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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

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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 = 14 912 098). 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 191 911 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 Strömgrens 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 zygosity 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 11 949 patients with recorded dates of onset. In the National Inpatient Register and Stockholm registries, 27 078 additional individuals with multiple sclerosis were found, comprising a data set of 28 396 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

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	11 949	1083	33.7	1959	1994	70.8	11 248 (94.1)
National Inpatient Register	27 078	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.

Table 2 Age at onset and age at first hospitalization for patients with multiple sclerosis

	Swedish Multiple Sclerosis Registry			Combined		
Age range	*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	3950	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

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

Proband	Female			Male			Total		
Relative	*n* (affected)	Crude risk (%)	Age-adjusted risk (%) (95% CI)	*n* (affected)	Crude risk (%)	Age-adjusted risk (%) (95% CI)	*n* (affected)	Crude risk (%)	Age-adjusted risk (%) (95% CI)
Monozygotic							78 (12)	15.38	17.26 (8.38–26.14)
Dizygotic							237 (4)	1.69	1.92 (0.00–0.38)
Child							43 078 (526)	1.22	2.03 (1.86–2.20)
Daughter	14 206 (251)	1.77	2.96 (2.60–3.32)	6737 (107)	1.59	2.57 (2.09–3.05)	20 943 (358)	1.71	2.83 (2.54–3.12)
Son	15 003 (99)	0.66	1.12 (0.90–1.34)	7132 (69)	0.97	1.55 (1.12–1.91)	22 135 (168)	0.76	1.26 (1.07–1.45)
Sibling							28 531 (652)	2.29	2.55 (2.09–3.01)
Sister	9537 (288)	3.02	3.36 (2.98–3.74)	4379 (136)	3.11	3.43 (2.86–4.00)	13 916 (424)	3.05	3.38 (3.16–3.60)
Brother	10 038 (136)	1.35	1.52 (1.13–1.78)	4577 (92)	2.01	2.23 (1.77–2.69)	14 615 (228)	1.56	1.74 (1.51–1.97)
Maternal half-sibling							4359 (62)	1.42	1.68 (1.26–2.10)
Sister	1382 (29)	2.10	2.40 (1.26–2.94)	681 (13)	1.91	2.14 (0.96–3.32)	2063 (42)	2.04	2.46 (1.72–3.20)
Brother	1569 (12)	0.76	0.95 (0.52–1.49)	727 (8)	1.10	1.31 (0.41–2.21)	2296 (20)	0.87	1.51 (0.96–2.06)
Paternal half-sibling							4117 (44)	1.07	1.40 (0.99–1.81)
Sister	1400 (16)	1.14	1.54 (0.79–2.29)	647 (10)	1.55	2.01 (0.78–3.24)	2047 (26)	1.27	1.69 (0.99–1.81)
Brother	1468 (10)	0.68	0.92 (0.35–1.49)	662 (8)	1.21	1.55 (0.05–2.62)	2130 (18)	0.85	1.12 (0.60–1.64)
Adopted child							497 (2)	0.4	0.67 (0.00–1.58)
Adopted sibling							65 (1)	1.54	1.76 (0.00–5.18)
Adoption							562 (3)	0.53	0.84 (0.00–1.79)

