Modest familial risks for multiple sclerosis: a registry-based study of the population of Sweden

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Data on familial recurrence rates of complex diseases such as multiple sclerosis give important hints to aetiological factors such as the importance of genes and environment. By linking national registries, we sought to avoid common limitations of clinic-based studies such as low numbers, poor representation of the population and selection bias. Through the Swedish Multiple Sclerosis Registry and a nationwide hospital registry, a total of 28 396 patients with multiple sclerosis were identified. We used the national Multi-Generation Registry to identify first and second degree relatives as well as cousins, and the Swedish Twin Registry to identify twins of patients with multiple sclerosis. Crude and age corrected familial risks were estimated for cases and found to be in the same range as previously published figures. Matched population-based controls were used to calculate relative risks, revealing lower estimates of familial multiple sclerosis risks than previously reported, with a sibling recurrence risk ($\lambda_s = 7.1$; 95% confidence interval: 6.42–7.86). Surprisingly, despite a well-established lower prevalence of multiple sclerosis amongst males, the relative risks were equal among maternal and paternal relations. A previously reported increased risk in maternal relations could thus not be replicated. An observed higher transmission rate from fathers to sons compared with mothers to sons suggested a higher transmission to offspring from the less prevalent sex; therefore, presence of the so-called ‘Carter effect’ could not be excluded. We estimated the heritability of multiple sclerosis using 74 757 twin pairs with known zygosity, of which 315 were affected with multiple sclerosis, and added information from 2.5 million sibling pairs to increase power. The heritability was estimated to be 0.64 (0.36–0.76), whereas the shared environmental component was estimated to be 0.01 (0.00–0.18). In summary, whereas multiple sclerosis is to a great extent an inherited trait, the familial relative risks may be lower than usually reported.

Keywords: familial recurrence; multiple sclerosis; familial risk; twin study

Introduction

Multiple sclerosis is a complex disease with over 100 confirmed associated genes or genetic loci [International Multiple Sclerosis Genetics Consortium (IMSGC) et al., 2013] and a low but steadily increasing number of confirmed environmental risk factors (Haahr et al., 1995; Munger et al., 2004; Hedström et al., 2009). By studying familial recurrence risks of a disease, several important questions can be answered such as the relative contribution of genes and environment in its aetiology, the number of genes...
contributing to disease susceptibility and if a parent-of-origin effect exists.

Familial recurrence risks of multiple sclerosis have been well studied and considerable efforts have been made to gather data on familial aggregation. A recent meta-analysis found >500 studies on familial risks in multiple sclerosis (O’Gorman et al., 2013). The results, however, have varied widely, with the highest risk estimates in the northern countries, often attributed to prevalence increasing with latitude (Ebers, 2005; Islam et al., 2006; O’Gorman et al., 2011, 2013). Differences in data collection have questioned the validity of meta-analyses (Hawkes and Macgregor, 2009). A commonality for the previously published studies on familial risk and twins is that most contain patients that are recruited either in a clinical setting or from public appeals, with a few exceptions using national or regional case registries (Prokopenko et al., 2003; Nielsen et al., 2005). These methods increase the risk that the sample will be skewed with a higher concordance rate than the population (Hawkes, 1997). It is not trivial to ascertain whether a population representative sample is obtained, as recruited groups often tend to have a higher proportion of females and concordant pairs (Lykken et al., 1987). Additional difficulties include recall bias as well as validating the diagnosis in the patients’ relatives (Ramagopalan et al., 2007).

By linking the medical registries to the population registries in Sweden, it is possible to match controls, and thereby control for different prevalence throughout time and between genders.

This method of using matched controls has previously been used in a number of studies to successfully determine familial recurrence risk in different disorders, including obsessive–compulsive disorder (Mataix-Cols et al., 2013), autism (Sullivan et al., 2012) and criminal conduct (Frisell et al., 2011), but so far has not be applied to multiple sclerosis.

Here, we present a comprehensive study of familial multiple sclerosis recurrence risks based on ~15 million individuals residing in Sweden.

Materials and methods

Registries

In Sweden, a unique personal identifying number (PIN) is assigned to everyone at birth or at immigration. This number was used to link several nationwide registries and obtain information on multiple sclerosis diagnosis and relatives.

The Multi Generation Registry contains parents, and adoptive parents, for all persons born in Sweden in 1932 or later and residing in Sweden since 1961 (Statistics Sweden, 2005). The total Population Registry has information on sex, year of birth and country of birth for all people with a Swedish personal identity number ($n = 14912098$). The Cause of Death Registry holds the date and cause of a person’s death.

