Commentary

Are multiple sclerosis patients risk-takers?

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Summary
Several factors appear to be associated with multiple sclerosis (MS), and each has a postulated immune or environmental explanation, but a common theme is lacking. This article suggests that a unifying premise could be risk-associated behaviour. Evidence is reviewed for associations with smoking, alcohol, recreational drug use, oral contraception, cholesterol intake, risk attitude and behaviour, ultraviolet light and vitamin D exposure, frequency of MS in healthy societies, and viral infection. The evidence associated with smoking, not taking vitamin D supplements and Epstein-Barr viral infection appears good. There may be a pattern of risk-associated behaviour that characterizes patients with MS and brings them into contact with one or more causative agents. Of the possible agents, viral infection seems the most likely.

Introduction
There is reasonably strong evidence that patients with Parkinson’s disease has rigid, more obsessional personality, and that they avoid potentially unhealthy habits such as smoking and drinking either alcohol or coffee. I suggest that patients with multiple sclerosis (MS) appear to be risk-disregarders—i.e. they are aware of various life-style and health hazards but chose to ignore them—and that their premorbid behavioural characteristics are in many respects the opposite of those who develop PD. Evidence will be evaluated from the following areas: (i) smoking; (ii) alcohol; (iii) other recreational drugs; (iv) use of the oral contraceptive; (v) cholesterol and animal fat intake; (vi) risk attitude and behaviour; (vii) ultraviolet light and vitamin D exposure; (viii) MS prevalence in healthy societies; (ix) viral infection.

Smoking
This habit has been regularly examined for its possible aetiological association with MS, but no firm conclusion can be drawn, in part due to variable methodology and problems with sampling. One of the earliest papers to include smoking habit was from Israel, where 241 MS patients were questioned about ever smoking prior to disease onset (Table 1). The control group comprised 61 subjects individually matched to patients by age, sex and region of birth. They found a significant excess of previous smokers in the patient group (44% vs. 36%, p < 0.02). Their survey included 141 questions without correction for multiple comparisons, and hence their observations must be interpreted with caution.
<table>
<thead>
<tr>
<th>Reference</th>
<th>MS patients</th>
<th>Controls</th>
<th>Quantity smoked (MS numbers)</th>
<th>OR/RR 95%CI</th>
<th>Adjustments</th>
<th>Method of MS diagnosis</th>
<th>Study type, region, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>241</td>
<td>61</td>
<td>Ever smoked (106)</td>
<td>1.4 OR 1.05–1.86</td>
<td>Age, sex, region of birth</td>
<td>Not stated</td>
<td>Retrospective, case-control. Israel. Controls matched for age, sex and region of origin. No adjustment for multiple comparisons.</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>126</td>
<td>Ex-smoker (9) 1–14/day (14)</td>
<td>1.5 RR 0.6–3.3</td>
<td>Age, parity</td>
<td>‘Hospital consultant’</td>
<td>Prospective, nested case-control study. Incident, based on diagnostic coding. All before disease onset. Females only. Large numbers lost to follow-up. Oxford, UK.</td>
</tr>
<tr>
<td>7</td>
<td>114</td>
<td>56</td>
<td>Non-smokers at recruitment</td>
<td>1.2 RR 0.8–1.8</td>
<td>Age, social class</td>
<td>Family practitioner and hospital colleagues</td>
<td>Prospective, cohort incident cases. All smokers before disease onset. All female. Oxford, UK.</td>
</tr>
<tr>
<td>8</td>
<td>197</td>
<td>202</td>
<td>Ever smoked (138) 20–40/day (71)</td>
<td>1.6 OR 1.0–2.4</td>
<td>Age, sex, education</td>
<td>Contact with general physician, neurologists and local MS society</td>
<td>Incident case-control. Smoking in year prior to diagnosis. Montreal, Canada.</td>
</tr>
<tr>
<td>9</td>
<td>315</td>
<td>128,638</td>
<td>Ever smoked (175) 10–24 pack-years before diagnosis (75)</td>
<td>1.6 RR 1.2–2.1</td>
<td>Age, latitude, longitude, ancestry, alcohol, coffee, body mass index</td>
<td>Poser criteria (1983)</td>
<td>Prospective, incident. Smoking 4 years prior to MS diagnosis. Only pooled data quoted here. All female nurses. USA.</td>
</tr>
</tbody>
</table>
A group in Oxford, UK studied obstetric patients—mainly in an attempt to dispel fears of MS risk in those taking the oral contraceptive—but also evaluated smoking. This was a prospective incident study, based on diagnostic coding records of 63 new MS patients. There was a borderline significant trend between number of cigarettes smoked at baseline and risk of MS (p = 0.05). At entry to the study, those smoking 4–15/day had a relative risk of 1.8 (95%CI 0.8–3.6), which is not significant. Ex-smokers displayed a similar magnitude of risk (RR 1.5, 95%CI 0.6–3.3). Comparable findings from the same region were demonstrated 5 years later in a prospective cohort study of 114 incident MS cases, giving a rate ratio of 1.4 (95%CI 0.9–2.2) for those smoking 15 or more cigarettes per day at recruitment, which is again just outside conventional confidence intervals.

Subsequently, Ghadirian and colleagues showed a significant effect in a case-control study of 197 incident MS cases from Montreal. Their analysis was based on reported cigarette consumption in the year prior to MS diagnosis, and adjusted for age, sex and education. There was an association for 'ever-smokers', more so for heavy smokers who consumed 20–40 cigarettes per day (OR 1.9, 95%CI 1.2–3.2) and higher still for those consuming >40 per day (OR 5.5, 95%CI 1.7–17.8). Of the many variables studied, smoking conferred the greatest risk for subsequent MS.

