A coherent consensus regarding the etiology of multiple sclerosis (MS) and immune-mediated chronic diseases (such as rheumatoid arthritis, juvenile diabetes, and autoimmune thyroid disease) has emerged over the past two decades: exogenous (including infectious), environmental, or behavioral (lifestyle) factors cause disease onset in genetically susceptible persons. Neither genes by themselves nor exogenous factors alone are sufficient to cause MS. The likely scenario is that, in a genetically susceptible person, the equilibrium among components of the trimolecular complex (major histocompatibility complex molecules, T-cell receptors, and foreign or self antigens) is disrupted sufficiently to induce a chronic state of autoimmune damage. Despite theories, however, no infectious agent has been established as a causal agent in MS. An environmental etiology for MS is suggested by the strong north–south gradient in disease frequency, by disease clusters, and by evidence that migration to and from high-risk areas in early life influences the likelihood of cause MS.

More sophisticated investigations regarding lifestyle factors associated with MS have recently emerged. Smoking appears to have important but modest associations with MS and other autoimmune disorders; the basis for this association is not yet clear. Riise et al., in this issue of Neurology, identified a nearly twofold risk of developing MS in ever smokers in a population-based study of prevalent cases of MS from one region in Norway. Beyond smoking, diet has also been a behavioral risk factor of interest since two early ecologic studies suggested an association between high fish intake and lowered risk of MS and between high animal fat-based caloric intake and increased risk of MS. Whether specific components of diet can alter risk for developing any chronic disease is extremely difficult to study. Retrospectively collected dietary history for intake patterns that occurred 10 to 20 years prior to disease onset may be plagued by imprecise recall. Increased linoleic acid intake, but not other specific fat sources, has been associated with lower MS risk (RR = 0.3, 95% CI 0.1 to 1.1) in a prospective cohort study. Linoleic acid supplementation can also lessen the severity of experimental allergic encephalomyelitis in guinea pigs.

Vitamin D has also been considered as a potential risk factor. The latitude effect on MS prevalence may be related to decreasing gradients of sunlight and decreased production of vitamin D. There is strong correlation between regional MS prevalence and ultraviolet radiation levels in Australia. Vitamin D can completely inhibit induction of experimental allergic encephalomyelitis in mice, perhaps by stimulating anti-encephalitogenic cytokines. Finally, vitamin D receptor (the site of vitamin D action) gene polymorphisms are associated with MS in Jap-
Table Smoking and the risk of MS: Findings from population-based studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design, location</th>
<th>Smoking measure</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference 4</td>
<td>Prospective cohort study of incident cases among British women</td>
<td>&gt;15 cigarettes/day*</td>
<td>1.4 (0.9–2.2)</td>
</tr>
<tr>
<td>Reference 5</td>
<td>Prospective cohort study of incident cases among British women</td>
<td>&gt;15 cigarettes/day*</td>
<td>1.4 (0.9–2.2)</td>
</tr>
<tr>
<td>Reference 6</td>
<td>Case-control study of incident cases in Montreal</td>
<td>ever vs never smoked</td>
<td>1.6 (1.0–2.4)</td>
</tr>
<tr>
<td>Reference 7</td>
<td>Prospective cohort study among U.S. women</td>
<td>20–40 cigarettes/day*</td>
<td>1.9 (1.2–3.2)</td>
</tr>
<tr>
<td>Reference 3</td>
<td>Case-control study of prevalent cases in Hordaland, Norway</td>
<td>ever vs never smoked</td>
<td>1.7 (1.2–2.4)</td>
</tr>
</tbody>
</table>

* Comparison group for cigarette dosage categories is never smokers.

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References


