Multiple sclerosis (MS) is known to accumulate within families. The magnitude of the familial risk, however, remains uncertain. Using a nationwide MS register and other national registers, the authors estimated relative and absolute risks of MS in a population-based cohort that included 19,615 first-degree relatives of 8,205 Danish MS patients followed from 1968 to 1997. The ratio of observed to expected numbers of MS cases served as the measure of the relative risk of MS. Lifetime risks of MS in first-degree relatives were estimated as the product of the relative risk and the national lifetime risk of MS. Overall, first-degree relatives had a sevenfold increased risk of MS (relative risk $= 7.1$, 95% confidence interval: 5.8, 8.8) ($n = 90$) compared with the background population.

By modeling the individual incidence rate of MS as the sum of a familial component and a sporadic risk component, the familial excess lifetime risk was found to be 2.5% (95% confidence interval: 2.0, 3.2) among first-degree relatives of MS patients, irrespective of the gender of the proband and the relative. This percentage should be added to a sporadic absolute risk in the general population of 0.5% in women and 0.3% for men. Spouses of MS patients did not experience an increased risk of MS, suggesting no major role for environmental factors acting in adulthood.

cohort studies; Denmark; family; multiple sclerosis; risk

Abbreviations: CI, confidence interval; MS, multiple sclerosis; RR, relative risk.

Multiple sclerosis (MS) is an inflammatory autoimmune disorder of the central nervous system characterized by recurring neurologic symptoms (1). MS typically presents in early adulthood and is considered the most common cause of neurologic disability in young adults (2).

Although most MS cases occur sporadically, a considerable proportion, as many as 20 percent, of the patients are related by family (2). While this accumulation of cases clearly suggests that first-degree relatives of MS patients are at increased risk of MS, previous attempts to assess the magnitude of the familial MS risk have arrived at variable estimates. Thus, the risk of MS has been reported to be increased from 12- to 38-fold in siblings, from seven- to 26-fold in parents, and from six- to 25-fold in children of MS patients (3–10).

Studying national MS data in Denmark, a high-incidence area of MS (11), we aimed to provide more precise information on the relative and absolute risks of MS in first-degree relatives of MS patients. We used information from the unique nationwide Danish Multiple Sclerosis Register and the Danish Civil Registration System, the latter containing updated demographic information including family history for all Danes born since the beginning of the 1950s.
MATERIALS AND METHODS

Subjects

Since 1956, the Danish Multiple Sclerosis Register has collected information on all patients diagnosed with MS in Denmark. All reported cases have been evaluated and classified by neurologists, and only cases fulfilling the diagnostic criteria of Allison and Millar (12, 13) or Poser et al. (14) (including possible MS) are considered MS cases (15, 16). The same two neurologists (N. K-H., Egon Stenager) have classified all cases of MS with onset after 1965.

The Danish Civil Registration System was established on April 1, 1968, and since then all Danish citizens alive on that date or later have been assigned a unique personal identification number. For individuals born since the beginning of the 1950s, the Civil Registration System also contains updated information on familial relations, allowing identification of a person’s parents, offspring, and siblings (17).

Identification of first-degree relatives of MS patients and follow-up of cohorts

We identified all patients registered with MS who were alive on April 1, 1968, or later in the Danish Multiple Sclerosis Register. Next, using the personal identification number as key, we identified all their first-degree relatives (parents, offspring, and siblings) in the Civil Registration System. In families with more than one case of MS, the person first diagnosed with MS was considered the proband. The first-degree relatives of MS patients were followed for the occurrence of MS from April 1, 1968, midyear (July 1) of MS diagnosis in the proband, or date of birth, whichever came later, to MS diagnosis, death, emigration, or December 31, 1997, whichever came first. Half-siblings, twins, and spouses were similarly identified in the Civil Registration System.

Statistical analysis

The ratio of observed to expected cases of MS, that is, the standardized incidence ratio, served as the measure of the relative risk of MS in the cohort of relatives. The expected number of MS cases was estimated as the sum of the products of sex, age (in 5-year strata), and period-specific population-based sex, age, and period-specific MS incidence rates. Analyses were stratified by kinship and gender of proband and relative.