In a large prospective study of 315 incident MS cases in American nurses, pooled data showed increased risk for MS in those ever smoking (RR 1.6, 95%CI 1.2–2.1) and a similar ratio in those smoking >25 pack-years (RR 1.7, 95%CI 1.2–2.6). The elevated risk was higher in those smoking prior to onset of MS diagnosis, and adjusted for age, latitude and ancestry. A further questionnaire-based study from Italy recruited 140 MS cases and 131 sex- and age-matched controls, and found that 41% of cases were current smokers, compared to 27% of blood donor controls (OR 1.5, 95%CI 1.0–2.4). The male rate was higher than the female rate (RR 2.7, 95%CI not given) and just under half the risk found in the same study for myocardial infarction. The most recent study used a population-based prevalent case-control approach in 86 Norwegian MS cases, and likewise showed near doubling of risk ratio (RR 1.8, 95%CI 1.1–2.9). On average, smoking commenced 15.2 years before the disease began. The male rate was higher than the female rate (RR 2.7, 95%CI not given) and just under half the risk found in the same study for myocardial infarction.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Cases Matched</th>
<th>Age, Sex, Educational Level</th>
<th>Smoking Prior to Disease Onset</th>
<th>Ever Smoked</th>
<th>Odds Ratio (OR)</th>
<th>95% Confidence Interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxford</td>
<td>63</td>
<td>Blood donors</td>
<td>Sex, age, race, residence</td>
<td>1.9 OR 1.1–3.2</td>
<td>1.5 OR 0.9–2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rome</td>
<td>114</td>
<td>Blood donors</td>
<td>Age, sex, educational level</td>
<td>1.8 RR 1.1–2.9</td>
<td>1.6 RR</td>
<td>Not given</td>
<td></td>
</tr>
<tr>
<td>Trieste</td>
<td>140</td>
<td>Blood donors</td>
<td>Age, sex, family practice</td>
<td>1.3 OR 1.0–1.7</td>
<td>2.7 RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oslo</td>
<td>86</td>
<td>Blood donors</td>
<td>Age, sex, race, education</td>
<td>1.9 OR 1.5–2.4</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Montreal</td>
<td>197</td>
<td>Blood donors</td>
<td>Age, sex, education</td>
<td>1.9 OR 1.5–2.4</td>
<td>5.5 OR 1.7–17.8</td>
<td></td>
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</table>
prior smoking and MS, but also showed that those who continued to smoke were more likely to progress from the relapsing-remitting stage to the secondary progressive variety.

A drawback with all these studies is that although smoking habit was usually explored before MS onset, patients regularly confuse the time of MS onset with the time of MS diagnosis, hence some results may relate to smoking after the condition has begun, and possibly unknown to the patient. Two studies\textsuperscript{9,12} make this objection unlikely, as they are prospective, and data were derived at least 4 years prior to first symptoms. A further problem particularly with the earlier studies, is that the diagnosis was not rigorously verified, and many surveys would have been undertaken before MRI imaging was readily available (Table 1).

The identified studies vary in design, some are retrospective, others prospective, and they differ in measure of effect, i.e. odds ratio (OR) or rate ratio (RR). In order to resolve this, a meta-analysis was undertaken, based on the eight most informative studies as described above.\textsuperscript{13} Under the ‘rare disease assumption’, OR and RR are approximately equivalent\textsuperscript{14}, so results from studies with both these measures have been combined. There was no evidence of heterogeneity between studies, and accordingly the method of inverse variance weighting was used in Stata 8.2 (Stata Corporation). For the retrospective meta-analysis, ever vs. never smoking habit was extracted from four sources,\textsuperscript{5,8,10,11} giving a pooled estimate of 1.51 (95%CI 1.24–1.83, \(p < 0.0001\)). A prospective analysis used a conservative and non-conservative approach to represent the likely exposure to cigarettes. For the conservative approach, three categories were incorporated: ever\textsuperscript{12}, previous smoker\textsuperscript{6,9} and smoking 1–14/day,\textsuperscript{7} which gave a pooled estimate of 1.25 (95%CI 1.05–1.49, \(p < 0.01\)). In the less conservative analysis, three other groups were used: ever\textsuperscript{12}, current\textsuperscript{9} and >15/day,\textsuperscript{6,7} which yielded a pooled risk of 1.45 (95%CI 1.22–1.72, \(p < 0.0001\)). The pooled analysis of all eight studies (retrospective and prospective), using the most conservative comparisons, gave OR 1.36 (95%CI 1.19–1.54) (Figure 1). A combined analysis using less conservative comparisons gave OR 1.47 (95%CI 1.29–1.67) (Figure 2). It would be reasonable to conclude that smoking prior to the onset of MS symptoms is a significant, but not powerful, risk factor for subsequent development of MS.

### Alcohol

There have been few studies of this variable. Uncontrolled observations suggest that many patients with MS and depression have alcohol-related problems. In one article,\textsuperscript{15} which was designed primarily to look for factors associated with suicidal intent, and did not contain a healthy control group, the rate of previous alcohol abuse was 13.6\%. This value was thought to be no different from that found elsewhere for the general population.\textsuperscript{16} In a subsequent paper,\textsuperscript{17} there were 140 MS patients, of whom 16\% drank to excess at some point in their lifetime, and were more likely to be anxious, take recreational drugs and have suicidal tendency. Again no specific control group was established, but it was commented that if gender differences are taken into account, comparison with other population-based studies suggested a markedly increased risk of alcohol abuse in female MS sufferers. In another uncontrolled study of 136 MS patients,\textsuperscript{18} 43\% consumed alcohol and 18.4\% (of the whole MS group) were current heavy drinkers, defined as those consuming >5 drinks per day. Obvious drawbacks with all these papers are the lack of a matched control group and absence...
of data regarding drinking habit prior to MS onset, but there is no evidence that patients alter their alcohol intake after diagnosis. In fact MS patients appear to drink less as disability increases,\textsuperscript{19,20} and if so this would increase the significance of observations made on current sufferers.