The Swedish Twin Registry is one of the most complete twin registries in the world, with birthdate and zygosity for 191911 twins born in Sweden since 1876 (Lichtenstein et al., 2002, 2006). Zygosity is determined through a questionnaire and/or DNA testing. This is further described in Magnusson et al. (2013).

The National Inpatient Register, also referred to as the hospital discharge register, is held by the National Board of Health and Welfare.

It contains information on admission date, discharge date, primary diagnoses and up to eight secondary diagnoses, classified according to International Classification of Disease standards, for all public health service inpatient admissions since 1964. The registry became nationwide in 1968 and since 2001 it also includes information from outpatient visits to specialist care. The study presented here had access to the data from 1968. An external validation of the register made by Ludvigsson et al. (2011) showed that the National Inpatient Register has had full coverage since 1989. The National Inpatient Register was complemented with the local Primary Care Registry for the Stockholm region. Established in 2002, the Primary Care Registry for Stockholm carries diagnosis codes in the International Classification of Disease (ICD) standard with dates for visits to primary healthcare providers in the region. Although in reality the National Inpatient Register and the Primary Care Registry in Stockholm are two different registries, throughout this article they are jointly assessed and addressed as the National Inpatient Register.

The Swedish Multiple Sclerosis Registry is a nationwide quality registry for patients diagnosed with multiple sclerosis. Most multiple sclerosis specialists in Sweden use the Swedish Multiple Sclerosis Registry to enter information on age at onset and sex as well as clinical parameters, such as disease course, bouts and treatment. The registry dates back to 2002 and contains mostly prevalent cases, although some clinics have entered data retrospectively. The validation study of the National Inpatient Register by Ludvigsson et al. (2011) found the overlap between the National Inpatient Register and Swedish Multiple Sclerosis Registry to be 52.9%, and 76.4% of all the cases in Swedish Multiple Sclerosis Registry were in the National Inpatient Register (Ludvigsson et al., 2011).

Classification of patients

To be classified as a multiple sclerosis patient, the individual had to be either in the Swedish Multiple Sclerosis Registry or in the National Inpatient Register with a diagnosis code for multiple sclerosis according to ICD-10 (G35), ICD-9 (340) or ICD-8 (340), or in the Primary Care Registry for Stockholm with ICD-10 code G35. If the person was not in the Swedish Multiple Sclerosis Registry, the first admission with a multiple sclerosis diagnosis was chosen as the date of onset. For simplicity, this date will be referred to as age at onset, despite the fact that it reflects the first recorded admission to hospital, which often is much later than the first symptom.

Statistical methods

The cumulative age at onset distribution was estimated for the Swedish Multiple Sclerosis Registry and the full data set. Crude and age-adjusted risks were calculated using Strömberg unmodified method (Risch, 1983) for the latter, with the age at onset distribution from the Swedish Multiple Sclerosis Registry used to obtain the previous distribution.

For the relative risks analyses, we constructed a data set with up to 10 randomly selected control pairs per case. Multiple sclerosis pairs for whom no suitable matched controls were available were excluded from the risk ratio analyses. The controls were matched on year of birth and sex, and their relatives were matched on the multiple sclerosis patient’s relative’s year of birth, sex and, where applicable, maternal/paternal relation to the index patient. Any control that had died before reaching the age of the multiple sclerosis index patient’s age of onset were excluded from the analysis, as were offspring adopted away. Index patients were included once for every relation investigated, and could thus occur more than once in the analyses. A Cox
proportional hazards model (‘coxph’ function from the ‘survival’ package (Therneau and Grambsch, 2000; Therneau, 2013) in R (R Core Team, 2013)) with a robust sandwich estimator was used to estimate risk ratios and 95% confidence intervals (CI). Included in this model were sex and year of birth for the control(s), and age at onset, sex, year of birth, and if matched on maternal/paternal relation for the patient with multiple sclerosis. For confidence intervals, the robust standard error was used. To correct for multiple testing, the Bonferroni method was applied using a factor of 76. The PROC FREQ statement in the SAS software version 9.2 was used to estimate tetrachoric correlations and confidence intervals were calculated using the estimated asymptotic standard error.

