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4 Epidemiology of Multiple Sclerosis: Environmental Factors

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Epidemiology in Perspective

Epidemiology is the study of the distribution and determinants of disease frequency in human populations. By studying who is affected, where, and when, epidemiologists try to obtain clues about the causes of a disease, develop hypotheses, and design specific studies to test those hypotheses. At the core of epidemiology is the notion of "webs of causation"[1]; that is, the awareness that diseases are almost always the result of multiple contingencies, most often including several aspects of the environment as well as genetic predisposition, so that no single cause can be identified. Epidemiologists consider some aspect of the environment as "causally associated" with a disease if their modification results in a change in disease frequency. Well-known historical examples include the relations between poor sewage disposal and cholera, consumption of a diet deficient in thiamine and pellagra, and, more recently, prone sleep position and risk of sudden infant death. Evidence of causality and even disease prevention (e.g., reduction in infant deaths after implementation of the "back to sleep" campaign[2]) have often occurred without a complete understanding of the underlying biologic mechanisms. Indeed, reliance on the identification of biologic mechanisms as a *sine qua non* for establishing causality is probably unwise, because it may delay progress in disease prevention. On the other hand, knowledge of molecular mechanisms clearly strengthens the evidence for causality. Multiple, well-conducted epidemiologic investigations may lead to experimental studies, but experimental proof of causality is not uncommonly unfeasible, unethical, or unaffordable, and public health decisions need to rely primarily on observational

data. Such has been the case, for example, with interventions to reduce lung cancer incidence by reducing exposure to tobacco smoke.

As discussed in this chapter, epidemiologic evidence points to three environmental risk factors—infection with the Epstein-Barr virus (EBV), low levels of vitamin D, and cigarette smoking—whose association with multiple sclerosis (MS) seems to satisfy in varying degrees most of the criteria that support causality, including temporality (i.e., the cause must precede the effect), strength, consistency, biologic gradient, and plausibility. None of these associations, however, has been tested experimentally in humans, and only one (vitamin D deficiency) is presently amenable to experimental interventions. This chapter also summarizes the evidence, albeit more sparse and inconsistent, linking other environmental factors to MS risk.

Descriptive Epidemiology of Multiple Sclerosis

For many years, it appeared that the "who, where, and when" of MS epidemiology was well understood. However, some aspects of MS epidemiology may be changing, notably the observations of an attenuation of the latitude gradient[3,4] and the increasing female-to-male ratio.[5] In this section, we discuss the "classic" view of MS epidemiology, some of which has been known for more than 50 years, and then some recent developments that may provide new clues to the etiology of MS.

CLASSIC VIEW

MS is the most common neurologic disease in young adults. Incidence rates are low in childhood and adolescence (<6/100,000/year) high in the middle to late twenties and early thirties (11 to 18/100,000/year in high-risk populations), and gradually decline thereafter, with rates less than 9/100,000/year among those older than 45 years of age.[3,6] Women are approximately twice as likely as men to develop MS,[7,8] and the lifetime risk among white women is about 1 in 200.[3,9] MS exhibits a worldwide latitude gradient, with high prevalence and incidence in Northern Europe,[7] Canada,[10,11] the northern United States,[3,12,13] and southern Australia[14] and decreasing prevalence and incidence in regions closer to the equator.[15] Exceptions to the latitude gradient exist and include a lower than expected prevalence in Japan[16] and higher than expected prevalence and incidence in the Mediterranean islands of Sardinia and Sicily.[7] Kurtzke[17] summarized the early descriptive studies by depicting areas of high (≥30/100,000), medium (5 to 29/100,000), and low (<5/100,000) prevalence of MS; we have updated his figures with more recent prevalence estimates[7,16,18-24] (Fig. 4-1). A more comprehensive review of MS incidence and prevalence worldwide was published in 2005.[18] It is important to note that differences in estimated incidence across countries or time periods can result from differences in study design, case ascertainment, or diagnostic criteria, rather than from real changes in disease occurrence. Differences in prevalence are even more difficult to interpret, because they may reflect increased survival or earlier diagnosis, both of which can occur even if the incidence is the same.[25] In spite of these limitations, the collective data do support a higher risk of MS at higher latitudes, both north and south of the equator.

Figure 4–1 Worldwide prevalence estimates of multiple sclerosis. Blue, more than 90 cases per 100,000 population; purple, 60 to 89/100,000; green, 30 to 59/100,000; orange, 5 to 29/100,000; yellow, fewer than 5/100,000; white, insufficient data. An asterisk indicates that data for that region or country are older and should be interpreted cautiously.

The existence of the latitude gradient alone is not enough to support an environmental component, because it could be explained by genetic differences.[18,26] However, studies of MS incidence and prevalence among migrant populations also support a role for environmental factors. These studies have limitations, in that migrants may be different from nonmigrants in socioeconomic and health status, may not utilize local health care resources, and therefore they may be less likely to be diagnosed; in addition, enumeration of the immigrant population for disease statistics may be difficult or impossible.[25,27] Nevertheless, migrant studies on MS collectively support a decreased prevalence of MS among those who migrate from high- to low-risk areas, particularly if the migration occurs before 15 years of age.[27] Moreover, one study found a decreased prevalence of MS in all age groups among immigrants from Europe to Australia, suggesting that the protective effect may extend into adulthood as well.[28] Studies within the United States have also supported a decreased risk of MS among migrants from northern (>41° to 42° N),

high-risk parts of the country to southern (<37° N), low-risk regions.[29,30] The study of U.S. veterans[30] is particularly compelling because of its large sample size and rigorous design. In this study, Kurtzke observed that individuals who were born in the northern United States but migrated to the southern part of the country before joining the military had a 50% reduced risk of MS compared with those who did not migrate (Fig. 4-2).