In a case-control study from Montreal,\textsuperscript{21} 108 subjects with MS were tested for 15 variables by cluster analysis. The control group (n=108) consisted of patients with rheumatoid arthritis matched by age, gender and time since diagnosis. Patients were asked about their use of alcohol, tobacco, regular medication and unspecified recreational drugs prior to the diagnosis of MS. The only definite association was with recreational drugs (see below). Alcohol abuse was a significant risk factor (OR 3.0, 95%CI 1.15–7.86, \( p = 0.02 \)) for MS in the category of mildly disabled females without a family history of MS. Other subgroups relating to family history, gender or disability showed no association, and analysis of the group as a whole revealed no significant association between alcohol consumption and MS. Given that others have suggested patients with more severe MS are unlikely to drink, the correlation between MS and alcohol assumes more significance. This study has obvious drawbacks, such as the use of another suspected autoimmune disease as a control group, which might cause overmatching and loss of power. However, this would lessen case-control differences and add more weight to proposed associations. Their survey was questionnaire-based, and consequently vulnerable to selective recall bias and the numbers in each group are relatively small. The possible and somewhat unexpected link between mild disability from MS and alcohol abuse has been found by others, and is discussed below.

A study from Washington\textsuperscript{20} examined alcohol abuse in 739 subjects who were members of the local MS association. The survey was questionnaire-based for current alcohol consumption. Other variables were examined, such as drug abuse, depression, fatigue and disability. The response rate was poor (54%). Overall, 14% reported possible alcohol problems within the previous month (18.6% male, 12.6% female). Many thought they should cut down on their use of alcohol, and 6.7% admitted to binge drinking. Those with possible alcohol problems were significantly younger, more likely to be in employment, reported depressive symptoms and were less disabled, but the duration of disease was similar to those not reporting a drink problem. There was no specific healthy control group, although the authors commented that the rate of 14% ‘appeared higher’ than that found (12%) in their earlier study of 1000 primary care subjects.

Lindegard\textsuperscript{22} conducted a 10-year prospective population-based case-control study of 159 200 urban native Swedes born 1911–1922 and 1923–1940. Data were acquired mainly from hospital coding records, and prevalence was recorded of diseases associated with either MS or epilepsy. A total of 351 MS cases were identified, in whom the most striking finding was increased risk of tuberculosis. The rate of male alcoholism in MS was 8.5–10%, three times the population control group (\( p < 0.001 \)). Surprisingly, there were no cases of alcoholism in females, and no explanation was offered. Despite the fact that this study was based on coding records (which may contain inaccuracies) its strength lies in its prospective nature and presence of a control group.

Ghadirian et al.\textsuperscript{23} undertook a case-control study of 197 newly diagnosed Canadian MS patients designed primarily to explore dietary differences, and this is described in more detail below. Subjects were questioned about alcohol intake in the year prior to diagnosis, but no difference was found between cases and controls. No association was defined either in a case-control study of 100 MS patients attending the University of Alberta MS Research Clinic,\textsuperscript{24} but here the control group consisted of rheumatoid arthritis patients, and the question arises of overmatching.

Current evidence does not support a clear relationship between alcohol consumption and the development of MS, but two surveys\textsuperscript{21,22} suggest a link with alcohol abuse, particularly in mildly affected patients. Assessment is difficult, because only these two studies had a control group, and there was variable measurement of alcohol intake in terms of current or previous exposure. A large prospective study would be needed to resolve these issues. It is not known whether patients who develop MS alter their drinking habits, but the data suggest that early/mild MS is associated with alcohol abuse, and alcohol intolerance would be expected only in more disabled patients, because of interaction with prescribed drugs for spasticity, etc.

**Other recreational drugs**

In a study of suicidal intent in MS,\textsuperscript{15} the prevalence of cannabis use was 7.2% and in the whole MS group, 2.9% were still using the drug. This study did not have a control group, as it was designed primarily to look at factors associated with depression. More informative is the study from Montreal\textsuperscript{21} referred to in the Alcohol section. The association between prior drug abuse and development of MS was highly significant (OR 4.3, 95%CI 2.2–8.8,
were introduced first in the 1960s, there were alarming reports of vascular episodes. These dangers, which were associated with high-oestrogen tablets, have now been reduced, but only in the past two decades has an acceptable level of safety been achieved. Those taking OCT are aware that they still run a small risk of vascular or neoplastic complications, which is offset by the lowered chance of pregnancy. Some suggest that oestrogens are protective against MS. For example MS tends to stabilize during pregnancy and relapse in the puerperium and oestrogens reduce the severity of experimental allergic encephalomyelitis in female rodents. There is preliminary evidence that in humans, oestrogen treatment may suppress relapses. If there were an important protective effect of this hormone, then a reduction in prevalence or severity of MS would be found in patients taking the oral contraceptive tablet, particularly those containing oestrogen.

Initial studies showed no significant association between OCT use and subsequent MS. In 1998, the situation was re-examined by a study examining the period from 1968 to 1996, using diagnostic data supplied by UK General Practitioners. There were 23 000 women who had used OCT from which 114 incident cases of MS were extracted. Overall, they found the incidence of MS (standardized for age, social class and smoking) to be similar for current and former users of OCT, and no different from that of never-users. The incidence rates, standardized by age, parity, social class, and smoking history, were 19.8% for current OC users, 21.9% for former OC users, and 17.1% for never-users. There was a trend suggesting that former users were more likely to develop MS (rate ratio 1.3, 95%CI 0.9–2.0); similarly with all current users (RR 1.2, 95%CI 0.7–2.0), which they suggested was related to those taking the older combined preparation containing >50 μg oestrogen. Besides the small numbers and lack of power, many patients were lost to follow-up (at least 49%) and there was no verification of diagnosis, but it seems unlikely that they missed any major effect from OCT.

