Parental Age, Family Size, and Risk of Multiple Sclerosis

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Background: Family structure, such as having siblings, provides proxy measures for a variety of characteristics relevant to disease risk. The etiology of multiple sclerosis (MS) is not well defined and analysis of family structure may provide etiologic clues. We conducted a case–control study to examine possible associations.

Methods: Using the Swedish Inpatient Register, we identified 4443 patients with a diagnosis of MS. From the general Swedish population, using birth and death registers, we selected 24,194 controls with similar characteristics for year, county of birth, and survival until at least age at diagnosis of the matched cases. The Multi-Generation Register linked data on siblings and parents. The Census provided father's social class based on occupation.

Results: Having 3 or more younger siblings, compared with none, produced an adjusted odds ratio (OR) for MS (with 95% confidence interval) of 0.80 (0.70–0.92) (adjusting for number of siblings, twins, maternal and paternal age, parental MS, sex, father's social class, county and year of birth). With 3 or more older siblings, the adjusted OR was 0.83 (0.72–0.96). Different-sex twin pairs compared with singletons had an OR of 0.59 (0.37–0.95) for MS. The risk of MS increased steadily with father's age but not mother's age, up to 2.00 (1.35–2.96) for 51- to 55-year-old fathers (compared with 21- to 25-year-old fathers).

Conclusions: Parents who have offspring with MS may have subtly impaired fertility. The unexpected association with paternal age may be the result of an increased risk of accumulating germ cell mutations among older men.

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Multiple sclerosis (MS) is an inflammatory disease of the nervous system with demyelination (damage to the myelin sheaths) as an important component. Its etiology is not fully understood. The risks for the disease are likely to involve a combination of genetic susceptibility and environmental exposures.[1,2] A variety of infectious exposures have been postulated as important in the etiology of MS,[3–7] but a causal association has not been demonstrated convincingly for any specific infectious agent.[8] Pattern of infection such as age at infection may also be important in conferring the risk of MS.[6,9] It has been suggested that an inherited or induced tendency to a Th1 skewed immune response may increase the risk of MS, because Th1 bias has been theoretically associated with increased risk of T-cell responses to myelin basic protein.[10]

Family structure has been examined in research into the etiology of a number of diseases. Family structure can indicate relevant environmental exposures as well as familial markers for disease susceptibility. For example, the negative association of older siblings with the risk for asthma and allergy has been used to hypothesize that some patterns of early infection protect against these diseases.[11] The Swedish Multi-Generation Register[12,13] facilitates linkage of data on familial characteristics with other population registers, making large studies of the associations between such characteristics and disease risk possible. Our group has been using these data to identify familial characteristics that are markers of exposure and susceptibility relevant to the etiology of several diseases.[13–15] In these studies, associations with number of siblings and with parental age with disease risk have suggested an infectious etiology in Crohn's disease and ulcerative colitis,[14] a possible influence of maternal immune function on the risk of pediatric Crohn's disease in offspring,[15] and subfertility among parents of children who develop testicular cancer.[13]

We use family characteristics here to investigate several indictors of susceptibility or exposure that may be relevant to the etiology of MS. Age at some childhood infections had been suggested as etiologically important,[6] and associations with number of older or younger siblings can provide evidence of such a mechanism. Siblings influence pattern of infection. Older siblings tend to infect younger family members, who are secondary cases at an earlier age and often with

greater disease severity than those without older siblings.[16,17] Previous research using this marker for pattern of infection risk failed to find an association with MS,[18] but our study has greater statistical power.

Maternal Th1/Th2 balance may influence parental fertility,[19] and an inherited tendency to a Th1 response in offspring may increase their risk of MS.[10] We therefore investigated number of siblings and twining ratio as markers of parental fertility. Associations with number of siblings (regardless of a pattern for younger and older siblings) and ratio of monozygotic to dizygotic twins are both indicators of parental fertility.[20] Time between births was also used as a marker of parental fertility. As immune function alters with age,[21] maternal age may influence infectious exposures in young offspring as well as influencing direct stimulation of the fetus in utero. To investigate associations of siblings, twins, and parental age with MS risk, we performed a population-based case–control study using Swedish population register data.