Fewer studies have been conducted among migrants from low- to high-risk areas. In general, these studies have found that a low risk of MS is retained after migration, but that the offspring of migrants have a higher risk of MS, similar to that in the host country.[27,31-35] In the U.S. veterans study,[30] individuals who were born in the southern part of the country and migrated to northern states before entering the military had a 20% increased risk of MS, and those migrating from the middle tier of states to northern regions had a 31% increased risk (see Fig. 4-2). More recently, in a study conducted in the French West Indies (a low-risk area), an increased risk of MS was found among individuals who had moved to France (a high-risk area) and then returned to the West Indies. The increase in risk was greatest among those who migrated to France before the age of 15 years.[36]

RECENT DEVELOPMENTS

The incidence of MS appears to have been relatively stable over the past 50 years in several high-risk areas, including Denmark[6] and the northern United States,[37] but there is some evidence that MS may be increasing in Japan[16] and in parts of Southern Europe, most notably in Sardinia.[38] Interestingly, the island of Malta has continued to experience low, stable rates of MS[39] despite its proximity to Sardinia and Sicily and a high frequency of the MS-associated HLA-DRB1*1501 allele.[40] There is also evidence of an increased female-to-male ratio in MS incidence. In Canada, the

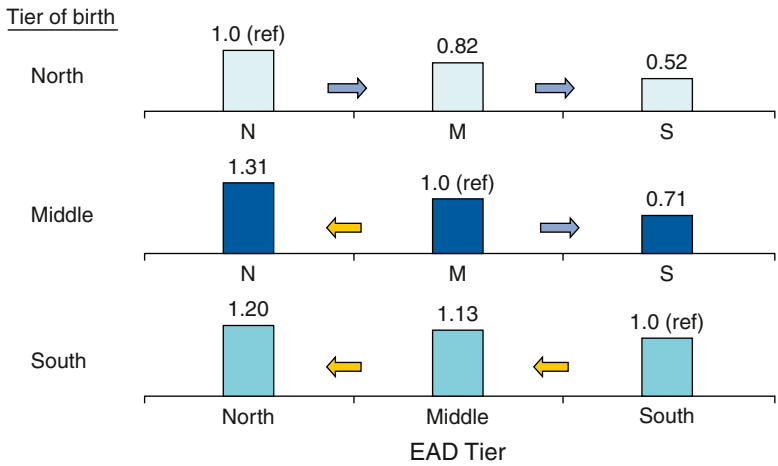


Figure 4–2 Relative risk for multiple sclerosis among white male veterans of World War II or the Korean conflict, by tier of residence at birth and at entry into active duty (EAD). Data are for coterminous United States only. *P* values for no change in birthplace risk are as follows: All, .0003; North, .003; Middle, .002; and South, .57. Adapted from Kurtzke, Beebe, and Norman. Epidemiology of multiple sclerosis in US veterans: III: Migration and the risk of MS. Neurology 1985;35:672-678.

female-to-male ratio apparently has increased from approximately 2:1 among individuals born in the 1930s and 1940s to approximately 3:1 among those born in the 1970s.[5] This change is strongly correlated with, and could be at least in part explained by, a sharp increase in the female-to-male ratio in smoking behavior (unpublished data), because smoking is a strong risk factor for MS (see later discussion).

An attenuation of the latitude gradient was observed independently in a population of U.S. nurses[3] and in U.S. military veterans.[4] Among nurses born between 1920 and 1946 and among veterans of World War II or the Korean conflict, those living in the northern tier of states (>41° to 42° N) had a greater than threefold increased risk of MS compared to those in the southern tier (<37° N). Among Vietnam and Gulf War veterans, however, this gradient was attenuated to less than twofold, and among nurses born between 1947 and 1964 it completely disappeared (Fig. 4-3). Because the methods used to determine rates of MS in the early and later cohorts were the same, and because the individuals in the cohorts had similar socioeconomic status[3] or access to health care,[4] this attenuation was unlikely to be due to artifact. A change of this magnitude over such a short period of time argues for an environmental, rather than a genetic, explanation of the latitude gradient; as discussed later, this environmental factor may involve changes in patterns of infection or sun exposure, or both. Further, the attenuation was probably caused by an increase in MS incidence in the southern United States, because incidence rates in the northern states, based at least on data from the longitudinal study in Olmsted County, Minnesota, seem to have remained relatively stable.[37] An attenuation of the latitude gradient in Europe has also been observed; however, no systematic studies have assessed this gradient within the same population over

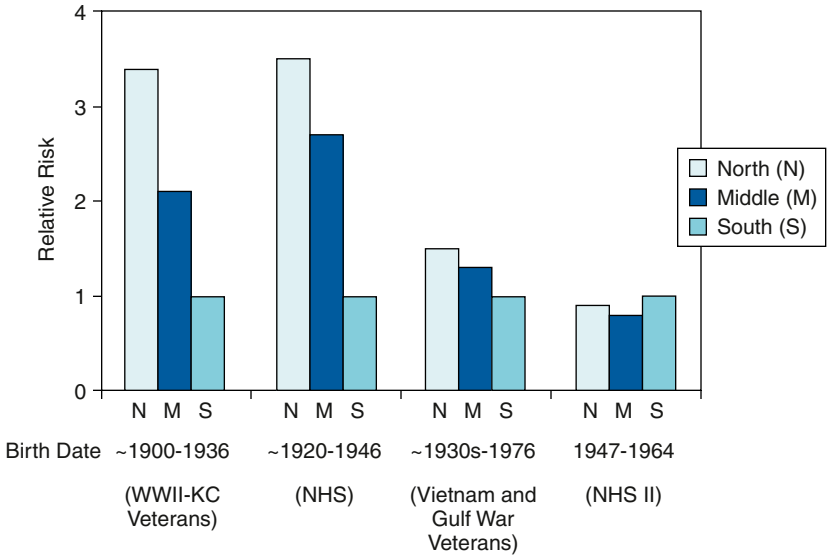


Figure 4–3 Relative risk for multiple sclerosis by latitude at birth in different birth cohorts of U.S. white women. KC, Korean conflict; NHS, Nurses Health Study; NHSII, Nurses Health Study II; WWII, World War II. Adapted from Hernan et al. Neurology 1999;53:1711-1718 and Wallin et al. Ann Neurol 2001;55:65-71.

time, and the attenuation therefore may be due to improved study methodology and case ascertainment, particularly within the United Kingdom.[18]

Infection and Multiple Sclerosis

The possibility of an infectious cause was considered early in MS history, and numerous viruses and bacteria were, at different times, implicated as likely etiologic agents. The results of early studies, based on microscopic examination of pathologic material and attempts to transmit the disease to animals, often were null or spuriously positive because of contamination and could not be replicated. Later, numerous serologic studies were conducted, often demonstrating significantly elevated antibody titers against several viruses in MS patients compared with healthy controls, but these differences were probably an epiphenomenon of the immune activation rather than being of etiologic significance.[41] In part as a consequence of these investigations, many researchers became skeptical about the existence of an infectious agent causing MS, and this skepticism persists today.