The largest survey to have looked for a link between MS and OCT usage comes from the US Nurse Health Study. This is of particular value, as it was prospective and comprised two large groups of female nurses, one of 121 700, established in 1976 ('NHS') and a second of 116 671, established in 1989 ('NHS II'). The authors found no evidence of a protective effect against MS. In fact, the unadjusted figures showed more cases of MS in those receiving OCT. Taking data pooled from both cohorts, their table shows in some categories an increased age-adjusted relative risk for MS, when

**Use of the oral contraceptive tablet**

Hazards of oral contraceptive tablet (OCT) are well known to the public, and when these preparations
measured by duration of OCT use 4 years before diagnosis. This is significant for pooled data in both cohorts: those using OCT for 6–7 years had a relative rate (RR) of 1.7 (95% CI 1.2–2.6, age-adjusted) and a trend in RR of 1.4 (95% CI 0.9–2.1) for 8 or more years use, but not for shorter durations (Figure 3). The authors interpreted this to mean that the OCT had no protective effect on MS, although they admitted that a slightly increased risk of MS from OCT use could not be excluded. Although the initial sample had large case numbers, the power of their study was diluted considerably by adjustment for variables such as smoking, latitude and Scandinavian ancestry. Their data can be interpreted to mean enhanced MS risk for those taking OCT for 6 or more years, and this would fit with the Oxford data.7 None of these studies suggested a major effect, but they suggest that prolonged use of OCT may slightly increase the subsequent risk of MS. It should be emphasized that the Oxford survey7 and that of Hernan and colleagues31 would have incorporated many patients who commenced OCT during the 1980s, when the risk of such tablets was greater because the oestrogen content was then higher.

It may be reasoned that OCT use is risk-avoidance behaviour, in that pregnancy is averted; but conversely, the OCT allowed sexual freedom, permitting more partners and increasing the chance of sexually transmitted diseases. Overall, this behaviour pattern would be consistent with those who at least used to pay less attention to health risks.

**Cholesterol and animal fat intake**

It was suggested over 50 years ago that a diet high in animal or saturated fat and low in polyunsaturated fat (PUFA)/omega-3 fatty acids might increase the risk of MS.32,33 One mechanism might relate to increased platelet aggregation and ischaemic damage to the blood–brain barrier,34,35 changes in the composition of the central myelin structure36,37 or effects of prostanoids, resulting in altered immune response.36 This plausible theory has been supported by ecological studies where the prevalence of MS is positively correlated with animal/saturated fat intake and inversely with PUFA intake. This was apparent in Norway and Holland, where reductions in population total fat consumption paralleled the decreasing incidence of MS.31 The notion was given more credence in community-based studies of fat consumption, where higher rates of MS were more often found in farming communities than coastal fishing towns.33 A similar trend has been found with international patterns of MS and diet.36 Although this evidence is persuasive at population level, it may not apply to individuals: the so-called ‘ecological fallacy’.38

Other studies have relied on a case-control approach of prevalent cases and recall of dietary habit prior to MS onset. Ben-Shlomo et al.,39 having reviewed publications up to 1992, concluded that evidence supporting the dietary-fat hypothesis was weak. A subsequent meta-analysis40 assessed all major dietary studies using a grading score for quality of methodology (‘a’–‘c’) and the body of epidemiological evidence for each risk factor. Fifteen studies were excluded because the lipid content of food was not measured. Only one case-control study23 achieved ‘b’ grading, where daily intake of fat was measured. This was a questionnaire-based study that enquired about fat intake in the year prior to MS diagnosis. In brief, they found a mild, significant positive association between energy, animal fat intake and MS, with a protective effect for consumption of fruit/vegetables and cereal. MS patients ate less dietary fibre and fewer vitamins/mineral supplements, although vitamin D intake was not assessed specifically. The same meta-analysis graded only one cohort study41 as ‘b’. This was based once more on the NHS study referred to earlier and excels because it is prospective, containing dietary data many years before MS onset. Their study revealed no unequivocal risk or protective factors relating to dietary fat intake. There was a non-significant lower risk of MS in those consuming higher quantities of linoleic acid, and in the second cohort (NHS II), low animal fat intake had a significant inverse association with MS risk but not in the first cohort (NHS). The main drawback of this study is that although it was based on a dietary questionnaire prior to diagnosis, there was no actual measurement of food fat content or blood level. Measurement of blood lipid level is more objective, but indicates only recent dietary intake and there is evidence that...
up to two-thirds of patients who develop MS change to a healthier diet. Of 15 biochemical studies of linoleic acid level reviewed by Ben-Shlomo et al., six that showed significant differences between MS and controls and nine did not. There are clear confounders from the effect of the disease itself, and change of diet as a result of medical advice. Many MS patients begin to reduce animal fat intake after diagnosis, but this will tend to lessen case-control differences so that if there are differences from controls, they are more likely to be meaningful.

If MS patients consume more animal fat and cholesterol, then a higher rate of myocardial infarction should be seen. According to two studies with 123 and 119 patients respectively, the likelihood of coronary thrombosis was similar in MS and matched control groups, but a recent prospective study of 9881 patients in the Danish MS Registry found a significantly higher death rate from cardiovascular disease, with a standardized mortality ratio of 1.32 (95%CI: 1.22, 1.43). This study did not allow for confounding by physical inactivity, smoking, or the effect of dietary change after MS was diagnosed. A further difficulty that has come to light only recently is that during relapse, blood cholesterol may rise temporarily.

No firm conclusion can be drawn from any of these studies but the overall impression is that MS patients are likely to consume more animal fat prior to disease onset. This concurs with the elevated rate of MS observed in higher social classes and in affluent regions where animal fat intake is in general higher, but might also equate with a more casual attitude to diet and health.

**Risk attitude and behavioural aspects**

This section reviews the literature that (a) addresses risk attitudes, and considers whether: (b) there is a particular premorbid personality in MS; (c) the disease is less common in morally strict societies; (d) patients are more likely to indulge in athletic activity (some of which may be associated with risk taking); and (e) there is associated adverse health behaviour in MS patients.