We also estimated the relative risk of MS among spouses of MS patients. Only spouses where neither of them was diagnosed with MS before marriage were included. Subsequently, husbands and wives were followed up from April 1, 1968, or midyear of the spouse’s MS diagnosis, whichever came later, until MS diagnosis, death, emigration, or December 31, 1997, whichever came first.

To estimate the absolute lifetime MS risk in members of MS-afflicted families, we first estimated gender-specific lifetime risks of MS (sporadic lifetime risks) in the general population. These were approximated by the cumulative age- and gender-specific incidence rates of MS in Denmark in 1968–1997 at age 90 years. Lifetime risks of MS in first-degree relatives to MS patients were expressed as the product of the gender-specific sporadic lifetime risk and corresponding relative risks, assuming that the familial and sporadic incidence components had similar age distributions.

To evaluate the magnitude of the absolute familial MS risk, we modeled the incidence of MS in first-degree relatives as the sum of a sporadic component, equal to the age-, gender-, and period-specific, population-based incidence rates of MS, and a familial component, depending on the age and the gender of the relative, gender of the proband, and kinship (parent, sibling, offspring). Thus, the parameters of such a model concern only the familial component, since the sporadic component is based on known parameters. The estimation proceeded as previously described (18, section 4), based on collapsed data. All tests were performed as two-sided likelihood-ratio tests.

RESULTS

A total of 8,205 MS patients alive on April 1, 1968, or later had information on offspring (n = 13,316), parents (n = 3,556), siblings (n = 2,710), or twins (n = 33); 6,132 spouses of MS probands were identified.

We observed 90 cases of MS in the combined group of first-degree relatives versus 12.6 cases expected (relative risk (RR) = 7.1, 95 percent confidence interval (CI): 5.8, 8.8) (table 1). Analyses stratified according to kinship showed largely similar relative risk estimates for parents (RR = 6.4, 95 percent CI: 3.4, 12.4; nine cases), offspring (RR = 6.8, 95 percent CI: 5.3, 8.7; 64 cases), and non-twin siblings (RR = 8.6, 95 percent CI: 5.2, 14.2; 15 cases) (P_homogeneity = 0.77) (table 1). Stratification of analyses by relatives’ gender indicated that the relative risk of MS was lower in female (RR = 5.9, 95 percent CI: 4.5, 7.9; 48 cases) than in male (RR = 9.3, 95 percent CI: 6.8, 12.5; 42 cases) relatives (P_homogeneity = 0.04) (table 1). Analyses stratified by the gender of the proband suggested a higher relative risk in relatives of male MS patients (RR = 8.8, 95 percent CI: 6.6, 11.8; 45 cases) compared with relatives of female MS patients (RR = 6.0, 95 percent CI: 4.5, 8.0; 45 cases), although this difference was not formally statistically significant (P_homogeneity = 0.07) (table 1).

Among the 33 twin siblings to MS patients, we observed two cases of MS versus 0.02 cases expected (RR = 85.8, 95 percent CI: 21.5, 343). According to the MS register, both pairs of twins were monozygotic. Three cases of MS were observed in spouses of MS patients against 5.0 cases expected (RR = 0.6, 95 percent CI: 0.2, 1.9).

Using national sex- and age-specific incidence rates, we estimated the lifetime risk of MS in the general population to be 0.5 percent in women and 0.3 percent in men. Based on these estimates, the lifetime risk of MS was calculated to be 2.9 percent in female and 2.8 percent in male first-degree relatives of MS patients (table 1). In the statistical analyses assuming that MS incidence rates consist of familial and sporadic components, the familial incidence component was found to depend only on attained age and to follow the age pattern observed for the sporadic component. Thus, the gender of the proband and relatives did not have any

<table>
<thead>
<tr>
<th>Male proband</th>
<th>Female proband</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observed cases (no.)</strong></td>
<td><strong>Expected cases (no.)</strong></td>
<td><strong>Relative risk</strong></td>
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<tr>
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<tr>
<td>Mother</td>
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<td>0.36</td>
</tr>
<tr>
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<td>0.16</td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>Brother</td>
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<td>0.26</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>0.73</td>
</tr>
</tbody>
</table>