Epidemiologic clues to the hypothetical role of infection in MS are complex and often seem to point in opposite directions. On the one hand, results of family studies, including investigations of half-siblings, adopted children, and spouses of individuals with MS, support a strong genetic component as the leading explanation of MS clustering within families and provide little evidence of person-to-person transmission.[42] On the other, there are well-documented, albeit controversial,[43] reports of epidemics of MS, most notably in the Faroe Islands,[44] that are most easily explained by the introduction and transmission of an infectious agent. To reconcile these findings, it has been postulated that MS is a rare complication of a common infection, with the disease occurring in genetically or otherwise predisposed individuals. In this scenario, the epidemics would be a consequence of the introduction of the MS-causing agent for the first time in remote, previously naïve populations.[45] Two hypotheses as to the nature of this infection have been proposed: (1) the responsible microorganism is more common in areas of high MS prevalence (the "prevalence" hypothesis), and (2) the MS-causing agent is ubiquitous and more easily transmitted in areas of low MS prevalence, where infection occurs predominantly in infancy, when it would be less harmful and more likely to confer protective immunity. The latter proposal is called the "poliomyelitis" hypothesis, by analogy with the epidemiology of poliomyelitis before vaccination.[46] The poliomyelitis hypothesis is also consistent with the higher prevalence of MS in communities with better hygiene,[47] in individuals with higher education,[48,49] and in those with late age at infection with common viruses,[50] as well as the general lack of increase in MS incidence among individuals migrating from low- to high-prevalence areas.[27] However, the poliomyelitis hypothesis cannot explain the reduced risk of MS among migrants from high- to low-risk areas and, in fact, would predict an *increase* in MS risk in this circumstance, whereas the prevalence hypothesis is consistent with the observations.

Failure to identify a specific microbe as the cause of MS, despite evidence that is consistent with some role for infection in at least modulating MS risk, has strengthened support for a third, more general, "hygiene" hypothesis, according to which exposure to multiple infections in childhood primes the immune responses later in life toward a less inflammatory and a less autoimmunogenic profile.[51] The hygiene

hypothesis can explain all the features of MS epidemiology that are explained by the original formulation of the poliomyelitis hypothesis. In addition, the protective effect of migration from high- to low-MS areas, which is paradoxical under the poliomyelitis hypothesis, could be beneficial because of increased exposure of migrants to parasitic and other infections in the low-risk area. At the population level, prevalence of MS is positively correlated with high levels of hygiene, as measured, for example, by prevalence of intestinal parasites.[52] The improving hygienic conditions in southern Europe in the last few decades could explain the increased prevalence of MS reported in multiple surveys (although whether there was a true increase in MS incidence remains unsettled).[7] It is also interesting that infection with intestinal helminths, which is highly prevalent in developing countries, had been reported to cause an immune deviation with attenuation of helper T-cell 1 cellular immune responses and remission of MS.[53] Finally, the hygiene hypothesis provides a convincing explanation for the observations that infectious mononucleosis (IM) is associated with an increased risk of MS (relative risk [RR] = 2.3; $P < .00000001$)[54] and that the epidemiology of IM is strikingly similar to that of MS (Table 4-1).[55] Because IM is common in individuals who are first infected with EBV in adolescence or adulthood[56] but rare when EBV infection occurs in childhood, it is a strong marker of age at EBV infection, which is itself strongly correlated with socioeconomic development across populations and with socioeconomic status within populations.[57] An exception to this pattern is seen in Asia, where EBV infection occurs uniformly early in life and IM is thus rare. It is noteworthy that the incidence of MS remains relatively low in Asian countries, including Japan, despite the fast industrialization and reduction of infectious diseases,[58] although there is evidence that the incidence may be increasing in Japan.[16]

According to the hygiene hypothesis, the association between IM and MS risk does not reflect a causal effect of EBV but rather the indirect manifestation of a common cause; that is, both MS and IM are the result of high hygiene and a resulting low burden of infection during childhood. An important prediction of this hypothesis is that MS risk will be high among individuals reared in a highly hygienic environment, even if they do not happen to be infected with EBV later in life, whereas,

TABLE 4–1 Similarities between Multiple Sclerosis (MS) and Infectious Mononucleosis (IM) Epidemiology

Parameter	MS	IM
Age at peak incidence (yr)	25-34	15-24
Age at onset	F < M	F < M
Geography:		
Extremely rare in the tropics	+++	+++
Latitude gradient within temperate regions	+++	+++
Rare in Japan	+++	+++
Rare in Inuits	++	++
Positive association with SES	+	++
Incidence in blacks < whites	+	++
Incidence in Asians < whites	++	++

+++, Strong evidence; ++, moderate evidence; +, weak evidence; F, female; M, male; SES, socioeconomic status.

if EBV has a causal role in MS, individuals who are not infected with EBV would have a low risk of MS.[59] The data on this point are unequivocal: individuals who are not infected with EBV, even though they have the same hygienic upbringing as those with IM, have an extremely low risk of MS (odds ratio [OR] from meta-analysis = 0.06; $P < .00000001$) (Table 4-2). The contrast could not be sharper or more consistent: MS risk among individuals who are not infected with EBV is at least 10-fold lower than that of individuals who are EBV-positive, and 20-fold lower than that of individuals with a history of IM.[59] Because studies in pediatric MS[60,61] rule out a common genetic resistance to MS and EBV infection,[59] we can conclude either that EBV itself or some other factor closely related to EBV is a strong causal risk factor for MS or that MS itself strongly predisposes to EBV infection.