**Risk attitude**

Only one study has directly addressed attitude to risk in MS, and this explored why many patients with MS who were eligible for β-interferon or glatiramer acetate chose to forgo or discontinue treatment. Sixty-two patients with MS completed a survey on risk preference, and risk attitude was measured using a standard gamble question on short-term health outcomes. It found that risk-taking patients were less likely to choose standard treatment compared to risk-adverse patients. There was no matched control group, but another survey from the same authors, currently available only in abstract form, involving 56 MS patients and 57 controls, also assessed risk attitude. This was based on standard gamble questions relating to money or health outcomes. Both controls and patient groups were risk-adverse for money but risk-neutral for health outcome, and there was apparently no difference between cases and controls. Few details are supplied, and this result can only be regarded as preliminary. There are also potential biases within the MS group. For example, it is well established that even in mild MS there may be cognitive impairment, which could either increase or decrease risk-taking behaviour, depending on variables such as depression or euphoria. Risk attitudes need to be assessed prior to disease, ideally by prospective study and this has yet to be done.

**Premorbid personality**

Some maintain that there is a prior personality profile characterizing MS, and that it is similar to ulcerative colitis—a condition with unproven associations but some interesting similarities to MS. An early study examined 100 MS patients, compared to 100 patients with other neurological disease. No significant difference was found with respect to emotional disturbance. Similar negative findings were documented in two case-control studies. Cohen concluded that there is no distinctive MS personality, although some traits were observed more frequently than others including high dependency needs, depression, anxiety, preoccupation with self, and insecurity. According to Paulley’s large but uncontrolled series of over 300 personal cases, the typical personality was that of a smiling or unsmiling mask, separation or engulfment problems and pathological dependence on a key parental figure. Some studies draw attention to personality characteristics such as neuroticism, reduced empathy, agreeableness and conscientiousness, in keeping with a frontal lobe syndrome. Wilson et al. found no particular personality type, and the observed profiles on the Minnesota Multiphasic Personality Inventory did not differ from those of control patients with chronic disease. In the study from Israel, patients appeared to react differently from controls to emotional factors suggesting repression of hostility. Warren and colleagues interviewed 100 MS cases and 100 controls with rheumatoid arthritis or other...
neurological disease matched on age, sex, race and zone of residence before 15 years age. In the 2-year period prior to symptom onset, a history of severe or prolonged emotional stress was noted. This included death/illness of a close family member or friend, marital or pregnancy-related problems, financial difficulty, or change in place of residence or lifestyle. There were no differences in childhood happiness.

The issue of a premorbid personality type for MS is still not resolved, and uncertainty has resulted from the accumulation of uncontrolled, sometimes anecdotal, reports. Even those using control groups have sometimes chosen unsatisfactorily—for example, patients with rheumatoid arthritis or hospital controls that might conceal any difference by overmatching. There appears to be no common theme to those who claim a premorbid personality: some find extroversion, others introversion. Similar criticism applies to the studies of prior stress, although the study by Warren et al. takes account of most confounders. If Warren et al. are correct, it might be argued that certain premorbid stressors could result in risk-taking behaviour as a means of escapism.

**Strict societies and MS**

If risk-associated behaviour is relevant to MS, then the disease might be less common in societies with a strict religious code and overall healthier lifestyle. One such group is the Mormons (Latter Day Saints) of Utah, whose health code forbids the use of tobacco in any form (smoking or chewing) and the drinking of alcoholic beverages, tea, or coffee, while encouraging a diet rich in grains, fruit, vegetables and moderate consumption of meat. Extramarital relationships are forbidden, and the former practice of polygamy is now virtually unheard of. This is reflected by the lowest rate in USA for smoking prevalence, heart and cancer deaths (United Health Group 11th Annual report). The state also has low rates of obesity, tuberculosis, sexually transmitted disease and was ranked third healthiest US state overall in 2003 (United Health Group 11th Annual Report). An estimate of MS prevalence was derived from diagnosis or treatment claims for MS from the Deseret Mutual Benefit Administrators (DMBA), which provides medical insurance just for employees of this Church and their families. To be admitted, all must observe strictly their Church health standards. This group would therefore contain highly compliant Mormons, at least at the time of registration with the insurance agency. The diagnosis was recaptured by inspection of prescriptions for medication specific to MS (e.g. β-interferons) for which take-up in USA is high. In a 5-year period of observation there were 206 MS patients, an overall prevalence of 45–64/100 000, depending on methodology. This rate is comparable to medium-risk areas such as France or Italy, but less than that suggested for N. California (University of California, San Francisco Resource Centre, 150/105) at similar latitude or Olmsted County, which is 200 miles north of Utah (Figures 4 and 5). The Latter Day Saints emigrated from Northern Europe mainly from 1840–1890, and would be expected to have a high MS rate on genetic grounds, and because of the frequency of intermarriage. Indeed the large state-wide study of military records showed regional variance that was explained in part on the basis of Scandinavian lineage. This trend would add significance of these observations. Our study has clear drawbacks in

![Figure 4. MS prevalence in Mormons subscribing to DMBA, pooled 1998–2002. Latitude of Salt Lake City (Utah) is 41°N. Conservative analysis is shown (this gives a lower limit to estimated prevalence rate). Mean annual population at risk: 60844.](https://academic.oup.com/qjmed/article-abstract/98/12/895/1569696/305555)

![Figure 5. Crude MS prevalence rate for Olmsted County, December 2000. Population at risk: 123 386. Latitude 44°N.](https://academic.oup.com/qjmed/article-abstract/98/12/895/1569696/305556)
that it was based on recorded diagnosis from a medical insurance agency; mild cases may not have been included and we may have underestimated the true rate. Also no measurement of the background MS prevalence in Utah is currently available, and comparison can be made only with some adjacent states.

There are studies of MS prevalence in other highly religious groups such as the isolated Muslim community in Thugbah, Saudi Arabia, where door-to-door survey revealed just one instance of MS in 23,227 inhabitants. Likewise in rural Kashmir (also largely Muslim), there were no cases of MS at all in a house-to-house survey of 63,645 individuals. The significance of these surveys are tempered by the effect of genetic isolation, and despite door-to-door access, the disease may have been under-ascertained due to limited diagnostic resources.

These three studies give limited support to the concept of protection against MS by low-risk behaviour. Strict Muslims would be unlikely to consume alcohol or recreational drugs, and adultery would not be permitted, but they are allowed to smoke cigarettes. Conversely, it could be argued that the scarcity of MS in Saudi Arabia and Kashmir relates to their southerly latitude.