* Multiple sclerosis cases among twins (n = 2) are included in the overall relative risk for all first-degree relatives.
† In one family, the mother and both offspring (twins) developed multiple sclerosis. Therefore, one of the twins (the one latest diagnosed with the disease) appears in both the offspring and the twin cohort.
‡ This estimate is for full siblings. For half siblings, no cases were observed while 0.13 cases were expected (n = 387).
bearing on the observed risk estimates. Moreover, the observed incidence rates of MS in the cohorts of first-degree relatives were consistent with an excess familial lifetime risk of 2.5 percent (95 percent CI: 2.0, 3.2) that was equal for male and female relatives.

**DISCUSSION**

We believe that this is the first truly nationwide study to address familial aggregation of MS. By use of data covering the entire population of Denmark, we observed a sevenfold increased risk of MS in relatives of MS patients, with little variation among parents, siblings, and offspring. Supplementary analyses showed that kinship with MS patients is associated with an excess absolute risk of 2.5 percent in all first-degree relatives, which should be added to an absolute sporadic risk of 0.5 percent in women and 0.3 percent in men in Denmark.

The relative risk of MS was lower in female than in male relatives, especially among female relatives of female probands. The literature is inconsistent on this issue. Some studies report a paucity of father-son pairs compared with other parent-child combinations (19) or that sisters have higher risk than brothers regardless of the proband sibling’s gender (20), and yet another investigation reports a higher lifetime risk in siblings of male probands than in siblings of female probands (5). The difference in relative risks according to the gender of the proband observed in the present follow-up analyses is, however, consistent with the classic multifactorial threshold model of inheritance, which predicts that risks are higher for relatives of probands who are themselves from a low-risk group (i.e., relatives of male probands have higher risk than relatives of female probands), because of a higher genetic load among probands of the low-risk group (21, 22). However, by splitting up the observed incidence of MS into two components, reflecting the presumed independent effects of familial and sporadic risk factors, we showed that kinship to MS patients, irrespective of the gender of the proband, was associated with the same excess absolute MS risk to male and female relatives. Consequently, the observed variation in relative risks in female and male first-degree relatives could be attributed entirely to gender-specific variations in the background MS incidence rate, that is, the higher sporadic incidence rate of MS in women than in men.

Possible bias in the ascertainment of patients and family disease history needs consideration in family studies. In the present study, we used routinely collected registry information to assess the risk of MS in relatives of MS patients. The Danish Multiple Sclerosis Register is the longest running population-based MS register, and it is estimated to be more than 90 percent complete with a diagnostic validity of 94 percent (15). In an additional analysis in which cases registered with possible MS were excluded, no major changes in the risk estimates were seen. We therefore find misclassification or ascertainment bias to be unlikely explanations for our findings. However, information on familial relations was not available for persons who died before April 1, 1968. Accordingly, cases among first-degree relatives to MS patients who had died before April 1, 1968, will not be classified as familial cases but as sporadic cases. This bias would most likely lead to conservative risk estimates.

Our study provides further epidemiologic evidence of a strong familial component in the etiology of MS. Familial aggregation of MS can argue for both shared genes and shared environmental factors. However, we do not believe that shared environmental factors can account for the remarkably high risk in monozygotic twins or the uniformly high relative risk estimates among first-degree relatives who share half their genes with the proband (23). Our observation that spouses of MS patients were not at increased risk of MS furthermore suggests no major role of environmental factors acting in adulthood.

Whereas familial aggregation of MS is a well-known phenomenon in high prevalence areas (3, 6, 7, 24), it is considered very rare in Asia, a low prevalence area (25). However, the few studies that have addressed the familial risk of MS in low prevalence areas have been seriously limited by modest numbers of MS patients (25, 26).

In conclusion, our findings strongly support the involvement of genetic factors in the etiology of MS. Of interest, our data moreover suggested that a single estimate of the absolute excess risk was applicable to all first-degree relatives of MS patients. Upon confirmation in other settings, this may be of clinical relevance.

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Conflict of interest: none declared.

**REFERENCES**