Twins and their zyosity were identified through the Swedish Twin Registry. An analysis of the heritability was made using OpenMx (Boker et al., 2011) in R. In OpenMx, twin pairs are used to estimate the variation within a trait, which is then explained by three parameters. ‘A’, more commonly referred to as h2, denotes the genetic part of the contribution to disease. ‘C’ is the shared environmental component within a family, and ‘E’ is the non-shared environmental component (Neale and Cardon, 1992). Sex was included in the model as a covariate. To increase power, from every family in the Multi Generation Registry the two oldest siblings and half-siblings with no more than 5 years of age difference were included in the analysis. All siblings adopted or adopted away were excluded.

Testing for a possible increase in transmission from the lower prevalent sex to offspring, also known as the Carter effect, was conducted with Pearson’s chi-squared test by assessing the differences in transmission rates between maternal and paternal parent to children using the stats package in R. Confidence intervals for the odds ratios (OR) were calculated with Fisher’s conditional maximum likelihood estimation in R using the ‘oddsratio’ function from the ‘epitools’ package (Aragon 2012).

**Results**

**Demographics**

The Swedish Multiple Sclerosis Registry contained data on 11949 patients with recorded dates of onset. In the National Inpatient Register and Stockholm registries, 27078 additional individuals with multiple sclerosis were found, comprising a data set of 28396 unique multiple sclerosis patients. Out of these, 235 lacked onset data and were only included in the calculation of the crude risks. For a flow chart of the selection process, see Supplementary Fig. 1. In total, 38.6% of the cases appeared in both the Swedish Multiple Sclerosis Registry and the National Inpatient Register, and 189 patients were only in the Stockholm registry. For characteristics and differences between the Swedish Multiple Sclerosis Registry and the National Inpatient Register individuals, see Table 1. At the time of the study, 67% of the patients were alive.

**Age at onset**

A mean age at onset of 33.7 years of age was observed in the Swedish Multiple Sclerosis Registry. See Table 2 for details and

| Age range | Swedish Multiple Sclerosis Registry | Combined |
|-----------|-------------------------------------|----------|
| n         | Proportion (%) | Cumulative proportion (%) | n | Proportion (%) | Cumulative proportion (%) |
| 0-9       | 26        | 0.2                        | 0.2  | 52        | 0.2                        | 0.2  |
| 10-19     | 971       | 8.1                        | 8.3  | 1167      | 4.1                        | 4.3  |
| 20-29     | 3390      | 33.1                       | 44.4 | 5234      | 18.6                       | 22.9 |
| 30-39     | 3717      | 31.1                       | 72.5 | 6297      | 22.4                       | 45.3 |
| 40-49     | 2286      | 19.1                       | 91.6 | 5848      | 20.8                       | 66.1 |
| 50-59     | 834       | 7.0                        | 99.9 | 4660      | 16.5                       | 82.6 |
| 60-69     | 150       | 1.3                        | 100  | 2817      | 10.0                       | 92.6 |
| 70-79     | 15        | 0.1                        | 100  | 1519      | 5.4                        | 98   |
| 80-89     | 0         | 0                         | 100  | 514       | 1.8                        | 99.8 |
| 90+       | 0         | 0                         | 100  | 53        | 0.2                        | 100  |

Note that the data in the Swedish Multiple Sclerosis Registry reflect the actual age at onset determined by a neurologist, whereas the National Inpatient Register reflects the first recorded contact for multiple sclerosis to a hospital if before 2001, and first visit to a hospital or first visit to a specialist if after 2001.

*Assessed from both registries.

**Table 1** Characteristics of the multiple sclerosis patients

| Group | n | Individuals unique for registry, n | Mean age at onset, years | Mean year of birth | Mean year at onset | % Female | Alive at time of study (%) |
|-------|---|-----------------------------------|--------------------------|--------------------|--------------------|----------|------------------------------|
| Swedish Multiple Sclerosis Registry | 11949 | 1083 | 33.7 | 1995 | 1994 | 70.8 | 11 248 (94.1) |
| National Inpatient Register | 27078 | 16 212 | 47.3 | 1946 | 1994 | 66.1 | 17 801 (65.7) |
| Total | 28 161 | 10 866* | 43.8 | 1947 | 1991 | 66.20 | 18 872 (67.0) |

Note that the data in the Swedish Multiple Sclerosis Registry reflect the actual age at onset determined by a neurologist, whereas the National Inpatient Register reflects the first recorded contact for multiple sclerosis to a hospital if before 2001, and first visit to a hospital or first visit to a specialist if after 2001.

*Assessed from both registries.

