RE: “FAMILIAL RISK OF MULTIPLE SCLEROSIS: A NATIONWIDE COHORT STUDY”

In a recent register-based Danish cohort study on multiple sclerosis, Nielsen et al. (1) reported a 7.1-fold increased risk of multiple sclerosis in first-degree relatives of multiple sclerosis patients and an 8.6-fold risk in nontwin siblings. Brothers had a high relative risk of 12.6, as compared with sisters’ risk of 6.3. The study was based on the Danish Multiple Sclerosis Register for diagnostic data and on the Danish Civil Registration System for family data, available for persons born in the early 1950s. No age-specific data were given, but, at least for siblings, the age span was probably about 0–45 years, because follow-up was terminated at the end of 1997. Based on uniform diagnostic data and registers with high coverage, the results of this study would be expected to be highly reliable. They provide further evidence for the heritable etiology of this disease, for which a family history is thought to be present in up to 20 percent of cases (2–4).

The possibility of family linkage studies also exists in Sweden through the Multigeneration Register, maintained by Statistics Sweden. This resource has been extensively used in the study of familial cancer, because a nationwide cancer register is available (5). For diseases lacking register data, hospital discharge data can be used—as we have shown, for example, for migraine and other headache syndromes (6). We have also used these resources for the study of multiple sclerosis. We constructed a neurologic disease database through linkage of Swedish Hospital Discharge Register data from 1987 onwards to the Multigeneration Register, which contains data on all persons born in Sweden in 1932 or thereafter and their parents. Sibships were constructed for the generation born after 1931. Dates of hospitalization for multiple sclerosis were obtained for all patients who stayed at least one night in the hospital, usually in wards with specialist consultation or neurology departments; the Register does not include data on hospital out-patients or patients seen at health-care centers. Diagnoses were reported according to the Ninth (1987–1996) and Tenth (1997–2001) Revisions of the International Classification of Diseases.

Person-years were calculated from the start of follow-up on January 1, 1987, to hospitalization for multiple sclerosis,

### Table 1. Estimated familial risk of hospitalization for multiple sclerosis among siblings of multiple sclerosis patients in Sweden, 1987–2001

<table>
<thead>
<tr>
<th>Age (years) at diagnosis</th>
<th>Men</th>
<th>Women</th>
<th>All subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>SIR*</td>
<td>95% CI*</td>
</tr>
<tr>
<td>&lt;30</td>
<td>0</td>
<td>9.9</td>
<td>1.8, 36.3†</td>
</tr>
<tr>
<td>30–39</td>
<td>8</td>
<td>8.1</td>
<td>2.5, 22.7†</td>
</tr>
<tr>
<td>40–49</td>
<td>16</td>
<td>17.3</td>
<td>7.0, 39.9†</td>
</tr>
<tr>
<td>50–59</td>
<td>7</td>
<td>11.0</td>
<td>3.1, 32.3†</td>
</tr>
<tr>
<td>60–69</td>
<td>1</td>
<td>34.0</td>
<td>0.0, 275.7</td>
</tr>
<tr>
<td>All</td>
<td>32</td>
<td>12.2</td>
<td>5.9, 24.4†</td>
</tr>
</tbody>
</table>

* Obs, observed number of cases; SIR, standardized incidence ratio; CI, confidence interval.
† 95% confidence interval excludes 1.00.
Standardized incidence ratios (SIRs) were calculated as the ratio of the observed number of cases to the expected number of cases. The expected number of cases was calculated for age- (5-year groups), sex-, period- (5-year groups), region-, and socioeconomic status-specific standard incidence rates for persons lacking an affected sibling. Sibling risks were calculated for men and women whose siblings had been diagnosed with multiple sclerosis, using the cohort methods described by Hemminki et al. (7). Confidence intervals were calculated under the assumption of a Poisson distribution and were adjusted for dependence between the sibling pairs.

Between 1987 and 2001, 1,405 male patients and 3,002 female patients were hospitalized for multiple sclerosis in Sweden prior to age 70 years. The hospitalization rate was 2.9/100,000 for men and 6.5/100,000 for women. Seventy-seven non-twin siblings were affected (table 1), with an overall familial risk of hospitalization of 8.2. Familial risk was homogenous over age groups, ranging only from 7.3 to 8.9. Familial risk was twice as high for men (SIR = 12.2) as for women (SIR = 6.6). The numbers of cases were small, but there was a tendency toward a relatively high risk for women at young ages, whereas for men the age group 40–49 years showed the highest risk.

The Swedish Hospital Discharge Register has operated only since 1987, and the present study covered a time period of no longer than 15 years. Thus, our age-specific data may not be very accurate, because some persons in the early part of the study were likely to enter the hospital even before the study began. The overall diagnostic accuracy was probably good, because hospitalization normally involved diagnosis by several physicians, including a neurologist. The results were remarkably similar to the Danish ones (1), the SIRs differing by only a few decimal points: The risk for siblings in our study was 8.2, as compared with 8.6 in Denmark (1); fraternal risks in the two studies were 12.2 and 12.6, respectively, and sororal risks were 6.6 and 6.3, respectively. Women showed a higher background rate of multiple sclerosis compared with men, but the opposite was true for the familial risk. This phenomenon—a higher familial risk in the gender with a lower background rate—has been called “the Carter effect” (8). The familial risks in both of these register-based cohort studies were lower than those cited in the literature, ranging from 12 to 38 (1). This discrepancy conforms to the overall difference in familial risk estimates between interview-based studies and register-based studies that is repeatedly observed in cancer research (5). Interview data on family histories almost invariably exaggerate familial risks. Unfortunately, much of the global literature on familial disease risks is still based on interviews. The inaccuracies of studies based on interviews may have consequences for clinical genetic counseling (9).

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REFERENCES


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Editor’s note: In accordance with Journal policy, Nielsen et al. were asked if they wished to respond to this letter, but they chose not to do so.

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