METHODS

The government agency responsible for Swedish population statistics, Statistics Sweden, provided data for a population-based case–control study. For subjects born between 1936 and 1990, information was obtained from several registers with linkage using the personal identity number.[22] The Inpatient Register records the diagnoses of all hospital inpatients (excluding outpatients or patients undergoing day procedures). This register identified all inpatients in Sweden with a diagnosis of MS between 1964 and 1998. Date of diagnosis is based on the first time the diagnosis was made or confirmed. A diagnosis of MS was designated by *International Classification of Disease* (ICD) codes 345 in ICCD-6, 345.00 in ICD-7, 340.99 in ICD-8, 340X in ICD-9, and Q87.0 in ICD-10. The controls did not have this diagnosis. Up to 6 controls were matched with the cases to provide a similar geographic distribution (throughout 24 counties). Controls were born in the same year as matched cases and lived to at least to the age of the case's diagnosis (birth and death registers). Statistics Sweden conducted the case and control selection and then provided the data stripped of information that would allow identification of individuals. The Karolinska Institutet Ethical Committee approved the study.

The Multi-Generation Register allowed linkage of subjects with their biologic parents and siblings.[12] This register is based on a variety of population data sources, and the completeness of linkage has increased over time.[12,13] Since 1991, tax offices have been responsible for local population registration, and they have supplied very complete data to the Multi-Generation Register. However, before 1991, parish civil registration offices were responsible for local population registration, and they deleted deceased individuals from their records. Approximately half of these deceased individuals could be identified through other registers and were then included in the Multi-Generation Register.[12] Because individuals who died before 1991 are less likely to be identified in the Multi-Generation Register, we restricted our analysis to subjects with linkage to both parents to reduce the risk that associations with family size are the result of incomplete linkage. Diagnoses of MS in parents and siblings were identified using the Inpatient Register.

From among 6121 potential cases, 67 (1%) were excluded because they could not be linked with their mother, 842 (14%) could not be linked with their father, and a further 601 (10%) could not be linked with either parent. Among 28,750 potential controls, 243 (1%) were excluded because they could not be linked with their mother, 3313 (12%) could not be linked with their father, and a further 512 (2%) could not be linked with either parent. Using data from the Immigration and Emigration registers that have been maintained since 1969, and after exclusion as a result of incomplete linkage, 90 (2%) available cases and 488 (2%) available controls with incomplete follow up were excluded. A further 78 (2%) cases were excluded because they did not have data on county of birth, which was used as a pairing criterion in the sample selection. Overall, 4443 cases (74% of the potential cases) and 28,637 controls (84% of the potential controls) were used in the analysis.

Father's social class was based on occupation from the Census taken nearest in time to the subject's birth and was coded in the 9 occupational categories defined by the Census: owner of a business in agriculture or forestry; workers in agriculture or forestry; owner of a business in industry, transportation, or service; owner of any other type of business; executive (employee); salaried employee responsible for supervision, including foremen; employees not defined by previous categories; employees in service occupations; and those employed by the armed services. Unclassifiable occupations or unemployment were coded in a separate category. To facilitate interpretation, the occupations were also coded as manual or nonmanual.

Statistical Analysis

The analysis adjusted for potential confounding factors using unconditional logistic regression, in which case status was the dependent variable. We modeled all measures as series of binary dummy variables coded as shown in Table 1. Mother's age was coded using the same categories as father's age, year of birth was in 10-year categories, and the 24 counties at birth were modeled as individual binary dummy variables. We adjusted for all variables shown by Table 1, as well as maternal age at birth of subject, year of birth, county of birth, and father's social class based on occupation. All adjustment for social class was performed using the multiple-category variable. The dichotomized variable for manual and nonmanual