Temporality is the only truly necessary criteria for causality. The association between EBV infection and MS is strong and consistent across multiple studies in different populations, and there is to some extent a biologic gradient (higher risk associated with severity of infection, as indicated by history of IM). Until recently, all studies on MS and infection used a cross-sectional design and could not completely rule out the possibility that EBV infection was a consequence rather than a cause of MS. However, the results of four longitudinal serologic studies have now been published (Table 4-3).[62-65] The most consistent finding across these studies is that, among individuals who will develop MS, there is an elevation of serum antibodies against the EBV nuclear antigen 1 (EBNA1) that precedes the onset of MS symptoms by many years. The presence of anti-EBNA1 antibodies is a marker of past infection with EBV, because titers typically rise only weeks after the acute infection. Further, there is no evidence in clinical studies of acute primary EBV infection in individuals with MS.[66] Taken together, these results indicate that MS is a consequence rather than a cause of EBV infection.

Until recently, EBV had not been found in MS lesions,[67,68] and therefore the link between EBV and MS was postulated to be mediated by indirect mechanisms. The leading hypothesis was that the immune response to EBV infection in genetically susceptible individuals cross-reacts with myelin antigens (molecular mimicry). The discovery that MS patients have an increased frequency and broadened specificity of CD4-positive T cells recognizing EBNA1[69] and the identification of two EBV peptides (one of which is from EBNA1) as targets of the immune response in the cerebrospinal fluid of MS patients[70] provided support to the molecular mimicry theory. Other proposed hypotheses included the activation of superantigens,[71] an increased expression of alpha B-crystallin,[72] and infection of autoreactive B lymphocytes.[73]

However, in a recent, rigorous pathologic study,[74] large numbers of EBV-infected B cells were found in the brain of most of MS patients. These cells were more numerous in areas with active inflammatory infiltrates, where cytotoxic CD8-positive T cells displaying an activated phenotype were seen contiguous to the EBV-infected cells. Alone, these pathologic findings provide only suggestive evidence for a causal role of EBV in MS, because the infiltration of EBV-infected B cells could be secondary to the inflammatory process that is the hallmark of MS, but their convergence with the epidemiologic evidence described earlier[59] is so striking that noncausal explanations become improbable. However, independent replication of these findings is needed before any conclusion can be drawn. The strong increase in MS risk after EBV infection and (if confirmed) the presence of EBV in MS lesions suggest that antiviral drugs or a vaccine against EBV could contribute to MS treatment and prevention. Although antiviral drugs have been

TABLE 4–2 Odds Ratio (OR) of Multiple Sclerosis (MS) in Epstein-Barr Virus (EBV) Seronegative Versus Seropositive Subjects

		EBV Status					
		Cases		Controls		OR of MS for	Exact
Study	Ref. No.	+	–	+	–	Seronegativity	95% CI
Sumaya et al., 1980	186	155	2	76	5	0.2	0.02-1.24
Bray et al., 1983	187	309	4	363	43	0.11	0.03-0.31
Larsen et al., 1985	188	93	0	78	15	0	0-0.05
Sumaya et al., 1985	189	104	0	99	5	0	0-1.07
Shirodaria et al., 1987	190	26	0	24	2	0	0-5.29
Ferrante et al., 1987	191	29	1	31	11	0.1	0-0.76
Munch et al., 1997	192	137	1	124	14	0.06	0-0.44
Myhr et al., 1998	193	144	0	162	8	0	0-0.67
Wagner et al., 2000	194	107	0	153	10	0	0-0.66
Ascherio et al., 2001	62	143	1	269	18	0.1	0-0.68
Haahr et al., 2004	195	153	0	50	3	0	0-0.82
Sundstrom et al., 2004	63	234	0	693	9	0	0-1.5
Ponsonby et al., 2005	196	136	0	252	9	0	0-0.96
Total		1770	9	2374	152	OR_{MH} = 0.06	0.03-0.13[†]

OR_{MH}, Mantel-Haenszel odds ratio.

[*]Confidence interval calculated as described in Mehta CR, Patel NR, Gray R: Computing an exact confidence interval for the common odds ratio in several 2 x 2 contingency tables. J Am Stat Assoc 1985;78:969-973.

[†]Cornfield confidence interval; $P < .000000001$.

From Ascherio A, Munger KL: Environmental risk factors for multiple sclerosis: Part I. The role of infection. Ann Neurol 2007;61:288-299.

tried in the past for MS treatment with borderline results,[75-77] none of the treatment regimens used was sufficiently effective against latent EBV infection.

Several aspects of MS epidemiology cannot be explained by EBV infection, indicating that other factors must contribute.[59] Genes are clearly important, and it is of interest that the association between anti-EBNA1 titers and MS risk has been found in both HLA-DRB1*1501–positive and HLA-DRB1*1501–negative individuals.[78] Variations in EBV strains could also play a role, although evidence in support of this hypothesis remains limited.[79,80] Many other infectious agents have been hypothesized to be related to MS, mostly because of pathologic studies or their role in animal models. Recent candidates include *Chlamydia pneumoniae*,[81-84] human herpesvirus 6,[85-87] retroviruses,[88,89] and coronaviruses,[90] but there are no convincing epidemiologic studies linking these infections to

TABLE 4–3 Comparison of Four Prospective Case-Control Studies of Immunoglobulin G Antibodies against Epstein-Barr Virus (EBV) and Risk of Multiple Sclerosis (MS)