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

Proband	Female			Male			Total		
Relative	*n* (affected)	Crude risk (%)	Age-adjusted risk (%) (95% CI)	*n* (affected)	Crude risk (%)	Age-adjusted risk (%) (95% CI)	*n* (affected)	Crude risk (%)	Age-adjusted risk (%) (95% CI)
Grandparent							23 073 (66)	0.29	0.28 (0.18-0.38)
Maternal grandmother	4632 (19)	0.41	0.35 (0.18–0.52)	1858 (0)	–	–	6490 (19)	0.29	0.25 (0.13–0.37)
Maternal grandfather	4433 (15)	0.34	0.37 (0.06–0.19)	1756 (3)	0.17	0.17 (0.00–0.36)	6189 (18)	0.29	0.30 (0–16–0.44)
Paternal grandmother	3766 (12)	0.32	0.33 (0.14–0.52)	1564 (4)	0.26	0.26 (0.00–0.51)	5330 (16)	0.30	0.31 (0.16–0.46)
Paternal grandfather	3598 (9)	0.25	0.26 (0.09–0.43)	1466 (4)	0.27	0.28 (0.00–0.55)	5064 (13)	0.26	0.26 (0.12–0.40)
Aunt/uncle							20 024 (202)	1.01	1.00 (0.86–1.14)
Maternal aunt	3841 (61)	1.59	1.63 (1.22–2.04)	1543 (20)	1.30	1.29 (0.71–1.87)	5384 (81)	1.50	1.53 (1–20–1.86)
Maternal uncle	4009 (32)	0.80	0.81 (0.53–1.09)	1645 (13)	0.79	0.83 (0.38–1.28)	5654 (45)	0.80	0.81 (0.57–1.05)
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	1.12 (0.80–1.44)
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	0.50 (0.29–0.71)
Cousin							34 424 (127)	0.37	0.57 (0.47–0.67)
Female maternal cousin	6287 (26)	0.41	0.66 (0.41–0.91)	2550 (11)	0.43	0.70 (0.29–1.11)	8837 (37)	0.42	0.67 (0.45–0.89)
Male maternal cousin	6498 (15)	0.23	0.38 (0.19–0.57)	2739 (8)	0.29	0.47 (0.14–0.77)	9237 (23)	0.25	0.40 (0.24–0.56)
Female paternal cousin	5497 (33)	0.60	0.91 (0.60–1.22)	2378 (14)	0.59	0.83 (0.38–1.28)	7875 (47)	0.60	0.89 (0.63–1.15)
Male 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	0.34 (0.19–0.49)

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.

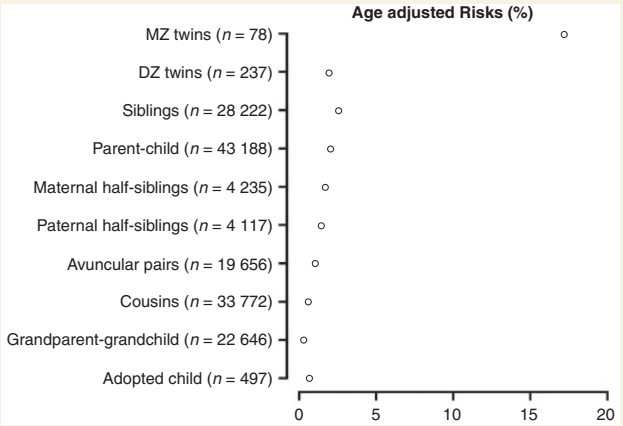

Figure 1 Age-adjusted risks for the different groups of relatives. DZ = dizygotic; MZ = monozygotic.

risks were <1%, except for maternal aunts. Figure 1 shows the age-adjusted risks for the different relations.

Relative risks

Relative risks are presented in Tables 5 and 6. After matching with controls, the proportions of cases remaining in the analysis were all >98%. Compared with matched controls, which account for the lower prevalence in males, similar risk estimates between relatives to males and female probands were found. The confidence intervals were largely overlapping, showing a non-significant difference between the sexes. Among children of affected parents, daughters had a slightly lower point estimate of risk compared with that of sons, and for fathers, the risks for daughters and sons were significantly different, with a higher risk for the sons. The overall highest risk was for brother–brother pairs, with no overlap with either mother–daughter or father–daughter pairs, which both had significantly lower risk. Among cousins, paternal female–female cousins were the only significant relation (uncorrected *P*-value = 0.00024). Figure 2 shows the relative risks with confidence intervals for the different groups.

Adoption

Four hundred and ninety-seven 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 groups (Table 5). It should be noted that 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 to date.