TABLE 1. Family Characteristics and Risk of Multiple Sclerosis

	Cases (n=4443) %	Controls (n=24,194) %	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Younger siblings				
0†	48	45	1.00	1.00
1	31	32	0.89 (0.83–0.96)	0.92 (0.85–0.99)
2	14	14	0.89 (0.80–0.97)	0.92 (0.83–1.03)
3+	8	9	0.77 (0.68–0.87)	0.80 (0.70–0.92)
Older siblings				
0†	50	51	1.00	1.00
1	32	30	1.10 (1.02–1.18)	1.06 (0.98–1.14)
2	11	12	0.93 (0.84–1.04)	0.87 (0.78–0.97)
3+	7	7	0.93 (0.81–1.06)	0.83 (0.72–0.96)
Twin				
No†	99	98	1.00	
Same sex	1	1	0.81 (0.59–1.12)	0.82 (0.59–1.13)
Different sex	1	1	0.61 (0.38–0.99)	0.59 (0.37–0.95)
Father's age at birth of subject (years)				
<21	2	2	1.10 (0.86–1.39)	1.05 (0.82–1.34)
21–25†	15	1	1.00	1.00
26–30	29	30	1.08 (0.97–1.19)	1.08 (0.96–1.20)
31–35	26	26	1.12 (1.01–1.24)	1.13 (1.00–1.29)
36–40	17	16	1.18 (1.05–1.32)	1.23 (1.06–1.42)
41–45	9	8	1.25 (1.09–1.44)	1.27 (1.06–1.52)
46–50	2	2	1.06 (0.85–1.33)	1.04 (0.80–1.35)
51–55	1	1	2.05 (1.43–2.93)	2.00 (1.35–2.96)
>55	0	0	0.89 (0.35–2.28)	0.85 (0.32–2.23)
Mother's age at birth of subject (years)				
<21	8	9	1.03 (0.91–1.17)	1.05 (0.92–1.21)
21–25†	26	29	1.00	1.00
26–30	30	30	1.06 (0.98–1.16)	1.02 (0.92–1.12)
31–35	21	21	1.10 (1.00–1.21)	1.01 (0.89–1.13)
36–40	11	10	1.10 (0.98–1.23)	0.95 (0.82–1.11)
41–45	3	3	1.25 (1.04–1.52)	1.11 (0.88–1.40)
46–50	0	0	1.92 (0.90–4.10)	1.57 (0.71–3.49)
51–55	0	0		
>55	0	0		
Maternal MS				
Yes	1	0	8.58 (5.57–13.21)	8.98 (5.77–13.97)
No†	99	100	1.00	1.00
Paternal MS				
Yes	1	0	5.99 (3.31–10.83)	5.61 (3.05–10.35)
No†	100	100	1.00	1.00
Sex				
Male†	3	51	1.00	1.00
Female	67	49	2.14 (2.00–2.29)	2.15 (2.01–2.30)

*Adjustment is for all variables shown and also maternal age at subject's birth, year of birth, county of birth and father's social class (10 categories).
†Reference category.

workers was used in a separate model to summarize associations with class. We conducted tests for trend in logistic regression by modeling measures as ordinal categorical variables using the same cutpoints as presented in Table 1.

Interactions of social class, year of birth, and father's age with the other main results were investigated using interaction testing in logistic regression and by stratification.

To investigate associations of a maternal or paternal history of MS with parental age at birth of subject, we limited the analysis to subjects with MS (cases). Paternal age (as a continuous log-transformed variable) was the dependent variable in multiple linear-regression model. Dummy variables for a maternal or paternal history of MS, as well as a continuous log-transformed measure of maternal age, were included in the model. A similar analysis using maternal age as the dependent variable, with adjustment for paternal age, was also conducted.

RESULTS

The presence of both younger and older siblings was independently and negatively associated with MS risk (Table 1). Subjects who were twins, particularly different-sex twins, were less likely to have MS. To further reduce the possibility of confounding between older and younger siblings, the analysis was repeated among those without any older siblings and those without any younger siblings. Among subjects without older siblings, the adjusted odds ratios (with 95% confidence interval) were 0.89 (0.79–0.99) for 1 younger sibling, 0.86 (0.74–0.99) and for 2 and 0.70 (0.58–0.85) for 3 or more, compared with none. Among subjects without younger siblings, the adjusted odds ratios were observed as 0.93 (0.83–1.05) for 1, 0.76 (0.65–0.88) for 2, and 0.73 (0.60–0.89) for 3 or more older siblings.