Study	Population	No. Cases/ Controls	% Females	Age at MS Onset (Median [Range])	Time from Blood Collection to MS Onset, Yr (Median [Range])	*RR (95% CI)*[†]	
						EBNA1	VCA
Ascherio, 2001	Nurses' Health Study	18/36	100	52 (39-66)	1.9 (<1-6.5)	2.7 (1.0-7.2)	1.6 (0.7-3.7)
Sundström, 2004	Västerbotten County, Sweden	73/219	67	34 (22-65)	NA (<1->15)	4.5 (1.9-11)	0.86 (0.38-2.0)
Levin, 2005	U.S. Army	83/166	35	27 (18-41)[*]	4 (<1-11)[*]	3.0 (1.2-7.3)	1.3 (0.6-2.9)
DeLorenze, 2006	Kaiser Permanente, northern California	42/79	86	45 (24-69)	15 (<1-32)	1.8 (1.1-2.9)	1.2 (0.66-2.4)

EBNA1, EBV nuclear antigen 1; NA, not applicable; RR, relative risk; VCA, viral capsid antigen.
[*]Mean (range).
[†]For the Ascheno, Levin, and DeLorenze studies, reported RR is for a fourfold increase in antibody titers; for Sundström, RR is for "high" vs "low" activity to EBV antigen.
Data from Munger K, Ascherio A: Risk factors in the development of multiple sclerosis. Expert Rev Clin Immunol 2007;3:739-748, Future Drugs Ltd.

MS risk. Noninfectious factors may also be important, and prominent among them are vitamin D and cigarette smoking.

Sunlight Exposure and Vitamin D

One of the strongest correlates of latitude is the duration and intensity of sunlight, which in ecologic studies is inversely correlated with MS prevalence.[92-94] Because exposure to sunlight is for most people the major source of vitamin D,[95] average levels of vitamin D also display a strong latitude gradient. Ultraviolet B (UV-B) radiation (290 to 320 nm) converts cutaneous 7-dehydrocholesterol to previtamin D_3. Previtamin D_3 spontaneously isomerizes to vitamin D_3, which is then hydroxylated to $25(OH)D_3$ (25-hydroxyvitamin D_3), the main circulating form of the vitamin, and then to $1,25(OH)_2D_3$ (1,25-dihydroxyvitamin D_3), the biologically active hormone.[95] However, during the winter months at latitudes greater than 42° N (e.g., Boston, MA), even prolonged sun exposure is insufficient to generate vitamin D,[96] and levels decline.[97,98] Use of supplements or high consumption of fatty fish (a good source of vitamin D) or vitamin D–fortified foods (mostly milk in the United States) may partially compensate for this decline, but few people consume large enough amounts of vitamin D, and seasonal deficiency is common. A link between vitamin D deficiency and MS was proposed more than 30 years ago as a possible explanation of the latitude gradient and of the lower prevalence of MS in fishing communities with high levels of fish intake[99]; however, the immunomodulatory effects of vitamin D were not known, and the hypothesis did not generate much interest at the time. After the discovery that the vitamin D receptor is expressed in several cells in the immune system and is a potent immunomodulator,[100] a series of experiments revealed a protective role of $1,25(OH)_2D_3$ in several autoimmune conditions and in transplant rejection.[100] The effects in experimental autoimmune encephalomyelitis, an animal model of MS, were particularly striking: injection of $1,25(OH)_2D_3$ was found to completely prevent the clinical and pathologic signs of disease,[101,102] whereas vitamin D deficiency accelerated the disease onset.[102,103]

With vitamin D deficiency becoming a biologically plausible risk factor for MS, several epidemiologic studies were conducted to determine whether exposure to sunlight or vitamin D intake is associated with MS risk. The main results of these studies are shown in Table 4-4, and their strengths and limitations are discussed in the following paragraphs.

ECOLOGIC STUDIES

As mentioned earlier, the results of ecologic studies support an inverse association between sunlight exposure and MS risk. However, because people living in the same area share many characteristics other than the level of sunlight, the consensus is that evidence from these studies is weak.

DATABASE/LINKAGE ANALYSES

In an exploratory investigation based on death certificates, working outdoors was associated with a significantly lower MS mortality in areas of high, but not low, sunlight.[104] In a separate study in the United Kingdom, the skin cancer rate,

TABLE 4–4 Summary of Studies on Sun Exposure, Vitamin D, and Risk of Multiple Sclerosis (MS)

Author and Year	Population	No. Cases and Controls	Exposure	Main Results
Ecologic Studies				
Acheson et al., 1960	U.S. military veterans	556 MS cases	Average annual hours of sunshine	Correlation with MS prevalence: –0.73
			Average December solar radiation	Correlation with MS prevalence: –0.80
Leibowitz et al., 1967	Immigrants to Israel	—	Average annual hours of sunshine	Correlation with MS prevalence: –0.88
van der Mei et al., 2001	Australia	—	Ambient ultraviolet radiation	Correlation with MS prevalence: –0.91
Database/Linkage Analyses				
Freedman et al., 2000	United States	4,282 MS deaths; 115,195 deaths from other noncancer causes	Residential sun exposure	High vs low exposure: OR = 0.53 (95% CI, 0.48-0.57)
			Occupational sun exposure	Outdoor vs indoor occupation: OR = 0.74 (95% CI, 0.61-0.89)
Goldacre et al., 2004	Oxford region, England	5,004 cases; 432,091 non-cases	Skin cancer diagnosis in MS patients	Rate ratio = 0.49 (95% CI, 0.24-0.91)
Case-Control Studies				
Antonovsky et al., 1965	Israel	241 cases, 964 controls	≥2 hr outdoors daily in summer as youngster	89% cases vs 82% controls (P = .02)
			>5 hr outdoors daily in summer	63% cases vs 55% controls (P = .05)
Cendrowski et al., 1969	Western Poland	300 cases, 300 controls	Average time spent outdoors daily in summer before age 15 yr	No significant differences between cases and controls

TABLE 4–4 Summary of Studies on Sun Exposure, Vitamin D, and Risk of Multiple Sclerosis (MS)