In the Swedish Multiple Sclerosis Registry cohort the age of onset is estimated by a neurologist. For the patients identified through the National Inpatient Register, the date is their first recorded inpatient hospital visit for multiple sclerosis or, if after 2001, first recorded hospitalization or visit out-patient visit to a neurologist.
comparison against the total cohort. As expected, the age at onset from the Swedish Multiple Sclerosis Registry deviated significantly from the age at first admission to hospital in the National Inpatient Register cohort. By age 59, 99.9% of the patients in the Swedish Multiple Sclerosis Registry had reached the onset of disease, whereas in the National Inpatient Register cohort some were not in the records for hospitalization as a result of multiple sclerosis until >90 years of age.

### Crude risks

Crude risks are shown in Tables 3 and 4. For parent-child pairs, the highest crude risk was for daughters, and for siblings the highest risk was found for sisters of patients with multiple sclerosis. The overall highest age-adjusted risk was for sisters of an affected brother. For half-siblings, maternal half-sisters had the highest risk, and among the remaining second degree relatives and cousins, the

### Table 3 Crude and age-adjusted risks for first degree, half-siblings and adopted relatives

| Relative | Proband | Female | | Male | | Total | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | n (affected) | Crude risk (%) | Age-adjusted risk (% (95% CI)) | n (affected) | Crude risk (%) | Age-adjusted risk (% (95% CI)) | n (affected) | Crude risk (%) |
| Monozygotic | | | | | | | | |
| Dizygotic | | | | | | | | |
| Child | | | | | | | | |
| Daughter | 14206 (251) | 1.77 | 2.96 (2.60–3.32) | 6737 (107) | 1.59 | 2.57 (2.09–3.05) | 78 (12) | 15.38 |
| Son | 15003 (99) | 0.66 | 1.12 (0.90–1.34) | 7132 (69) | 0.97 | 1.55 (1.12–1.91) | 237 (4) | 1.69 |
| Sibling | 9537 (288) | 3.02 | 3.36 (2.98–3.74) | 4379 (136) | 3.11 | 3.43 (2.86–4.00) | 20943 (358) | 1.71 |
| Sister | 10038 (136) | 1.35 | 1.52 (1.13–1.78) | 4577 (92) | 2.01 | 2.23 (1.77–2.69) | 22135 (168) | 0.76 |
| Maternal half-sibling | 1382 (29) | 2.10 | 2.40 (2.16–2.94) | 681 (13) | 1.91 | 2.14 (1.96–2.32) | 7132 (69) | 2.03 |
| Brother | 1569 (12) | 0.76 | 0.95 (0.52–1.49) | 727 (8) | 1.10 | 1.31 (0.41–2.21) | 2296 (20) | 1.65 |
| Maternal half-sibling | 1400 (16) | 1.14 | 1.54 (0.79–2.29) | 647 (10) | 1.55 | 2.01 (0.78–3.24) | 2063 (42) | 2.17 |
| Sister | 1468 (10) | 0.68 | 0.92 (0.35–1.49) | 662 (8) | 1.21 | 1.55 (0.05–2.62) | 2130 (18) | 1.25 |
| Brother | 497 (2) | | | | | | | |
| Maternal half-sibling | 359 (4) | | | | | | | |
| Aun/uncle | 3424 (127) | 0.37 | 0.57 (0.47–0.67) | 1302 (6) | 0.46 | 0.58 (0.10–0.86) | 3424 (127) | 0.37 |
| Cousin | 65 (1) | | | | | | | |

The age adjusted risks were calculated using Strömgren’s unmodified method. The confidence intervals were estimated using the binomial distribution with the sum of the weights as the total sample size.