When the total number of siblings was combined into a single variable, this produced unadjusted odds ratios for MS of 0.91 (0.84–1.00), 0.84 (0.76–0.93), and 0.81 (0.73–0.89) for 1, 2, and 3 of more siblings, respectively, compared with no siblings. Adjustment for the potential confounding factors had a minimal impact on these odds ratios [0.92 (0.84–1.01), 0.85 (0.77–0.94), and 0.79 (0.71–0.88)].

The average time interval between subjects' births and the birth of nearest older or younger sibling was longer for cases. Among those with younger siblings, the mean (± standard deviation) duration between subject's' and nearest younger sibling's birth was 4.2 (± 2.7) years for cases and 4.0 (± 2.64) years. The mean duration between subject's and nearest older sibling's birth was 4.0 (± 2.7) years for cases and 3.8 (± 2.4) years for controls.

An association of increasing parental age, particularly for father's age, with MS risk was observed. Because a positive association of mother's and father's age is almost inevitable, both measures were included simultaneously in the model. The odds ratio with a 5-year increase in father's age was 1.05 (1.01–1.09) and 1.00 (0.96–1.04) for mother's age.

Although the association of older and younger siblings with MS risk was independent of father's age, stratification by father's age had some effect on the association of siblings with MS risk. Father's age was divided into those aged up to 30 years (48%) and those over 30 years. The associations of siblings with MS risk were not notably different from the overall sample in the stratum of younger fathers (data not shown). In the stratum with older fathers, the odds ratios appeared similar to those for the entire sample. Compared with no siblings, the odds ratios for having younger siblings in the stratum of older fathers were 0.81 (0.70–0.95), 0.84 (0.68–1.04), and 0.95 (0.73–1.24) for 1, 2, or 3 or more siblings, respectively. The odds ratio with each additional sibling was 0.95 (0.88–1.02). For older siblings in the stratum of older fathers, the odds ratios were calculated as 1.01 (0.87–1.18), 0.82 (0.64–1.04), and 0.70 (0.48–1.04) for 1, 2, or 3 or more siblings, respectively. The odds ratio with each additional sibling was 0.90 (0.83–0.98).

A diagnosis of MS in either parent was associated with an increased risk for MS in offspring (Table 1). Exclusion of cases with a history of MS (in either parent) did not notably alter any of the associations with siblings or paternal age. The group with a family history consisted of 55 cases and 75 controls. There was no statistical evidence for interaction between family history (in either parent or in mothers and fathers separately) and number of siblings. We explored the possibility that de novo mutations associated with older paternal age are more common among patients without a family history of MS. Because the distributions of mothers' and fathers' ages in individual years (not as grouped in Table 1) were skewed, these measures were log-transformed into normal distributions. Log-transformed father's age was the dependent variable in a linear regression analysis in which paternal and maternal histories of MS were modeled as 2 dummy variables. Adjustment was made for maternal age using a similar log-transformed measure. Among patients with MS (cases), a marginal association was observed for paternal MS with father's age producing a coefficient of −0.05 (−0.11 to 0.00). There was less evidence for an association of maternal MS with father's age among cases, with a coefficient of −0.02 (−0.05 to 0.02). When log-transformed mother's age was the dependent variable with adjustment for log-transformed father's age, neither paternal nor maternal MS was strongly associated with mother's age among cases (coefficients of 0.03 [−0.03 to 0.08] and −0.03 [−0.06 to 0.01], respectively).

A family member with MS may influence pregnancy decisions. However, exclusion of cases with pediatric onset and exclusion of all subjects with MS in siblings or parents did not influence the reported associations.