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 pairs), 237 were

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

Proband	Female			Male			Total		
	Cases	Controls	Relative risk	Cases	Controls	Relative risk	Cases	Controls	Relative risk
Monozygotic	**57 (8)**	**570 (5)**	**11.62 (6.47–20.85)**	21 (4)	210 (1)	127.14 (0.57–28572.27)	**78 (12)**	**780 (6)**	**23.62 (8.71–64.02)**
Dizygotic	83* (2)	830* (7)	2.84* (0.69–11.62)	39* (2)	390* (4)	2.03* (1.00–4.13)	237 (4)	2,361 (19)	2.18 (0.71–6.68)
Child							**42 743 (515)**	**426 808 (899)**	**5.77 (5.17–6.45)**
Daughter	**14 089 (245)**	**140 752 (413)**	**5.99 (5.82–6.16)**	**6695 (105)**	**66 776 (234)**	**4.54 (3.58–5.74)**	**20 784 (350)**	**207 528 (647)**	**5.46 (4.79–6.23)**
Son	**14 859 (96)**	**148 421 (170)**	**5.6 (4.41–7.26)**	**7100 (69)**	**70 859 (82)**	**8.43 (6.07–11.69)**	**21 959 (165)**	**219 280 (252)**	**6.56 (5.38–8.00)**
Sibling							**27 216 (639)**	**281 694 (905)**	**7.13 (6.42–7.93)**
Sister	**9443 (284)**	**94 290 (421)**	**6.82 (5.86–7.95)**	**4338 (133)**	**43 338 (189)**	**7.15 (5.68–9.00)**	**13 781 (417)**	**137 631 (610)**	**6.92 (6.10–7.86)**
Brother	**9903 (133)**	**98 828 (190)**	**7.02 (5.61–8.80)**	**4532 (89)**	**45 235 (105)**	**8.56 (6.38–11.55)**	**14 435 (9)**	**144 063 (295)**	**7.57 (6.32–9.06)**
Maternal half-sibling							**4322 (60)**	**43 140 (135)**	**4.45 (3.25–6.09)**
Sister	**1364 (27)**	**13 618 (60)**	**4.54 (2.90–7.12)**	**675 (13)**	**6737 (24)**	**5.41 (2.69–10.90)**	**2039 (40)**	**20 355 (84)**	**4.79 (3.28–6.99)**
Brother	**1557 (12)**	**15 529 (35)**	**3.39 (1.75–6.58)**	**726 (8)**	**7256 (16)**	**5.03 (2.14–11.82)**	**2283 (20)**	**22 785 (51)**	**3.90 (2.31–6.57)**
Paternal half-sibling							**4115 (44)**	**40 954 (134)**	**3.29 (2.29–4.72)**
Sister	**1367 (16)**	**13 620 (57)**	**2.80 (1.62–4.86)**	642 (10)	6,391 (33)	3.05 (1.40–6.62)	**2009 (26)**	**20 011 (90)**	**2.89 (1.84–4.53)**
Brother	**1451 (10)**	**14 425 (27)**	**3.71 (1.86–4.40)**	**655 (8)**	**6518 (17)**	**4.70 (1.96–1.29)**	**2106 (18)**	**20 943 (44)**	**4.10 (2.39–7.04)**
Adopted child							494 (2)	4,687 (11)	1.73 (0.37–8.04)
Adopted sibling							56 (1)	275 (3)	1.87 (0.23–15.46)
Adoption							550 (3)	4,692 (14)	1.78 (0.49–6.06)

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.