**Athletic activity**

Warren et al. found significantly more patients who listed sport or other physical activity as the way they had spent their leisure time before disease onset (p < 0.01). Control subjects preferred more sedentary hobbies such as painting, music or reading (again before disease onset). This survey infers that MS patients have an athletic behaviour pattern—in many ways at variance with earlier suggestions of premorbid personality traits. Some over-matching with their control group (rheumatoid arthritis) and MS is likely in this study; conversely, any positive finding is likely to assume more significance. An obvious weakness relates to the fact it was questionnaire-based, retrospective and unblinded. These results received some confirmation from the Montreal case-control study, where those with MS tended to be more active than controls in the year prior to diagnosis (OR 2.3, 95%CI 1.4–3.9). This was based on personal expression of the study subjects, in comparison to others of the same age and sex in the general population. Clearly this observation is not as precise as that of others, but it is broadly supportive.

**Associations with risk behaviour**

If sport and athletic activity are relevant premorbid activities, then it is relevant to enquire about their associated behavioural patterns. Lifestyle and health risks of collegiate athletes were investigated across seven institutions in the US. There were 2298 college athletes and 683 randomized non-athletic controls who completed a questionnaire addressing health risks. There were significantly higher risk-taking features in athletes such as: non-use of seat belts or motor cycle helmets; more often a passenger when the driver was under the influence of alcohol or recreational drugs; higher alcoholic exposure; greater consumption of smokeless tobacco and anabolic steroids; less safe sex; greater number of sexual partners; less contraceptive use; and more often involved in physical fights. Athletes with just one risk-taking item were more likely to have multiple risk taking behaviours. Similar findings are documented elsewhere in well-designed large case-control studies, although tobacco exposure is more closely associated with smokeless tobacco rather than cigarettes.

The study mentioned earlier implies that MS patients before disease onset are also less likely to consume dietary fibre, vitamins or mineral supplements, and are taller and lighter in weight. Another study comparing caffeine intake in MS subjects, although this referred to current usage in depressed patients. Risk-averse people will avoid tobacco, alcohol, recreational drugs, OCT and multiple sexual partners; they will consume vitamin supplements and monitor the animal fat content of their diet. Those who disregard risks will do the opposite. There is overwhelming evidence that people who smoke are particularly likely to indulge in other adverse health behaviour. A study of 697 women attending community clinics aged 18–49 years in the San Francisco Bay area showed that smokers in comparison to non-smokers consumed larger quantities of coffee, soft drinks, liquor and beer in the 24 h before interview. Smokers also had their coitarche before age 16, a greater number of lifetime sexual partners, and were more likely to have been pregnant. When the number of sexual partners was controlled for, smokers were found to have a history of *Chlamydia*, gonorrhoea and/or pelvic inflammatory disease more often than non-smokers. Valois et al. interviewed 3805 public high school students. Significantly more sexual partners were found in those who used alcohol, tobacco or marijuana. Ogletree et al. conducted a large study of health behaviour of 2591 unmarried college students all under 25 years derived from the 1995 National College Health Risk Behaviour Study. Females who smoked were more likely than female non-smokers and males (either smokers or not) to have had multiple sexual partners, after controlling for age and race. There was a strong
relationship between binge drinking and multiple partners as well. Students who smoked were less likely to eat fruit and vegetables. These findings have been confirmed in other large studies. For example, Bell et al.,72 on the basis of a questionnaire mailed to 17 592 students in 140 American colleges, found that college students who reported using marijuana (24.8%) also indulged in other high-risk behaviour such as binge drinking, cigarette smoking and having multiple sexual partners (all highly significant associations). In a longitudinal prospective study, Guo and colleagues73 studied patterns of substance usage in 808 urban youths in Seattle, where almost identical risk behaviour was found. The aforementioned meta-analysis of smoking13 shows a significant association with subsequent MS, which in turn supports a secondary association with these negative health risk behaviour patterns.

In summary, there is weak evidence in support of a particular personality type for MS from the rather unsatisfactory studies available, but there is a suggestion of stressful events prior to disease onset. The one study that directly addresses a tendency to gamble is not yet published in full. It appears that strict Mormons and Muslims may suffer less from MS. There is some evidence that athletic pursuits and smoking are both linked to subsequent development of MS, and smoking and athleticism are both strongly associated with negative health behaviour patterns, suggesting the possibility that MS develops after a period of risk-associated behaviour.

Ultraviolet light and vitamin D exposure

One popular theory for MS suggests that the disease may relate to deficiency of vitamin D, either from poor nutrition or low ultraviolet light exposure, and that increasing vitamin D levels, from diet or ultraviolet radiation, are protective. This would explain the low frequency of MS in non-emigrating Afro-Caribbean and Orientals,74 and the latitude gradient observed initially in the US75 and Australia.76 Evidence from experimental allergic encephalomyelitis implies that vitamin D is protective.77 There are effects on immune regulation which make the postulated link biologically plausible.78 Some suggest that MS patients have low blood Vitamin D levels, and are thereby more vulnerable to bone fracture.79,80

In a case-control study from Tasmania,81 the authors examined 136 definite MS patients and 272 community-based controls, matched for sex and year of birth. Higher sun exposure between ages 6–15 years was protective against MS. Higher sun exposure in winter was more important than higher sun exposure in summer. This was confirmed objectively by measurement of actinic (ultra-violet-related) skin damage. All common sources of bias were taken into account, e.g. from recruitment, interviewer and interviewee, selective recall bias. However, the link between MS and lower ultraviolet exposure may be an epiphenomenon. That is, MS is commoner in fair-skinned people, who tend to avoid sunshine because of a greater tendency to sunburn, and indeed more sunburn episodes were found in MS patients.