Author and Year	Population	No. Cases and Controls	Exposure	Main Results
van der Mei et al., 2003	Tasmania, Australia	136 cases, 272 controls	≥2 hr sun exposure daily in summer ages 6-10 yr	OR = 0.50 (95% CI, 0.24-1.02)
			≥1 hr sun exposure daily in winter ages 6-10 yr	OR = 0.47 (95% CI, 0.26-0.84)
			Actinic damage to skin	More vs less: OR = 0.32 (95% CI, 0.11-0.88)
Kampman et al., 2007	Northern Norway	152 cases, 402 controls	Time spent outdoors in summer ages 16-20 yr	OR = 0.55 (95% CI, 0.39-0.78)
			Consumption of boiled/fried fish ≥ 3 times/week	OR = 0.55 (95% CI, 0.33-0.92)
Islam et al., 2007	North American twins	79 disease- and exposure-discordant monozygotic twin pairs	Sun-exposure index determined by seasonal/temperature-related outdoor exposure, sun exposure–related activities, and participation in team sports	For every 1 unit increase in the sun-exposure index (i.e., greater sun exposure), OR = 0.75 (95% CI, 0.62-0.90)
Munter et al., 2004	Nurses' Health Study, Nurses' Health Study II	173 cases	Total dietary intake of vitamin D	Top vs bottom quintile of intake: Rate ratio = 0.67 (95% CI, 0.40-1.12)
			Vitamin D intake from supplements	≥400 IU/day vs none: Rate ratio = 0.59 (95% CI, 0.38-0.91)
Munger et al., 2006	Active-duty U.S. military personnel	257 cases, 514 controls	Serum levels of 25(OH)D	Top vs bottom quintile of 25(OH)D in whites: OR = 0.38 (95% CI, 0.19-0.75)

CI, confidence interval; OR, odds ratio.
Data from Munger K, Ascherio A: Risk factors in the development of multiple sclerosis. Expert Rev Clin Immunol 2007;3:739-748, Future Drugs Ltd.

a marker of sunlight exposure, was found to be about 50% lower than expected among individuals with MS (P = .03).[106] Although the results of these investigations are consistent with a protective effect of UV light exposure, they could also represent "reverse causation" (i.e., individuals with MS could reduce their exposure to sunlight after disease onset).

CASE-CONTROL STUDIES

The results of case-control studies comparing history of sun exposure in childhood (presumed to be a critical period, mostly from the results of studies in migrants) between MS cases and controls have been conflicting. The results of one study were contrary to a protective effect of vitamin D,[106] and no association between sun exposure in childhood and MS risk was found in another.[107] In contrast, results consistent with a protective effect of sun exposure were reported in a study in Tasmania in which information on time spent in the sun was complemented by measurement of skin actinic damage, a biomarker of UV light exposure,[108] as well as an investigation in Norway[109] and a study of monozygotic twins in the United States.[110] In the Norway study, an inverse association was also found between consumption of fish and MS risk. Selection and recall biases are potential problems in case-control studies, but recall bias cannot explain the inverse association observed in Tasmania with actinic damage,[108] and selection bias is unlikely in the twin study.

LONGITUDINAL STUDIES

The strongest evidence relating vitamin D levels to MS risk has been provided by two longitudinal studies, one based on assessment of dietary vitamin D intake, and one on serum levels of 25(OH)D. The relation between vitamin D intake and MS risk was studied in more than 200,000 women in the Nurses' Health Study and Nurses' Health Study II cohorts.[111] Dietary vitamin D intake was assessed from comprehensive and previously validated semiquantitative food frequency questionnaires administered every 4 years during the follow-up of the cohorts.[112,113] Total vitamin D intake at baseline was inversely associated with risk of MS: the age-adjusted pooled relative risk (RR) comparing the highest with the lowest quintile of consumption was 0.67 (95% confidence interval [CI], 0.40 to 1.12; P for trend = .03). Intake of 400 IU/day of vitamin D from supplements only was associated with a 40% lower risk of MS. These RRs did not materially change after further adjustment for pack-years of smoking and latitude at birth. Confounding by other micronutrients cannot be excluded, but adjustments for them in the analyses did not change the results.

Because dietary vitamin D is only one component contributing to total vitamin D status (the other being sun exposure), a determination of whether serum levels of vitamin D are associated with MS risk in healthy individuals would strengthen the evidence in favor of a causal role for vitamin D. The serum level of 25(OH)D is a marker of vitamin D status and bioavailability; therefore, if vitamin D is protective, high serum levels of 25(OH)D would be expected to predict a lower risk of MS in healthy individuals. This question was recently addressed in a collaborative, prospective case-control study using the Department of Defense Serum Repository (DoDSR).[114] The study included 257 military personnel with confirmed MS and

at least two serum samples collected before the onset of MS symptoms. Risk of MS was 51% lower among white individuals with 25(OH)D levels of 100 nmol/L or higher, compared with those levels lower than 75 nmol/L, and the reduction in MS risk associated with 25(OH)D levels ≥ 100 nmol/L compared with those levels < 100nmol/L was considerably stronger before the age of 20 years (16 to 19 years) than at ages 20 or older.

An important question concerning vitamin D and MS is the age intervals during which vitamin D may be important. The results of migration studies suggest that more pronounced changes in MS risk are likely to occur among individuals who migrate in childhood. The age of 15 years, chosen as an arbitrary cutoff point in early studies, is usually quoted in the literature, but the reality is that data are insufficient to identify a meaningful threshold above which migration would not alter MS risk,[27] and in at least one study a reduction in risk was also observed among individuals who migrated as adults.[115] The results of the case-control study in Tasmania suggest that exposure to sunlight is mostly protective in childhood.[108] Further, vitamin D exposure in utero has been proposed as a possible explanation for the peak in MS incidence among individuals born in May (whose mothers were not pregnant during the summer, when UV light levels are higher) and the dip among those born in November, according to recent data from Canada and Sweden.[116] On the other hand, the results of the longitudinal studies support a protective effect of vitamin D also later in life. Both the lower risk of MS among women taking vitamin D supplements[111] and the lower risk among men and women with higher levels of 25(OH)D[114] would be difficult to explain by a protective effect of vitamin D solely in utero or during childhood. Therefore, it seems likely that, if vitamin D effectively protects against MS, levels during early adult life are also important.