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

Proband	Female			Male			Total		
Relative	Cases	Controls	Relative risk	Cases	Controls	Relative risk	Cases	Controls	v
Grandparent							22 630 (63)	225 172 (322)	1.95 (1.49–2.55)
Maternal grandmother	4543 (16)	45 261 (83)	1.92 (1.13–3.27)	1828 (0)	18 206 (35)	–	6371 (16)	63 467 (118)	1.35 (0.80–2.27)
Maternal grandfather	4344 (15)	43 193 (38)	3.96 (2.17–7.25)	1,723 (3)	17 118 (21)	1.41 (0.42–4.76)	6067 (18)	60 311 (59)	3.05 (1.79–5.19)
Paternal grandmother	3693 (12)	36 786 (65)	1.85 (1.00–3.43)	1537 (4)	15 297 (30)	1.33 (0.47–0.77)	5230 (16)	52 083 (95)	1.68 (0.99–2.86)
Paternal grandfather	3523 (9)	35 004 (37)	2.42 (1.18–4.94)	1439 (4)	14 307 (13)	3.08 (1.00–9.49)	4962 (13)	49 311 (50)	2.59 (1.42–4.72)
Uncle/aunt							**19 844 (195)**	**197 697 (758)**	**2.58 (2.19–3.02)**
Maternal aunt	**3834 (61)**	**38 187 (193)**	**3.17 (2.35–4.28)**	1527 (20)	15 223 (89)	2.26 (1.38–3.69)	**5361 (81)**	**53 410 (282)**	**2.89 (2.23–3.73)**
Maternal uncle	4028 (31)	40 175 (94)	3.31 (2.21–4.97)	1638 (13)	16 344 (33)	3.94 (2.10–7.40)	5666 (44)	56 519 (127)	3.48 (2.47–4.89)
Paternal aunt	2995 (28)	29 846 (158)	1.77 (1.18–2.65)	1349 (20)	13 372 (79)	2.52 (1.52–4.617	4344 (48)	43 218 (237)	2.02 (1.47–2.77)
Paternal uncle	3201 (16)	31 904 (83)	1.93 (1.06–3.48)	1272 (6)	12 646 (29)	2.06 (0.88–4.86)	4473 (22)	44 550 (112)	1.96 (1.20–3.20)
Cousin							**33 754 (125)**	**335 910 (762)**	**1.63 (1.36–1.97)**
Maternal female cousin	6164 (26)	61 389 (214)	1.21 (0.81–1.81)	2490 (11)	24 807 (81)	1.35 (0.71–2.55)	8,654 (37)	86 196 (295)	1.25 (0.89–1.75)
Maternal male cousin	6381 (15)	63 477 (72)	2.07 (1.18–3.62)	2682 (8)	26 733 (32)	–	9063 (23)	90 210 (104)	2.49 (1.15–5.42)
Paternal female cousin	**5393 (33)**	**53 702 (10)**	**1.83 (1.26–2.65)**	2336 (13)	23 226 (75)	1.72 (0.96–3.08)	**7729 (46)**	**76 928 (255)**	**1.80 (1.32–2.44)**
Paternal male cousin	5891 (13)	58 592 (74)	1.75 (0.97–3.16)	2418 (6)	23 984 (34)	1.75 (0.73–4.22)	8308 (19)	82 573 (108)	1.75 (1.07–2.86)

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.

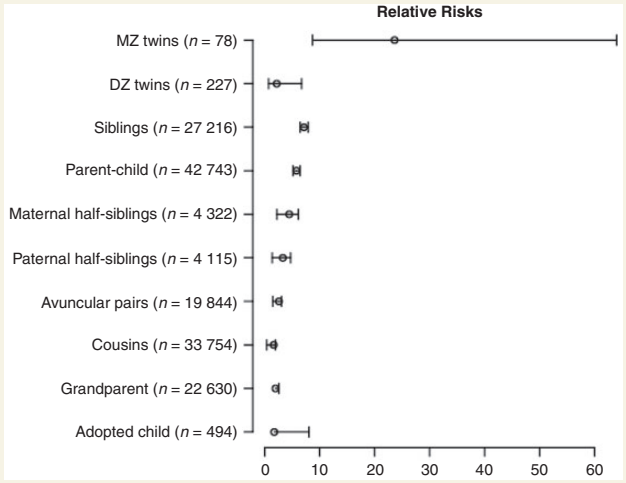

Figure 2 Relative risk ratios with confidence intervals for different groups of relatives. DZ = dizygotic; MZ = monozygotic.