The associations with MS for siblings and paternal age were not notably altered by adjustment for either measure of social class defined by occupation (in the original categories or collapsed into manual and nonmanual). A slight increase in risk of MS was observed for children born of fathers working in nonmanual occupations (23% of this population) compared with manual occupations. The unadjusted odds ratio for MS associated with a father in nonmanual employment was 1.07 (0.98–1.17) and 1.09 (0.99–1.19) after adjustment for the potential confounding factors. Stratification by occupation type (manual/nonmanual) did not notably alter the results in either stratum, and there were no important interactions of father's occupation type with number of siblings or paternal age.

Like in our previous paper,[13] year of birth was stratified into periods before 1960 and 1960 or later. There was no notable difference for the associations of siblings and paternal age with MS risk in either stratum. No interactions with birth year (dichotomized) were observed with either number of siblings or paternal age.

DISCUSSION

The results suggest that parents of MS patients may have subtly impaired fertility and that older father's (but not mother's) age may be associated with an increased risk for MS in offspring.

Infectious agents have been proposed as etiologically important in MS but without definitive evidence.[8] Several viruses can cause diseases involving demyelination, including measles, human immunodeficiency virus (HIV), and the human T-cell lymphotropic virus type I.[23] Therefore, it is biologically plausible for MS, as a demyelinating disease, to have a viral etiology. Viruses associated with MS have included measles,[3] Epstein-Barr virus (infectious mononucleosis),[4] human herpes virus 6,[5] and mumps.[6] Nonspecific respiratory tract infections[7] and bacterial infections, including *Chlamydia pneumoniae*,[5] are also potential candidates.

Pattern of infection, defined in part by age, may be important in influencing MS risk.[6] If candidate infections occur commonly in childhood,[6] an influence of siblings would be expected. Delayed infection with measles and mumps has been demonstrated to be associated with MS,[6] and such a delay would be more likely in those with fewer (particularly older) siblings.[16,17] Siblings are less likely to influence the pattern of infections occurring in adult life, and so associations with siblings would be weaker or nonexistent.[16,17]

In allergic diseases, both younger and older siblings are associated with a reduced disease risk, but the association with older siblings is stronger and independent of younger siblings.[11] This association has been used to argue a protective effect of some patterns of childhood infection, although no specific infection has been convincingly identified. Interestingly, allergy is less common among patients with MS than among the general population.[24] This finding suggests that a negative association of MS with number of siblings may be less likely unless an inherited (rather than environmentally induced) predisposition to a Th1 skewed immune response protects against allergic disease in patients with MS.

Cases' families included fewer younger and older siblings, both for subjects without either any older or any younger siblings and for the overall number of combined older and younger siblings. These results are not readily explained by the influence of siblings on pattern of childhood infections in which older rather than younger siblings tend to exert a greater influence.[16,17] Another study using Swedish register data revealed different patterns of association for older and younger siblings with chronic diseases in which infection or microbial colonization may be implicated.[14] It is still possible that the association of MS with lower numbers of both younger and older siblings may be the result of their influence on patterns of infection, but this is less plausible. The lack of difference in results following stratification by year of birth (before 1960 and 1960 or later) provides further evidence of a fertility effect rather than an infectious phenomenon, because patterns of infection have changed substantially over the 20th century.[25]

Further evidence for an association with parental fertility comes from 2 sources. There is a longer time interval between births in case compared with control families. The gradient from singletons through same sex (monozygotic and dizygotic) to different-sex (exclusively dizygotic) twins is also consistent with a parental fertility effect (because dizygotic twinning entails 2 separate fertilizations and 2 viable fetuses, indicating higher fertility[20]). Different-sex twins must be dizygotic, and this group has the lowest risk for MS compared with singleton births. Single-sex twins can be either monozygotic or dizygotic and represent an intermediate group.

We hypothesized that reduced fertility in parents of children who develop MS may be the result of greater Th1 responsiveness among mothers, producing a more hostile in utero environment that reduces fertility.[19] A tendency to Th1 skewing inherited by offspring may increase their MS risk, because the Th1 phenotype of lymphocytes may promote inflammatory processes involved in MS pathogenesis.[10] Heritability in MS is illustrated by the high risk associated with parental MS.