### Table 4 Crude and age-corrected risks for second degree relatives and cousins

| Relative | Proband | Female | | Male | | Total | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | n (affected) | Crude risk (%) | Age-adjusted risk (% (95% CI)) | n (affected) | Crude risk (%) | Age-adjusted risk (% (95% CI)) | n (affected) | Crude risk (%) |
| Grandparent | | | | | | | | |
| Maternal grandmother | 4632 (19) | 0.41 | 0.35 (0.18–0.52) | 1858 (0) | – | – | 23073 (66) | 0.29 |
| Maternal grandfather | 4433 (15) | 0.34 | 0.37 (0.06–0.19) | 1756 (3) | 0.17 | 0.17 (0.00–0.36) | 6490 (19) | 0.29 |
| Paternal grandmother | 3766 (12) | 0.32 | 0.33 (0.14–0.52) | 1564 (4) | 0.26 | 0.26 (0.00–0.50) | 6189 (18) | 0.29 |
| Paternal grandfather | 3598 (9) | 0.25 | 0.26 (0.09–0.43) | 1466 (4) | 0.27 | 0.28 (0.00–0.55) | 5330 (16) | 0.30 |
| Aunt/uncle | 3841 (61) | 1.59 | 1.63 (1.22–2.04) | 1543 (20) | 1.30 | 1.29 (0.71–1.87) | 5064 (13) | 0.26 |
| Maternal aunt | 4009 (32) | 0.80 | 0.81 (0.53–1.09) | 1645 (13) | 0.79 | 0.83 (0.38–1.28) | 5654 (45) | 0.80 |
| Paternal aunt | 3057 (33) | 1.08 | 1.44 (1.04–1.87) | 1368 (21) | 1.54 | 1.51 (0.85–2.17) | 4425 (54) | 1.22 |
| Paternal uncle | 3259 (16) | 0.49 | 0.51 (0.26–0.76) | 1302 (6) | 0.46 | 0.48 (0.10–0.86) | 4561 (22) | 0.48 |
| Cousin | 6287 (26) | 0.41 | 0.66 (0.41–0.91) | 2560 (11) | 0.43 | 0.70 (0.29–1.11) | 34424 (127) | 0.37 |
| Female maternal cousin | 6498 (15) | 0.23 | 0.38 (0.19–0.57) | 2739 (8) | 0.29 | 0.47 (0.14–0.77) | 8837 (37) | 0.42 |
| Male maternal cousin | 5497 (33) | 0.60 | 0.91 (0.60–1.22) | 2378 (14) | 0.59 | 0.83 (0.38–1.28) | 9237 (23) | 0.25 |
| Female paternal cousin | 6005 (14) | 0.23 | 0.33 (0.15–0.51) | 2470 (6) | 0.24 | 0.38 (0.08–0.68) | 8475 (20) | 0.24 |

The age adjusted risks were calculated using Strömgren’s unmodified method. The confidence intervals were estimated using the binomial distribution with the sum of the weights as the total sample size.
**Twins and heritability**

A total of 348 proband twins with MS were identified in the Swedish Twin Registry within 340 distinct sets of pairs. Of the probands, 78 were monozygotic (MZ), 72 were dizygotic (DZ), and 27 were adopted. The study assessed a full population and was one of the largest adoption studies in multiple sclerosis to date.

**Adoption**

Four hundred and eighty-nine adopted children to parents with multiple sclerosis and 65 adoptive siblings were identified. Among these, two children and one sibling were affected (Table 3). The result was not significant when compared with controls, both in the respective groups and when combining the controls. The numbers of adoptees are small, resulting in low power and correspondingly wide confidence intervals. However, in spite of this, the study assesses a full population and as such is one of the largest adoption studies in multiple sclerosis.