Overall, the epidemiologic evidence of a causal association between vitamin D and MS is strong but not compelling, mainly because there are few studies based on prospective measurement of levels of exposure to sunlight, vitamin D intake, or serum 25(OH)D concentration. However, the public health implications of a possible causal association are enormous. If vitamin D reduces the risk of MS, supplementation in adolescents and young adults could be used effectively for prevention. Based on studies among individuals with low sun exposure, supplements providing between 1000 and 4000 IU/day of vitamin D would increase serum 25(OH)D to the optimal levels.[117-120] There is an urgent need to conduct further longitudinal studies, preferably in a large, randomized controlled clinical trial assessing whether vitamin D supplementation in the general population prevents MS. The trial would have to be very large, because MS is a rare disease, but the sample size could be reduced by oversampling individuals who are at high risk, such as those with first-degree relatives who have MS. Alternative study designs might include national or multinational studies based on randomization of school districts or other suitable units.

Cigarette Smoking

Cigarette smoking was found to increase the risk of MS in some[121,122] but not all[123,124] case-control studies. A cross-sectional survey of the general population in Hordaland County, Norway, found an increased risk of MS in ever-smokers

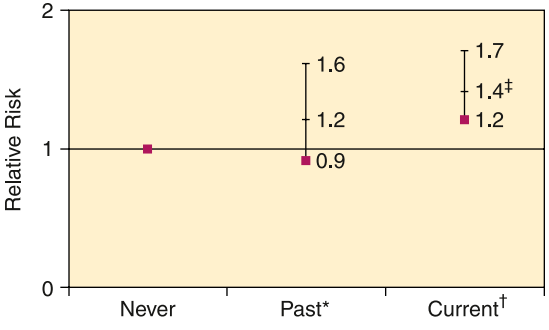
compared with never-smokers (RR = 1.8; 95% CI, 1.1 to 2.9).[125] Four prospective studies on smoking and MS have been conducted. Among 17,000 British women in the Oxford Family Planning Association Study, those who smoked 15 or more cigarettes per day were compared with never-smokers and had an 80% increased risk of MS (RR = 1.8; 95% CI, 0.8 to 3.6).[126] A total of 46,000 women from across the United Kingdom were enrolled in the Royal College of General Practitioners' Oral Contraception Study, which found that women smoking 15 or more cigarettes per day had a 40% increased risk of MS (RR = 1.4; 95% CI, 0.9 to 2.2), compared with never-smokers.[127] The Nurses' Health Study and Nurses' Health Study II cohorts included more than 200,000 U.S. women; those who smoked 25 or more pack-years had a 70% increased risk (RR = 1.7; 95% CI, 1.2 to 2.4; $P < .01$) compared with never-smokers.[128] In a prospective case-control study in the General Practice Research Database, which included both men and women, ever-smokers had a 30% increased risk of MS, compared with never-smokers (RR = 1.3; 95% CI, 1.0 to 1.7).[129] The suggestion of an increased risk of MS among smokers was consistent across all four studies, and pooled estimates of the relative risk were highly statistically significant when never-smokers were compared with past and current smokers (Fig. 4-4A) or with moderate and heavy smokers (see Fig. 4-4B). Additional support for a role of smoking includes a twofold increase in risk of pediatric MS among children exposed to parental smoking[130] and an increased risk of transition to secondary progressive MS among individuals with relapsing-remitting MS[129]; however, the latter finding was not confirmed in a recent investigation.[131]

Biologic mechanisms for smoking and increased risk of MS could be neurotoxic,[132] immunomodulatory,[133,134] or vascular (i.e., increased permeability of the blood–brain barrier), or they could involve increased frequency and duration of respiratory infections,[135] which may then contribute to increased MS risk. Smoking also appears to increase the risk of other autoimmune diseases, including rheumatoid arthritis[136-140] and systemic lupus erythematosus,[141] arguing for a more general effect of cigarette smoking on autoimmunity.

Other Possible Risk Factors

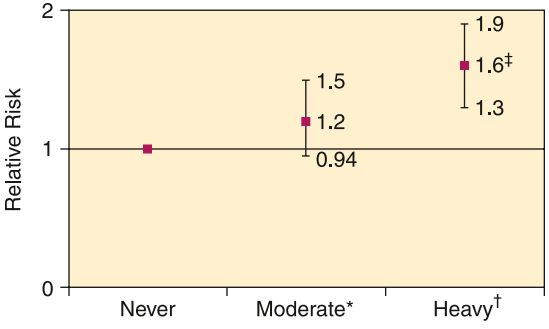
DIET

Although several foods or nutrients were found to be related to be MS risk in ecologic or case-control studies, the results overall were inconsistent and unconvincing. In ecologic studies, positive correlations were found between MS and intake of animal fat[142-144] and saturated fat,[144] as well as consumption of meat,[145] milk, and butter,[143,146] and inverse correlations were found with intake of fat from fish[143,145] and nuts[143] (sources of polyunsaturated fat). An increased risk of MS with increasing animal or saturated fat intake and a protective effect of increasing polyunsaturated fat intake were also reported in a case-control study,[147] but otherwise the results of case-control studies have largely not supported an association between increased MS risk and milk or meat consumption,[121,147-150] or decreased risk and consumption of sources of polyunsaturated fat such as fish or nuts.[121,147] However, in a recent study in Norway,[109] fish consumption 3 or more times per week among individuals living at latitudes between 66° and 71° N was inversely related to MS risk. Other results have included an inverse association of risk with



** Past smoking not available for Thorogood and Hannaford.[127]*
† 1-14 or ≥ 15 cigarettes/day for Villard-Mackintosh and Vessey[126] and Thorogood and Hannaford.[127]
‡ P < 0.001

A



** 1-9 pack-years for Hernán and colleagues[128]; 1-14 cigarettes/day for Villard-Mackintosh and Vessey[126] and Thorogood and Hannaford[127]; not available for Hernán and colleagues[129]*
† 10-24 and ≥25 pack-years for Hernán and colleagues[128]; ≥15 cigarettes/day for Villard-Mackintosh and Vessey[126] and Thorogood and Hannaford [127]; not available for Hernán and colleagues.[129]
‡ P < 0.001