The association of MS with older paternal age may be a novel finding. It is specific to father's age; mother's age is not associated with MS risk in combined analysis. Studies of schizophrenia have shown different distributions of paternal, but not maternal age, suggesting that older paternal age represents an increased risk for de novo mutations increasing the risk for sporadic disease.[26,27] Exclusion of the subjects with a family history of MS did not alter the associations with

paternal age, indicating that the presence of this group did not explain these findings. Among subjects with MS, we observed an association of paternal MS history with father's age. Fathers without MS had offspring with MS at a later age than fathers with MS, suggesting that older father's age may present a greater risk for sporadic rather than familial MS. One explanation for this finding is that father's MS prevented or discouraged men from fathering children at a later age. However, maternal MS was not notably associated with age at giving birth. Older paternal age and paternal MS appear to represent separate risks for MS in offspring.

Stratification by paternal age revealed a change in association of siblings with MS risk; among those with older fathers, the strength of association with younger, but not older, siblings was somewhat diminished. This may simply be because older fathers were less likely to produce further offspring, ie, younger siblings, either by choice and because of reduced fertility.

A similar association between older fathers and disease risk in offspring has been described in other diseases such as Apert syndrome.[28] The cause of Apert syndrome is a specific mutation, which in some case series arose from the father in every patient.[29] Interestingly, older father's age has been associated with other diseases of the nervous system in offspring, including sporadic cancers of the nervous system[30] and brain,[31] as well as schizophrenia.[26,27] Clinical and epidemiologic similarities between MS and schizophrenia have previously been described,[32] suggesting etiologic similarities. Our *a post priori* hypothesis is that older men may accumulate more de novo germline mutations or are more susceptible to risks for such mutations, possibly arising during gametogenesis, and some mutations may increase the risk of MS in offspring.

Father's occupation was used as a marker for social and cultural circumstance in childhood. Although nonmanual social class has previously been associated with an increased risk for MS,[33] we found only a modestly increased risk. Other studies have also reported no association with social class,[34] but the modest association reported here may be the result of the relatively flat social structure in Sweden. This minimal association has previously been observed in childhood growth and development rates; most developed countries show social class gradients in growth, weight gain, and age at puberty, but not Sweden.[35] There was no evidence to suggest that the associations of paternal age and number of siblings with MS risk were the result of confounding by material and social circumstances in childhood.

This study benefits from being population-based with considerable statistical power to detect even subtle markers of MS etiology. We minimized the risk of confounding by multiple adjustment. The fact that the estimates were altered only slightly with adjustment strengthens our conclusions. A potential concern is that that the results may be influenced by incomplete linkage resulting from early mortality in patients with MS, because linkage in the Multi-Generation Register would therefore be less complete. We investigated this issue by stratification on year of birth at the same time point used in a previous study that analyzed data from the same sources.[13] Those born in 1960 or later were more likely to be alive when the Multi-Generation Register was more completely compiled compared with those born earlier. Because the results were not notably different for subjects born in the 2 periods, differential mortality associated with MS, resulting in poorer linkage in the Multi-Generation Register, is unlikely to be the reason for the reported association of siblings and paternal age with MS risk.

The associations of MS risk with siblings and with paternal age were not notably altered by exclusions of families with MS in either parent or siblings or by exclusion of cases with pediatric-onset, indicating that the results are not the result of parents making decisions about pregnancy based on their own or their children's diagnosis of MS. There may be at least 4 separate pathologic patterns of MS,[36] and the relevant exposures may vary by phenotype. We could not differentiate among the pathologic forms of MS in this study, and so we could not determine if the associations identified are relevant to some or all of the pathologic forms.

It may be valuable to investigate risks for MS among parental exposures and characteristics. Subtle associations with fertility suggest that the immune profiles of mothers who have offspring with MS may be of interest. The association of father's age with MS risk suggests the possibility of germline mutations.

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