Acta Neurologica Scandinavica

Acta Neurol Scand 2015: 132 (Suppl. 199): 20–23 DOI: 10.1111/ane.12426

ACTA NEUROLOGICA
SCANDINAVICA

Review Article

Role of socio-economic and reproductive factors in the risk of multiple sclerosis

Magyari M. Role of socio-economic and reproductive factors in the risk of multiple sclerosis.
Acta Neurol Scand 2015: 132 (Suppl. 199): 20–23.

The incidence of multiple sclerosis is increasing in Danish women. Their risk of developing multiple sclerosis has more than doubled in 25 years while it has remained virtually unchanged for men. The explanation for these epidemiological changes should be sought in the environment as they are too rapid to be explained by gene alterations. We investigated the effect of numerous biological social physical and chemical environmental exposures in different periods of life. These data were available from population-based registries and were used in a case–control approach. This study database included all multiple sclerosis cases (n = 1403) from the Danish MS Registry with clinical onset between 2000 and 2004 as well as 35,045 controls drawn by random from the Danish Civil Registration System and matched by sex year of birth and residential municipality at the reference year. Having newborn children reduced the risk of multiple sclerosis (MS) in women but not in men. Childbirths reduced the risk of MS by about 46% during the following 5 years. Even pregnancies terminated early had a protective effect on the risk of developing MS suggesting a temporary immunosuppression during pregnancy. Our data on social behaviour regarding educational level income and relationship stability did not indicate reverse causality. A greater likelihood to be exposed to common infections did not show any effect on the risk of MS neither in puberty nor in adulthood. Socio-economic status and lifestyle expressed in educational level and sanitary conditions in youth were not associated with the risk of MS.

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Key words: childbirth; education; environmental factors; epidemiology; gender; multiple sclerosis; registries; reproduction

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Accepted for publication April 15, 2015

Danish women's risk of developing multiple sclerosis (MS) has more than doubled in the last 40 years, while it has remained virtually unchanged for men (1). The incidence rates for women increased from 4.61 to 11.85 in the period 1973–2002. These rapid epidemiological changes likely reflect unidentified changes in the environment, as the genes in the population have remained constant during this short interval. Exogenous factors that may influence the risk of MS differently in women and men can contribute to the increasing incidence of MS in women in Denmark. Better diagnosis and ascertainment cannot be the reason for the increased incidence of MS in women because in that case a similar trend would have been expected in men. Over the past century, the lives of women underwent major changes regarding lifestyle, education, work life, smoking and later and fewer childbirths.

Denmark has good resources for registry-based MS research due to the nationwide ongoing registration of MS cases in the Danish Multiple Sclerosis Registry (2) since the 1950s, and the possibility of linkage with other nationwide population registers and the Civil Registration System. This linkage is enabled by the uniquely assigned Civil Registration personal identification number.

In our recently published study (3), physical, social and reproductive factors were investigated in a case–control design. A study database was constructed by extracting from the Danish MS Registry all cases with confirmed MS with clinical

onset between 2000 and 2004. These 1403 native-born patients with MS (939 women and 464 men) were compared with 35,045 native-born Danes (23,445 women, 11,589 men) drawn by random from the Danish Civil Registration System. They were matched to the patients with MS by sex, year of birth and residential municipality and being alive by January 1st in the reference year, which was the year of clinical onset of MS of the corresponding MS case.

In this study, we found that more female cases than controls were childless or had fewer childbirths than controls before the reference year ($P = 0.018$). This difference was exclusively attributed to the last 5-year period before the reference year and was not significant for the periods >10 years and 10–5 years before the reference year. The odds ratio for having given birth to one child within 5 years before reference year was 0.54 when adjusting for educational level, age at reference year and use of contraceptives. The odds ratio of 0.54 indicates that pregnancy reduced the risk of MS with about 46%. There was no dose effect as the odds ratio for more than one birth was 0.67. When leaving aside the number of childbirths in the single subject, the probability of having given birth within 5 years before clinical onset was lower in patients with MS than in controls with an OR = 0.61 (95% CI 0.50–0.74, $P < 0.0001$). In comparison, the risk of MS was not influenced by parity in any of the periods in men. The parental age at the birth of the first child had no effect on the risk of MS neither in women nor in men.

Even pregnancies terminated at an early stage had a protective effect on the risk of developing MS, suggesting a temporary immunosuppression during pregnancy. Induced abortions within 5 years before clinical onset were also less common in cases than in controls (4.6% vs 6.4%) and reduce the risk of MS with an OR = 0.70 (95% CI 0.51–0.86, $P = 0.026$). The analysis was performed by including onset age, education and use of oral contraceptives as covariates. There was, however, no difference between cases and controls as to the occurrences of non-induced abortions (4% vs 4.7%, $P = 0.37$). The use of oral contraceptives and pregnancy complications were not more common in cases than in controls.