**Table 5** Relative risks and tetrachoric correlations for first-degree, half-siblings and adopted relatives

| Proband          | Female Cases | Female Controls | Male Cases | Male Controls | Relative risk | Total Cases | Total Controls | Relative risk |
|------------------|--------------|-----------------|-----------|---------------|---------------|-------------|---------------|---------------|
| Monozygotic      | 57 (8)       | 570 (5)         | 21 (4)    | 210 (1)       | 12.7 (0.57–28.97) | 78 (12)     | 780 (6)       | 23.6 (8.71–64.02) |
| Dizygotic        | 83* (2)      | 830* (7)        | 39* (2)   | 390* (4)      | 2.03* (1.00–4.13) | 237 (4)    | 2,361 (19)    | 2.18 (0.71–6.68)  |
| Child            | 14,089 (245)| 140,752 (413)   | 6695 (105)| 66,776 (234)  | 4.54 (3.58–5.74)  | 42,743 (515)| 426,080 (899)| 5.77 (5.17–6.45)  |
| Daughter         | 14,059 (96)  | 148,421 (170)   | 7100 (69) | 70,859 (82)   | 8.43 (6.07–11.69)| 20,784 (190)| 207,528 (647)| 5.46 (4.79–6.23)  |
| Son              | 9443 (284)   | 94,290 (421)    | 4338 (133)| 43,338 (189)  | 7.15 (5.68–9.00)  | 13,781 (417)| 137,631 (610)| 6.92 (6.10–7.86)  |
| Sibling          | 9,903 (133)  | 98,828 (190)    | 4532 (89) | 45,235 (105)  | 8.56 (6.38–11.55)| 14,435 (9) | 144,063 (295)| 7.57 (6.32–9.06)  |
| Sister           | 13,618 (60)  | 136,182 (35)    | 675 (13)  | 673,737 (24)  | 5.41 (2.69–10.90)| 43,222 (60)| 434,140 (135)| 4.45 (3.25–6.09)  |
| Brother          | 1557 (12)    | 15,259 (35)     | 726 (8)   | 72,656 (16)   | 5.03 (2.14–11.82)| 20,399 (20)| 20,355 (84)  | 4.79 (3.28–6.99)  |
| Maternal half-sibling | 1,364 (27) | 13,618 (60)    | 675 (13)  | 673,737 (24)  | 5.41 (2.69–10.90)| 22,812 (20)| 227,855 (91) | 3.90 (3.21–6.57)  |
| Maternal half-sibling | 1,557 (12) | 15,259 (35)     | 726 (8)   | 72,656 (16)   | 5.03 (2.14–11.82)| 41,154 (44)| 40,954 (134)| 2.99 (2.29–4.72)  |
| Sibling          | 1,367 (16)   | 13,620 (57)     | 642 (10)  | 6,391 (33)    | 3.05 (1.40–6.62) | 20,296 (26)| 20,011 (90)  | 2.89 (1.84–4.53)  |
| Brother          | 1,451 (10)   | 14,245 (27)     | 655 (8)   | 6,518 (17)    | 4.70 (1.96–12.9) | 210,96 (43)| 20,943 (44)  | 4.10 (2.39–7.04)  |
| Adopted child    | 494 (2)      | 4,687 (11)      | 1,73 (0.73) | 4,687 (11) | 1.73 (0.37–8.04)| 56 (1)      | 275 (3)       | 1.87 (0.23–15.46)|
| Adopted sibling  | 494 (2)      | 4,687 (11)      | 1,73 (0.73) | 4,687 (11) | 1.73 (0.37–8.04)| 56 (1)      | 275 (3)       | 1.87 (0.23–15.46)|

Results with a significant risk ratio are marked in bold. The number of affected relatives are given in the parenthesis. A 95% CI is shown for relative risk. *Only done for same sex pairs.
dizygotic (DZ, 235 pairs) and 33 pairs (10%) were excluded due to unknown zygosity. Of the monozygotic twins, six concordant pairs (12 probands) were identified and two concordant dizygotic pairs (four probands) were found, making the proband-wise concordance rate in monozygotic twins 15.38 and in dizygotic twins 1.69. No concordant dizygotic pairs of different sexes were found. For demographics, see Table 7.

Using the 189/100 000 prevalence for Sweden reported by Ahlgren \textit{et al}. (2011), we expect 363 twins out of the 191 911 in the registry to be diagnosed with multiple sclerosis. This suggests the study has coverage of 96%.

**Heritability**

Based on twin data, the twin estimate, adjusted for sex, was 0.36 (0.23–0.52). After adding沅江 and half-siblings to increase the power of the heritability analysis, a total sample size of \( n = 2534465 \) individuals (monozygotic = 19 122; dizygotic = 55 635; siblings = 2 262 902; maternal half-siblings = 96 577; paternal half-siblings = 100 499) was obtained. The resulting estimates were \( h^2 = 0.64 \) (0.36–0.76), the shared environmental component, \( C \), was 0.00 (0.00–0.18); and the individual variance, \( E \), was 0.36 (0.23–0.52).

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Parental transmission/the Carter effect

A total of 13 923 father–child and 29 265 mother–child pairs were identified. In contrast with previous studies (Kantarci \textit{et al}.., 2006; Herrera \textit{et al}.., 2007), a significant difference in transmission from father to son compared with mother to son was found (\( P \)-value = 0.013). There was no significant difference in transmission to daughter between mother and father, a difference that was found in the Kantarci \textit{et al}. (2006) study. Examining transmission from father to son/daughter and from mother to son/daughter, a significant difference existed for both genders, with a higher

