'c' [36, 70–72] and 1 of which we graded as 'b/c' [73]; (2) pregnancy: we found 3 case-control studies of which 1 was graded as 'b' [44] and 2 as 'c' [70, 74]; (3) parity: we found 3 cohort studies, 2 of which we graded as 'b' [75, 76] and the other as 'b/c' [77]. Two case-control studies were also identified, both of which we graded as 'c' [36, 70], and (4) oral contraceptives: we found 3 cohort studies, 2 of which we graded as 'b' [75, 76] and the other as 'b/c' [77].

In brief, we could not weigh the evidence for any of the above hormonal factors since the body of epidemiologic evidence for each of them was insufficient. Investigating the role of sex hormones in MS is difficult for a number of reasons. Measuring serum levels of hormones in cases and controls may be misleading, due to issues of temporality (i.e. whether such differences existed prior to disease onset or whether they were a result of the disease). Furthermore, it may not be the case that the same hormone is influencing susceptibility in both males and females, or even that a single hormone is involved: rather, it may be the ratio between two or more hormones that is important. In addition, sex hormones may increase receptor levels of other sex hormones, so even if the actual concentration of a hormone is not increased, its biological activity may be. In future, proxy measures of hormone status may be the most feasible way of characterizing exposure (such as irregular menstruation as a measure of lower cumulative exposure to ovarian hormones or shorter regular cycles as a measure of greater cumulative exposure [78], or greasy skin, acne and hirsutism as measures of hyperandrogenism [79]). Proxy measures of in utero hormone exposure may also be warranted, since it has been suggested that this may affect the immune system in offspring by influencing the balance between a Th1 and Th2 cytokine response [80, 81].

Dietary Fat/Fatty Acids

A number of ecologic studies have reported significant positive correlations for dietary fat and MS prevalence [82, 83] and mortality [84]. However, although geographic variations in diet certainly exist, we are aware of no study that examined dietary fat/fatty acids and latitude. Furthermore, the dietary hypothesis does not concur with the sex ratio and the age-incidence curve characteristic of MS. Moreover, while migration may alter dietary patterns, it is difficult to defend the view that this would occur among migrants moving from a high- to a low-risk area for MS, but would not occur among those moving from a low- to a higher-risk area.

Nevertheless, there is some evidence that fatty acids may affect the course of MS. A combined analysis of data from 3 randomized, double-blind trials found that linoleic acid, a polyunsaturated essential fatty acid, significantly reduced the progression of disability as measured by the Kurtzke score among patients with a baseline disability score of 0–2. Furthermore, it also significantly reduced the severity and duration of relapses across all baseline Kurtzke scores as measured by the mean relapse score [85]. Linoleic acid has also been shown to significantly reduce the severity of EAE in guinea pigs [86], while more than 50% of rats fed a diet lacking in polyunsaturated fatty acids developed paralysis of the neck or extremities after they had been immunized with guinea pig brain homogenate to induce EAE, compared to none of the control group fed a normal diet [87].

Various mechanisms have been proposed to explain these observations as reviewed by Mayer [88]. For example, myelin is composed of 75–80% lipids, of which polyunsaturated fatty acids are a major component [89]. Small changes in concentration of the latter may affect the stability and biochemical reactivity of the myelin and its supporting glia [90], thereby increasing susceptibility of the myelin sheath to demyelinating agents [91]. While myelin normally undergoes large changes in its lipid composition with aging with the structural stability of the myelin sheath being maintained [89], changes in the concentration of polyunsaturated fatty acids may be important during the postnatal period when myelination of the CNS is taking place.

In addition to membrane stability, polyunsaturated fatty acids also play a role in immune function. n–3 polyunsaturated fatty acids suppress the production of arachidonic-acid-derived eicosanoids, compounds that modulate the production of pro-inflammatory cytokines [92]. In one experiment, the ratio of production of Th1 (pro-inflammatory) to Th2 (anti-inflammatory) cytokines (as measured by the IFN-γ/IL-4 ratio) was lowest in mice fed diets rich in n–3 or n–6 polyunsaturated fatty acids compared with mice fed low-fat or saturated fatty acid diets [93].

Upon reviewing the epidemiologic literature, to allow comparability of results and to conform to the potential biologic mechanisms described above, only those studies were included that reported a precise measure of dietary fat or fatty acid consumption, such as total fat intake or total saturated fatty acid intake. Accordingly, we excluded 15 studies that reported: consumption of specific foods, such as meat or milk, without measurement of actual fat or fatty acid content; differences in overall diet; or breast-

feeding and risk of MS. We graded the remaining case-control study, which measured daily intake of total fat, saturated fat, oleic acid, linoleic acid, animal fat and vegetable fat, as 'b' [94]. One cohort study was graded as 'b' [95]. It reported dietary intake of total fat, animal fat, vegetable fat, saturated fat, monounsaturated fat, n–6 polyunsaturated fat, *trans*-unsaturated fat, oleic acid, linolenic acid, arachidonic acid, fish omega–3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid. Since there exist only 2 analytic studies to our knowledge that report precise measures of dietary fat and fatty acids, the body of epidemiologic evidence was ranked 'insufficient'.