Hypothetically, the reduced number of childbirths before the clinical onset of MS could be explained by reversed causality: The true onset of MS may in some patients precede the defined clinical onset by years and affect the social behaviour including the choice of being pregnant because of fatigue or subtle cognitive changes. If so, other social determinants could also reflect these changes. However, there were no significant changes in educational level, mean annual income or stability of partnership in the 5 years before the reference year. Thus, there were no indications that preclinical social effects of MS could explain the high reduction of the number of childbirths in this period in the female patients with MS. Accordingly, reverse causality probably only plays a minor role if any. The evidence of a beneficial effect of childbirths on the risk of MS is growing. However, some studies reported similar beneficial effects of having newborn children for both men and women (4, 5). Therefore, it was discussed whether the influence is due to other biological mechanisms, reverse causation or social factors. Hedstrom et al. (5) argue that reverse causation may account for a low frequency of childbirth in patients with MS before onset, a relationship not seen 10 years or more before onset of MS. However, nothing contradicts that the effect may wear off within some years. Moreover, in the Danish study (3), no effect of fatherhood on the risk of MS was found, which in itself weakens the notion of reversal causality. Therefore, pregnancy probably has a biological protective effect lasting up to approximately 5 years. However, there could be hypothetical unknown factors that independently increase the risk of MS and reduce fertility. Among women, 85 cases (9.1%) and 1824 (7.8%) control persons were diagnosed with female infertility ($P = 0.15$), but only one female case (0.1%) and 36 (0.2%) female controls were registered to have undergone artificial insemination. Fewer male index persons were diagnosed with infertility; 11 cases (2.4%) and 197 (1.7%) controls had a diagnosis of male infertility ($P = 0.27$). Infertility treatment in women before clinical onset had no influence on the risk of MS ($P = 0.71$).

Another effect that could confound the apparent effect of childbirths is that exposure to young children in the household could by itself affect the immune system by multiple infections, brought home by the children from kindergartens. We had the opportunity to test this hypothesis (6) as the high frequency of divorces and establishments of new relationships in the Danish population would result in a number of nulliparous women living together with non-biological children in the household. This enabled us to separate the effects of exposure to children from the effect of childbirths. Our study did not demonstrate differences in nulliparous women cohabitating with non-biological children between cases and controls. Of the 310 nulliparous female patients with MS, 86.1% had been domestically exposed to non-biological children for at least

3 years and the corresponding figures for female controls were 86.8% of 7193 ($P = 0.66$). Cohabitation with non-biological children in adulthood, and thereby more frequent exposures to infections, did not influence the risk of MS in any of the genders.

The decreasing birth rate of Danish women may have its share in the increase of incidence of MS in women, but quantitatively it is not the full explanation. The birth rate in Denmark decreased from 1.92 in 1973 to 1.75 in 2004, and the age at giving birth to the first child has increased in Denmark from 23.7 years in 1970 to 29.1 in 2011.

In another study, we investigated the role of other physical and socio-economic factors using the same database (6) to clarify whether environmental factors deriving from the modern lifestyle have affected the genders differently and have contributed to a higher risk for developing MS in women. However, distribution on educational level was the same in female patients with MS and controls.

One of the possible interesting explanations for the increased risk of MS is the hygiene hypothesis (7). This theory proposes that the risk of MS may be higher in individuals with a high level of sanitation and thereby reduced bacterial, viral and parasitic infections during their childhood.

Over the past century, Danish people have experienced improvements in household amenities, smaller family sizes, and higher standards of personal cleanliness, hygiene and sanitation that have reduced the likelihood of cross-infections among family members.

Puberty is the supposed key risk period of life, where environmental factors exert their influence on disease development, particularly in females (8). In our study (3) housing conditions and sanitation during puberty were similar for cases and controls between 10 and 15 years of age, and both cases and controls were exposed to the same good level of hygiene. Only 0.4% of the female cases and similarly 0.4% of the female controls lived under insufficient sanitary conditions, and for males, the figures were 0.4% and 0.3%.

The risk of MS was not associated with the educational level prior to clinical onset in Danish men or women (6). Over the last 50 years, women have been employed in various industrial sectors which were previously reserved for men; therefore, investigating the influence of occupational exposure on the risk of MS in women is a topic of much interest. The risk of MS was not correlated with occupational categories such as craftsman work, working in the health sector, in chemical industries or with organic solvents, except for a higher frequency in outdoor work or employment in agriculture, but this only involved six or 12 MS cases, respectively (6). When investigating exposure to outdoor work, we found the opposite of what we expected, as outdoor exposure seems to be associated with a reduced risk of MS (9, 10), but further investigations pointed to an overlap between exposure to outdoor work and the agricultural sector. The aetiologic fraction is negligible although the association was statistically significant. The study of occupational exposures did not have the statistical power to show a strong association between occupational exposures and the risk of MS. However, a relative high frequency of MS was recently reported among persons working in the agricultural sector. In particular, dairy operating (11), farming and exposure to livestock were shown to increase the risk for the first demyelinating symptom (12).

Denmark is not a country where social disparities are predominant. Cases as well as controls from all social strata have been exposed to better socio-economic conditions than earlier generations, and the risk of MS does not seem to be associated with measurable social factors. Socio-economic indicators are sometimes strongly linked to lifestyle and can vary by country and geographical area, which can further complicate epidemiological studies. It seems that in the case of MS, the epidemiological picture is more complicated.

Our studies (3, 6) were solely based on public register data and not interviews. Thus, the results could not be biased by false memory or by incomplete or differing response rates between cases and controls. However, the results are only applicable to the Danish population and cannot be expanded to countries with different social structures.

Acknowledgement and source of funding

Economic support was obtained from the Danish Multiple Sclerosis Society.

Conflict of interest

MM has served on scientific advisory board for Biogen Idec and TEVA; has received honoraria for lecturing from Biogen Idec, Merck Serono, Sanofi-Aventis, TEVA; and has received support for congress participation from Biogen Idec, Merck Serono, Novartis, and Genzyme.

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