If MS relates to reduced level of vitamin D from low sunshine exposure, then they should develop less skin cancer. In essence, such an effect has been demonstrated from the Oxford Record Linkage Study.82 They discovered about half the number of cases expected, with a rate ratio of 0.49 (95% CI 0.24–0.91, p = 0.03). Sources of confounding variables are addressed, including the fact that their data only included those admitted to hospital. Prevalent and incident cases of MS were incorporated, and would therefore contain an excess of longer-surviving cases, who would also have better medical surveillance. They also considered that those with MS might by reason of their disability spend less or more time in the sun, and the unpredictable effect of this. A similar inverse association between MS and skin cancer was found in two other studies.76,83 In the study from Australia,76 a correlation was found independently (standardized for age) between increased MS prevalence and lower mean annual maximum temperature, lower average annual UV radiation level, more southerly latitude and less mean annual bright sunshine. It could be argued that those who are health-conscious might avoid UV exposure, but it is also possible (again) that those with fair skin (who experience more MS) are more likely to become sunburnt and therefore expose their skin for a shorter period, and indeed more sunburn episodes were found in MS patients. Hence the suggested protective effect of sunshine once more may not be causally related.

In the first prospective investigation a protective action of vitamin D was suggested. This study once more drew on the wealth of information in the NHS study referred to above. Diet was assessed by questionnaire at baseline, and every 4 years thereafter. They identified 173 cases of MS after baseline assessment and calculated an age-adjusted relative risk of 0.67 (95% CI 0.40–1.2; p for trend 0.03) which was significant in those females who had the highest vitamin D intake. Those consuming vitamin D from supplements were protected from MS (RR 0.59, 0.38–0.91; p = 0.006), equating to a relative risk reduction of 40%. Their study is large,
controls. Asherio and colleagues showed that been significantly higher than that of age-matched patients is elevated in most surveys, it has seldom reviewed here. The theory does not explain the low prevalence of MS in females living in the Middle East, who typically cover up their skin, have a high incidence of rickets and low levels of MS.

Overall, the evidence linking MS to vitamin D/UV light is not strong, but it is compatible with a protective effect, more plausibly for vitamin D supplements than UV light. People who take vitamins are likely to pay attention to general health measures, and the apparent protection may be associated once more with lifestyle characteristics rather than any postulated immune action. It could be argued that those who disregard health risks would sunbathe more, and that their MS rate should be lowered. This aspect runs counter to the proposed risk theory, but is complicated by the relative lack of sunshine in areas of high MS prevalence (such as Scandinavia, Iceland, Scotland), so that even if risk takers wanted to sunbathe and could endure low ambient temperatures, there would not be enough sunshine for them to enjoy.

Viral infection

Risk-disregarding behaviour will bring an individual into contact with a whole range of micro-organisms, but the main pathogens claimed to have association with MS are viruses, particularly of the herpes group, which are acquired through close personal contact, and just this group will be reviewed here.

Although the percentage of EBV-seropositive MS patients is elevated in most surveys, it has seldom been significantly higher than that of age-matched controls. Asherio and colleagues showed that the incidence of preceding symptomatic infectious mononucleosis is commoner in those with MS compared to controls, and that antibodies were raised to EBV in the NHS prospective nested case-control study. Levin et al. undertook a nested case-control study on over 3 million US military personnel who had given blood samples over a 12-year period. The strongest predictors of MS were serum levels of IgG antibodies to Epstein Barr Nuclear Antigen (EBNA) complex or EBNA-1. Among individuals who developed MS, serum antibody titres to EBNA complex were similar to controls before 20 years but 2- to 3-fold higher at 25 years and older. The risk of MS increased with these antibody titres; the relative risk in persons with EBNA complex titres of ≥1280 compared with those <80 was 9.4 (95%CI 2.5–35.4, p for trend <0.001). In longitudinal analyses, a 4-fold increase in anti-EBNA complex or anti-EBNA-1 titres during the follow-up was associated with a 3-fold increase in MS risk. A simultaneous examination for cytomegalovirus antibodies (which is often associated with glandular-fever-like illness) was negative and helps confirm the specificity of their findings. The strength of their study is that it is prospective and relates the subsequent risk of MS to antibody level, although the confidence intervals are very wide.

Acquisition of Epstein Barr virus (EBV) is generally thought to occur in the context of kissing, which most would regard as innocuous risk-associated behaviour, but it does allow exchange of saliva and micro-organisms therein. Recent evidence suggests EBV can be a conventional sexually transmitted disease. For example Crawford and associates found EBV seropositivity to be significantly higher in those who had ever been sexually active (83% vs. 64%), and those with more sex partners. Two-thirds of glandular fever cases, but only one-tenth of asymptomatic primary EBV infections, were attributable to sexual intercourse. EBV can be recovered from the genital mucosa of women with acute glandular fever, or from uterine cervical washings even in those without evidence of recent EBV infection. EBV, HSV and cytomegalovirus can be detected in the semen of infertile men.

A prospective nested case-control study that used the UK General Practice Research Database suggested an association between prior exposure to recombinant hepatitis B vaccine and subsequent development of MS, based on 163 cases of MS and 1604 controls. The OR of MS for vaccination within 3 years before the index date, compared to no vaccination, was 3.1 (95%CI 1.5–6.3). No increased risk of MS was associated with tetanus and influenza vaccinations. Perhaps inevitably, an autoimmune mechanism was offered to explain the proposed association. This paper has been criticized on methodological grounds, and because most publications (including an earlier one from the same unit) have not supported an association. These adverse comments have been strongly rebutted by the authors (see correspondence) and their study was designed to avoid most sources of bias. Assuming the proposed association between MS and hepatitis B vaccine to be correct but not causal, the risk theory can be applied once more, because people who require hepatitis B vaccination are more...
likely to be in a riskier environment such as health care work, exposure to multiple partners, homosexual contact or use of intravenous drugs.