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 *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 h2 estimate, adjusted for sex, was estimated to be 0.64, CI: 0.28–0.77, the shared environmental component, C, was 0 (0–0), and the individual variance, E, was 0.36 (0.23–0.52).

After adding siblings and half-siblings to increase the power of the heritability analysis, a total sample size of $n = 2\,534\,465$ 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 h2, A: 0.64 (0.36–0.76); environmental component, C: 0.01 (0–0.18); and individual variance, E: 0.35 (0.24–0.51).

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 *et al*., 2006; Herrera *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 *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 7 Demographics for twins with multiple sclerosis

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.

Table 8 Transmission from parent to child

		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	6654	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)	$<2.2 \times 10^{-16}$
	Son	97	14,910		

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

Table 9 Comparison with O'Gorman *et al.* (2013) meta-analysis

Estimate	Age-corrected risks		Relative risks	
	O'Gorman *et al.* (2013)	This study	O'Gorman *et al.* (2013)	This study
Monozygotic	18.44	17.26	116.69 (83.32–163.41)	23.62 (8.71–64.20)
Dizygotic	4.61	1.92	29.84 (15.39–57.87)	2.18 (0.71–6.68)
Sibling	2.68	2.55	16.77 (13.89–20.26)	7.13 (6.42–7.93)
Child	2.07	2.55	14.12 (9.91–20.13)	5.77 (5.17–6.45)
Aunt/uncle	0.75	1.00	4.57 (2.70–7.73)	2.58 (2.19–3.02)
Cousin	0.73	0.57	4.79 (2.98–7.69)	1.63 (1.36–1.97)

different coverage of the registries during different years (Ludvigsson *et al*., 2011), have been taken into account and the variance reduced. The age-adjusted risks are similar to the meta-analysis (Table 9), but when comparing the relative risks, the risks presented here are maximally half of those in the meta-analysis. Although there could be differences among populations, it has previously been thought that the heritability in multiple sclerosis increases with latitude, a theory our results do not support. As the results from the registry-based study performed in Denmark by Nielsen *et al.* (2005) and a previous report from Sweden by Hemminki *et al*. (2009) also using registries, are similar to the ones presented here, we believe that the difference is best attributed to the use of matched controls, large sample sizes and the use of registries to identify patients with multiple sclerosis and their relatives. The distribution of relatives to probands, with ~2–3 times as big group of relatives to a female proband compared to the males, is the same as the general gender ratio of about 2–3:1 in multiple sclerosis, thereby demonstrating the rigidity of using nationwide registries for identification of both patients and relatives and speaking for the validity of the findings. Compared with the meta-analysis by O'Gorman *et al*. (2013), this study has the largest sample size for all relations except twins, for example containing 43 188 children to multiple sclerosis patients.

The Carter effect has long been debated in multiple sclerosis. Carter (1961) presented a liability threshold model with gender differences as an explanation for the lower prevalence of pyloric stenosis in females. Simply put, the lower prevalent sex requires a higher number of risk genes to develop disease. Chakraborty (1986) extended on this, discussing the importance of using correlation as a measure when investigating a Carter effect. In multiple sclerosis, a possible Carter effect would show up as a higher correlation between male–male and male–female pairs, and a lower correlation for female–male pairs. Previously published data have emphasized a maternal parent-of-origin effect (Ebers *et al*., 2004; Herrera *et al*., 2008). By using population-based matched controls, we were able to control for potential confounding introduced by a possible change in the proportion of females among patients with multiple sclerosis throughout the 1900s and sampling and/or recall bias that might be present in a clinic-based study. In this study, no maternal effect was observed. The similar distributions and overlapping confidence intervals in the sex-stratified analysis for both relative risks and correlations between parent-child, full siblings and half-siblings, speak for a modest difference in transmission. However, the significant difference in transmission rate from father to son compared to mother–son, and the lower difference in risk between the sons and daughters 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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