**Table 6 Relative risks and tetrachoric correlations for second degree relatives and cousins**

| Relative       | Female |          | Relative Risk | Male |          | Relative Risk | Total |          |          |          |          |
|----------------|--------|----------|---------------|------|----------|---------------|-------|----------|----------|----------|----------|
|                | Cases  | Controls |               | Cases | Controls |               | Cases | Controls |          |          |          |
| Grandparent    | 4543   | 45 261   | 1.92 (1.13–3.27) | 1828 | 18 206   | 1.30 (1.00–1.94) | 22 630 | 225 172  | 6371     | 63 467   | 3 050    |
| Maternal grandmother | 3693 | 36 786   | 1.85 (1.00–3.43) | 1537 | 15 297   | 1.33 (0.47–0.77) | 4170   | 41 583   | 6067     | 60 319   | 3 050    |
| Paternal grandmother | 3523 | 35 004   | 2.42 (1.18–4.94) | 1439 | 14 307   | 3.00 (1.00–9.49) | 19 484 | 197 697  | 4962     | 49 311   | 2 590    |
| Maternal aunt | 3834   | 38 187   | 3.17 (2.35–4.28) | 1527 | 15 232   | 2.26 (1.38–3.69) | 5361   | 53 410   | 5664     | 56 519   | 3 480    |
| Paternal aunt | 2995   | 29 846   | 1.77 (1.18–2.65) | 1349 | 13 372   | 2.52 (1.52–4.67) | 4344   | 43 218   | 3 480     | 3 459    | 2 020    |
| Coثرn           | 3201   | 31 904   | 1.93 (1.06–3.48) | 1272 | 12 646   | 2.06 (0.88–4.86) | 4473   | 44 550   | 1 960     | 1 920     | 1 220    |
| Maternal female cousin | 6164 | 61 389   | 1.21 (0.81–1.81) | 2490 | 24 807   | 1.35 (0.71–2.55) | 8 654  | 86 196   | 8 654     | 8 654     | 4 328    |
| Paternal female cousin | 5399 | 53 702   | 1.83 (1.26–2.65) | 2336 | 23 226   | 1.72 (0.96–3.08) | 7729   | 76 928   | 7 729     | 7 729     | 3 201    |
| Paternal male cousin | 5891 | 58 592   | 1.75 (0.97–3.16) | 2418 | 23 984   | 1.75 (0.73–4.22) | 8308   | 82 573   | 8 308     | 8 308     | 3 803    |

Results with a significant risk ratio are marked in bold. The number of affected relatives is given in the parenthesis. A 95% confidence interval is shown for relative risk and correlation.
transmission rate to daughters (OR 1.65 and 2.72 for fathers and mothers, respectively, see Table 8 for full details). Evaluating tetrachoric correlations (Supplementary Tables 1 and 2), sibling pairs and the parent–child pairs had equal point estimates of the correlation, and brother–brother full sibling pairs had the highest point estimate of the correlation (0.42, CI: 0.36–0.47), together with brother–sister pairs (0.42, CI: 0.36–0.45). The confidence intervals did not overlap for either mother–son pairs (0.31, CI: 0.26–0.36) or father–daughter pairs (0.29, CI: 0.25–0.34).

### Discussion

This paper presents strikingly lower risk ratios than most previous studies of familial recurrence in multiple sclerosis (Sadovnick and Baird, 1988; Ebers et al., 1995; Robertson et al., 1996; Sazdovitch et al., 2000; Marrosu et al., 2002; Prokopenko et al., 2003; O’Gorman et al., 2011, 2013). With 28,161 patients with multiple sclerosis and an estimated 96% coverage of the Swedish multiple sclerosis population, this is the most complete study of a single population to date. By using nationwide registries, problems that may be present in clinic-based studies such as recall bias and skewed sampling (Lykken et al., 1987; Hawkes, 1997) are minimized. The previously reported h2 estimates have ranged from 0.25 to 0.76 (Hawkes and Macgregor, 2009), placing the results of this study firmly within this range. This estimate once again confirms that multiple sclerosis is indeed a complex disease with a substantial genetic influence.

The twin study presented here is based on 96% coverage of the expected number of twins in Sweden. However, the number of concordant pairs is still low in absolute numbers, which makes sufficient power difficult to achieve. In a meta-analysis on familial recurrence data performed by O’Gorman et al. (2013), a combined proband-wise crude risk for monozygotic twins of 17.25% and an age-adjusted risk of 18.44% was reported, figures not far from the results presented here, based on a single population. In contrast, after adding controls and calculating recurrence risks, the relative risk estimates contrast sharply, with 23.6 in the current study, compared with 116.7 in the meta-analysis. Although this study is outnumbered by O’Gorman et al. (2013) the extensive coverage of our registries within a single population and the use of matched controls may offer an advantage. Previous studies, based on assumed prevalence figures rather than randomized controls, may have underestimated the population background risk of multiple sclerosis.