An association with herpes simplex virus type 2 (genital herpes HSV-2) was detected in the Italian Multicentre Case-Control Study,\textsuperscript{100} where serum and cerebrospinal fluid antibody titres were measured to HSV-1, HSV-2, EBV and HTLV-III in 124 MS patients, and compared to 42 controls with non-neurological or other neurological disease. The main finding was a significantly raised titre to HSV-2 in the sera of MS patients, in comparison to their control group. This suggestion is given further support by a study of HSV-2 seropositivity in 496 MS patients matched for age and gender and residence.\textsuperscript{101} London MS residents, compared to London blood donors, showed a significantly higher HSV-2 seroprevalence in two age brackets in an unadjusted comparison (16–34 years: $\chi^2 4.54, p=0.03$; 35–64 years: $\chi^2 13.8, p < 0.001$) (Figure 6). In a logistic regression analysis, increased age, female sex and MS positive status all independently increased the odds of HSV-2 seropositivity (after adjustment for each other). The logistic regression model tested for all two-way interactions, and none was significant at the 5% level. Exposure to many viruses has been claimed for MS; it is possible the association with HSV-2 is non-specific or that it represents low-affinity antigenic binding, but it does indicate past exposure. The study was initiated not because of a possible aetiological association between HSV-2 and MS (which is unlikely), but because antibody to this virus is a surrogate marker of sexual partner number.\textsuperscript{102} The data therefore suggest that people with MS are likely to have more partners than did controls, and this would be regarded as risk-associated behaviour.\textsuperscript{64}

![Figure 6. Comparison of London blood donors with London MS patients. Seroprevalence on vertical axis. There are significant differences in both age brackets (16–34 years: $\chi^2 4.54, p=0.03$; 35–64 years: $\chi^2 13.8, p < 0.001$).](https://academic.oup.com/qjmed/article-abstract/98/12/895/1569696)

![Figure 7. Risks (odds ratios, relative risks and rate ratios) for smoking, alcohol, substance abuse, oral contraceptives, skin cancer, vitamin D and EBNA titre. Note the upper confidence limit for EBNA titre is off scale. Author and reference number shown below x axis.](https://academic.oup.com/qjmed/article-abstract/98/12/895/1569696)

**Conclusions**

There is evidence that people with MS are more likely both to smoke and have raised antibodies to EBV before the onset of MS symptoms (Figure 7). The argument for a protective effect of vitamin D from multivitamins is also persuasive. Weaker evidence relates to alcohol consumption, substance abuse, high animal fat intake and use of the OCT. Just one preliminary study has directly examined risk behaviour in MS subjects, and that is negative. Indirect evidence from societies with strict religious codes (Mormon, Muslim) suggests lower MS prevalence. Prior athletic behaviour is associated with subsequent MS in two surveys, and several studies suggest that many athletes disregard health risks. There is strong evidence that smokers tend to disregard their health in general. The respective arguments are summarized in Table 2.

The proposed associations with MS discussed here may not all be casually linked, and most could be explained on the basis of risk behaviour. Clearly, someone who takes their health for granted would be less concerned about exposure to tobacco, alcohol and recreational drugs, and would be less likely to consume vitamin or mineral supplements; they would not worry about their cholesterol level, and take OCT; they would have more sexual partners and thereby more venereal disease. Many observations supporting this are derived from questionnaire surveys and therefore vulnerable to chance associations by virtue of the multiplicity of queries. Many earlier investigators have used purely clinically-based MS diagnostic criteria, due to the unavailability of MRI imaging. There is also the possibility of bias from the preconceptions of the research leader, interviewer or interviewee, but most investigators are aware of these pitfalls and have avoided them. Finally there may be bias from
<table>
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<tr>
<th>Proposed association</th>
<th>For</th>
<th>Against</th>
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<tbody>
<tr>
<td>Smoking</td>
<td>Eight studies suggest link between prior smoking and disease onset. Confirmed by meta-analysis</td>
<td>Evidence reasonably strong. Smoking may be immunosuppressive</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Three studies suggest link</td>
<td>No control group in two surveys</td>
</tr>
<tr>
<td>Recreational drugs</td>
<td>Three studies: one shows a clear association</td>
<td>Retrospective and two relate to current use, not prior to disease</td>
</tr>
<tr>
<td>Oral contraceptive tablet</td>
<td>Three prospective surveys suggest slight increase of risk, perhaps with high-oestrogen tablet</td>
<td>Weak evidence and not supported by animal work or recent oestrogen trials</td>
</tr>
<tr>
<td>Raised cholesterol and animal fat intake</td>
<td>One good study shows animal fat intake high before disease onset. More MS in farming communities. Increased risk of myocardial infarction in large Danish study</td>
<td>Many MS patients modify diet once diagnosed. No clear increased risk of myocardial infarction. Selective recall bias; confounded by smoking and inactivity</td>
</tr>
<tr>
<td>Risk attitude and behavioural characteristics</td>
<td>Suggest deprived upbringing, lack of affection and repression of anger. More athletic</td>
<td>Most are retrospective uncontrolled studies and unreliable</td>
</tr>
<tr>
<td>Ultra-violet light and vitamin D supplements</td>
<td>Modest protection against MS, particularly for vitamin D supplements</td>
<td>Weak effect but immune mechanism possible. Cannot view single dietary factor in isolation</td>
</tr>
<tr>
<td>MS prevalence in morally strict societies</td>
<td>MS rare or low in strict Mormon or Muslim societies</td>
<td>Mormon data based on insurance records with no secure local rate for comparison. Genetic resistance or isolation explains low rate elsewhere</td>
</tr>
<tr>
<td>HSV-2 viral infection</td>
<td>Two studies show association. High frequency of seropositivity correlates with greater number of partners</td>
<td>MS patients often show non-specific raised titre to several viruses</td>
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studies which have never been published because of negative results.

Given these potential shortcomings, it is possible that the behaviour pattern of patients with MS may be characterized by risk-disregarding behaviour. Apparent and disparate causal links can be explained on this premise, and not necessarily related to an immune mechanism, which is the usual explanation. A risk-associated environment would bring the individual into contact with causative or predisposing agents for MS. For example, smoking is associated with higher partner number and the secondary risks of infection, particularly venereal disease; hence it may just be a marker of risk behaviour and not a direct cause of MS. Although one or more associations may still be causally relevant, the proposed MS behaviour pattern may better explain many of the apparent relationships.

References