Many factors make it challenging to investigate the aetiologic role of diet in MS. There is a potential for recall bias, since some hypotheses concerning diet have become well-known among people with MS, which may lead to differential misclassification in a study that relies on questionnaire data [96]. One possible way to overcome problems of recall bias is to use more objective methods for dietary assessment, such as adipose tissue biopsies [97]. However, such an invasive procedure may decrease the response rate.

Establishing the correct exposure window is also problematic: should information on diet be sought for the period immediately preceding disease onset, or for childhood, the period during which migration studies indicate the disease process may be initiated [98–100]? In the latter case, the problem then becomes one of how to accurately measure food intake in the distant past. Current diet as a proxy measure for past diet may not be an accurate measure, since 1 study found that two thirds of people with MS had changed their diet following diagnosis [101]. Recall of past diet may also be poor since it is influenced by current diet [102, 103]. Nevertheless, recall, rather than current diet, has been found to be a more accurate indicator of past dietary intake [103].

Another issue concerns what aspects of diet are measured. For example, diet as a potential risk factor has been quite extensively investigated, as evidenced by the number of studies that were found. However, studies that may be relevant to dietary fat/fatty acids focus on consumption of different food items (e.g. meat versus milk consumption) or measure intake in different ways (e.g. a predominantly meat-based diet versus consumption of individual food items like meat, chicken and fish), making a synthesis of the results difficult. It may be more useful to state a priori a potential biologic mechanism by which diet may influence risk, and then formulate a specific hypothesis. This specificity may increase the precision of exposure measurement. For example, if the postulated biologic mechanism is that a deficiency of polyunsaturated fatty acids results in unstable myelin, which increases susceptibility to demyelination, then the hypothesis can be formulated that persons with MS will have a lower intake of polyunsaturated fatty acids at some period prior to disease onset than controls. When this aspect of diet is investigated, it would be more relevant to calculate the actual intake of polyunsaturated fatty acids, rather than reporting the frequency of meat or milk consumption.

Conclusion

This review has a number of shortcomings. We limited our search to articles in MEDLINE published in English and did not search for unpublished articles, abstracts or articles published in languages other than English. The reviewers were not blinded to the authors or results of the studies. Furthermore, the criteria we used to grade the methodological rigour of studies may not have been inclusive, and we also gave equal weight to each criterion.

Based on our set of criteria to assess the methodological rigour of published reports, the following criteria were fully reported by individual studies where applicable (certain criteria applied only to case-control studies): (1) base population specified; (2) comparison group selected from base population; (3) incident cases studied; (4) cases restricted to clinically definite MS according to established criteria; (5) overall response rate >80% or losses to follow-up <20%; (6) characteristics of respondents and non-respondents or losses to follow-up not significantly different; (7) validity of registry data/external data source reported; (8) statistical analysis specified and appropriate, and (9) confidence interval around risk estimate reasonably narrow. However, individual studies only partially reported on the remaining set of methodologically rigorous criteria: (1) exclusion criteria specified and same for all groups; (2) exposure ascertainment described and same for all groups; (3) exposure measured in a precise and valid manner; (4) interviewers and/or technicians and/or outcome assessors blinded, and (5) controlled for potential confounders.

Given that the methodological rigour was based on what was reported in the published article, the calculated score may not be reflective of the actual quality of the study (for example, a follow-up rate may not have been reported in the published article, even though losses to follow-up may have been low). Moreover, although we used epidemiologic principles as a guideline when we formulated the criteria used to rank plausibility, body of epi-

Table 4. Summary of rankings for plausibility, body of epidemiologic evidence and weight of evidence for several potential non-genetic risk factors for MS

Potential risk factor	Plausibility	Body of epidemiologic evidence	Weight of evidence
Solar UVR	good	insufficient	N/A
Sex hormones	good		
Age at menarche		insufficient	N/A
Pregnancy		insufficient	N/A
Parity		insufficient	N/A
Oral contraceptives		insufficient	N/A
Dietary fat/fatty acids	fair	insufficient	N/A

N/A = Not applicable (cannot be determined due to insufficient body of epidemiologic evidence).

demiologic evidence and weight of evidence, our rankings may be viewed as somewhat arbitrary.

In spite of this, we hope that this review fulfills our goal of providing an overview of the most plausible hypotheses that can be tested in a precise manner. Table 4 gives a summary of the rankings for the potential risk factors we chose to examine. According to our system of rankings, the body of epidemiologic evidence is insufficient at this time to weigh the evidence for any factor, and therefore it can be proposed that all of them need further study. However, we assigned the highest plausibility for a potential aetiologic role to solar UVR and sex hormones, and feel that there is a need for more research in these areas.

One issue that is highlighted in our review is how precisely exposure to a factor can or has been measured in past studies. More precise exposure measurement will allow more reliable conclusions to be drawn. It is possible to design studies that would enable much more precise measurement of exposure to solar UVR, as we discussed in the summary to that section. It is also possible to measure dietary fat and fatty acids much more precisely, as was done in the 2 studies we graded [94, 95]. For sex hormones, proxy measures of hormonal status prior to disease onset do not seem to have been investigated, and there is a need for more research in this area. In conclusion, we hope that the factors that contribute to MS susceptibility will soon be elucidated, as many of the agents postulated over 100 years ago as potential risk factors are still under investigation. We feel therefore that priority for research should be given to potential risk factors that meet the criteria of plausibility in terms of postulated biologic mechanisms and conformity to the epidemiologic features of MS, and for which exposure can be precisely measured.

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