B

Figure 4–4 **A,** Relative risk of multiple sclerosis (MS) by smoking status. (*Past smoking not available for Thorogood and Hannaford. Br J Obstet Gynecol 1998;105:1296-1299; †1-14 or ≥ 15 cigarettes/day for Villard-Mackintosh and Vessey. Contraception 1993;47:161-168 and Thorogood and Hannaford. Br J Obstet Gynaecol 1998;105:1296-1299). **B,** Relative risk of MS by duration/frequency of smoking. (‡1-9 pack-years for Hernán et al. Am J Epidemiol 2001;154:69-74; ≥15 cigarettes/day for Villard-Mackintosh and Vessey and Thorogood et al.; not available for Hernán et al 2005 Brain 2005;128:1461-1465. Villard-Mackintosh and Vessey. Contraception 1993;47:161-168 and Thorogood and Hannaford. Br J Obstet Gynaecol 1998;105:1296-1299. 10-24 and ≥ 25 pack-years for Hernán et al. 2001 Am J Epidemiol 2001;154:69-74; ≥15 cigarettes/day for Villard-Mackintosh and Vessey Contraception 1993;47:161-168 and Thorogood and Hannaford. Br J Obstet Gynecol 1998;105:1296-1299; not available for Hernán et al. Brain 2005;128:1461-1465. (From Ascherio A, Munger KL: Environmental risk factors for multiple sclerosis: Part II. Noninfectious factors. Ann Neurol 2007;61:504-513.)

intake of vitamin C and juice,[147] but no association with other antioxidant vitamins[147] or with fruits and vegetables[121,123,147,151] has been reported.

It is important to note that ecologic studies are prone to be confounding and in general provide only very weak evidence of the potential effects of diet on disease risk. Retrospective case-control studies are also prone to bias due to both control selection and differential recall. The latter effect is particularly problematic, because even a modest difference in diet recall between cases and controls can cause a large bias in relative risk estimates.[152] This problem is compounded in MS by changes in diet that may occur in the early clinical or preclinical phases of the disease. Therefore, although these studies have been important in drawing attention to several aspects of diet as potentially important risk factors for MS, their results, whether

in favor or against an hypothetical association, should be interpreted extremely cautiously. Understanding of the relation between diet and MS will require the conduct of large longitudinal investigations, with repeated assessment of diet using rigorous and validated methods and possibly measurements of biomarkers of nutrient intakes. So far, the only prospective studies of diet and MS were those conducted among women in the two Nurses' Health Study cohorts. In this population, neither animal fat nor saturated fat was associated with MS risk, but there was a suggestion of an inverse association with intake of the n-3 polyunsaturated fat linolenic acid.[153] There were also no significant associations between intakes of dairy products, fish, meat,[153] vitamins C or E, carotenoids, or fruits and vegetables and MS risk.[154] However, participants in these studies were already 25 to 55 years of age at time of recruitment, and therefore they shed little light on the possible effect of diet earlier in life and MS risk.

Studies have also examined whether intake of polyunsaturated fats affects MS progression. N-3 polyunsaturated fat supplementation in doses ranging from 2.85 to 3.90 g/day administered for periods of 6 to 24 months did not have significant effects on disability levels in two randomized controlled trials that included a total of 339 patients with relapsing-remitting MS,[155,156] although trends were in favor of the supplemented groups in both studies. Results of three randomized controlled trials examining the effects of n-6 polyunsaturated fat supplementation (17 to 20 g/day for 24 to 30 months) on MS progression, including a total of 279 patients with relapsing-remitting MS,[157-159] and a meta-analysis of these studies[160] suggested that supplementation may reduce the severity and duration of relapses.

In summary, there is no compelling evidence that dietary factors other than vitamin D play a causal role in MS, but neither can such a role be excluded, particularly for diet during adolescence or childhood, which may be important periods in the etiology of MS.

SEX HORMONES

Estrogen has been hypothesized to protect against MS, because in high levels it appears to promote the non-inflammatory type 2 immune response, rather than the pro-inflammatory type 1 response predominately seen in MS, and because during pregnancy, when estrogen levels are high, women with MS experience fewer relapses than during the puerperium.[161] In prospective studies,[126,127,162,163] neither oral contraceptive use, parity, nor age at first birth[162] was associated with MS risk. A decreased risk of MS during pregnancy followed by an increased risk during the first 6 months after delivery was shown in a study based on a general practice database in the United Kingdom.[163] In the same study, recent use of oral contraceptives was also associated with a reduced risk.[163] Collectively, these studies suggest that short-term exposure to estrogen may be protective against MS, but that this protection is transient.

HEPATITIS B VACCINE

Concerns that the hepatitis B vaccine may increase the risk of MS were raised after widespread administration of the vaccine in France,[164] but the results of most studies have not supported a causal association. Studies in the United States conducted among subjects included in a health care database,[165] among nurses,[166]

and among participants in three health maintenance organizations[167] found no association between hepatitis B vaccination and risk of MS. Further, in studies of children and adolescents, no association was found between hepatitis B vaccination and MS risk[168] or risk of conversion to MS among children with a first demyelinating event.[170] However, a case-control study conducted in the General Practice Research Database in the United Kingdom did find a threefold increased risk associated with receipt of the vaccine within 3 years before MS onset,[170] and a French case-control study reported a nonsignificant increased risk of MS among individuals with clinically isolated syndrome after vaccination.[171] Among individuals with MS, the vaccine does not appear to increase the risk of relapses.[172] Overall, there is no convincing evidence that hepatitis B vaccination increases MS risk.

OTHER FACTORS

Other environmental factors have been associated with MS, but the available evidence is sparse, and the relevance of these factors to MS etiology remains uncertain. An *increased* risk of MS has been reported in relation to exposure to organic solvents,[173-177] physical trauma,[178] and psychological stress from the loss of a child (bereavement),[179] whereas a decreased risk has been observed for use of penicillin[180] and antihistamines,[181] high levels of serum uric acid,[182-184] and tetanus toxoid vaccination.[185]

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