A decreased prevalence among dizygotic twins, as suggested by Hansen et al. (2005), was not confirmed, although the relative risk in this study was non-significant and the dizygotic concordance rate was in fact lower than that of other siblings. This may suggest that a possibly lower prevalence among dizygotic twins may exist and supports Hansen et al.’s (2005) suggestion of a beneficial effect for the immune system of placental exposure of a genetically different individual.

The relative risks presented in this paper are to our knowledge the first for multiple sclerosis using randomly selected controls from the general population. As the lifetime risk and prevalence in females are higher (Ahlgren et al., 2011), calculating relative risks by comparing with a single background risk estimate for both sexes would erroneously increase the risk for female relations and underestimate the risk for males. Also, by matching on sex and year of birth, the possible differences in prevalence during different time periods and in different sexes (Ahlgren et al., 2011), and

| Zygosity                      | Twins (affected co-twins) | Proband-wise concordance (%) | Mean age at onset | Mean year of birth | Females (%) | Nationwide rate of zygosity (%) |
|-------------------------------|---------------------------|------------------------------|------------------|-------------------|-------------|---------------------------------|
| Monozygotic                   | 78 (12)                   | 15.38                        | 41.37            | 1953              | 73.1        | 19.97                           |
| Dizygotic                     | 237 (4)                   | 1.69                         | 43.39            | 1948              | 67.9        | 58.05                           |
| Dizygotic same sex            | 122 (4)                   | 3.28                         | 45.52            | 1946              | 68.0        | 26.81                           |
| Dizygotic different sex       | 115 (0)                   | 0                            | 41.14            | 1951              | 67.8        | 31.24                           |
| Unknown                       | 33 (0)                    | 0                            | 37.29            | 1961              | 57.6        | 21.97                           |

The nationwide proportion of the sample is included for comparison.

| Zygosity     | Transmitted | Non-transmitted | OR (95% CI) | P-value |
|--------------|-------------|-----------------|-------------|---------|
| Father       | All         | 176             | 13,747      | 1.07    | (0.89–1.29) | 0.48     |
| Mother       | 345         | 28,920          |             |         |             |         |
| Father       | Daughter    | 107             | 6,654       | 0.91    | (0.72–1.15) | 0.44     |
| Mother       | 248         | 14,010          |             |         |             |         |
| Father       | Son         | 69              | 7,093       | 1.50    | (1.08–2.06) | 0.013    |
| Mother       | 97          | 14,910          |             |         |             |         |
| Father       | Daughter    | 107             | 6,654       | 1.65    | (1.21–2.28) | 0.0014   |
| Son          | 69          | 7,093           |             |         |             |         |
| Mother       | Daughter    | 248             | 14,010      | 2.72    | (2.14–3.48) | <2.2×10⁻¹⁶|
| Son          | 97          | 14,910          |             |         |             |         |

Table 7 Demographics for twins with multiple sclerosis

Table 8 Transmission from parent to child
of a father, compared to those of a mother (Table 8), is what would be expected if the Carter effect was present. The presence of a Carter effect in multiple sclerosis can thus not be excluded, although if present it is most likely not of great effect.

As seen in the result from the heritability analysis, a rather high non-shared environmental component is estimated. Inclusion of full and half siblings introduces more assumptions in the model, one of them being that paternal half siblings are assumed to share a household less frequently than maternal half siblings. This assumption is supported by a report from the Board of Social Welfare (Socialstyrelsen) (Statistics Sweden, 1994) showing that the majority of the children in Sweden live with their mother’s home as their primary address. The heritability analysis performed on the subset using only twins, can be considered a sensitivity analysis, and revealed almost identical results as the twin-only analysis. The risk for adoptees to a multiple sclerosis parent was not significantly different from that of controls, as previously reported by Ebers et al. (1995), and in line with the finding of the heritability study, as well as other observations, as the lack of increased risk for spouses of patients with multiple sclerosis (Nielsen et al., 2005). Many of the environmental factors associated with multiple sclerosis, such as smoking, night shift work and body mass index, are considered as risks that would contribute to the non-shared environmental component.

In conclusion, we present data that adjust familial recurrence risks for multiple sclerosis downwards, using an estimated 96% of the total Swedish multiple sclerosis patient population and matched controls. Lambda s, the standardized measure of familial aggregation (Rybicki and Elston, 2000), was found to be as low as 7.1. In the context of gene mapping efforts, our findings suggest a theoretically smaller number of multiple sclerosis risk genes, indicating that a greater proportion of the genes contributing to multiple sclerosis susceptibility have been identified than previously thought.

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Supplementary material

Supplementary material is available at Brain online.

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