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Linköping University Post Print



N.B.: When citing this work, cite the original article.

Original Publication:

Inger Boström and Anne-Marie Landtblom, Does the changing sex ratio of multiple sclerosis give opportunities for intervention?, 2015, Acta Neurologica Scandinavica, (132), 42-45.

<http://dx.doi.org/10.1111/ane.12430>

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<http://eu.wiley.com/WileyCDA/>

Postprint available at: Linköping University Electronic Press

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-119782>

Review

Does the changing sex ratio of multiple sclerosis give opportunities for intervention?

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Key words: environmental; multiple sclerosis; sex ratio

Short title:

Changing sex ratio of MS

Abstract

In several international studies an increasing women to men (w/m) ratio in patients with multiple sclerosis (MS) has been reported. Such sex ratios have been analysed by year of onset or by year of birth. In a Swedish study data from the Swedish MS register (SMSreg) were used to analyse the w/m ratio in Sweden. The sex ratio was analysed both by year of birth (8834 patients) and by year of onset (9098 patients). No increased w/m ratio was seen in this study. The age-specific sex ratio did not demonstrate any significant changes. However, a new investigation of the sex ratio in Sweden, based on data from all available data sources (19,510 patients) showed a significant increased w/m ratio of MS in Sweden from 1.70 to 2.67. Environmental factors like cigarette smoking, hormonal factors and nutrition are of interest in this context, but the cause of the increasing w/m ratio in MS is yet not possible to explain.

Introduction

The evident increase of the women to men (w/m) ratio in multiple sclerosis (MS) may be the effect of environmental factors and, theoretically, give opportunities for intervention, given that we can demonstrate the social/biological explanations for this change. Modern trends in the life of young females in the Western world must be taken into account when analysing these associations. Examples of such potential factors of interest are hormonal factors, such as age at first child-birth, number of pregnancies, use of contraceptives and breast feeding, as well as social factors such as stress, shift work, migration and finally nutrition with contents of vitamin D as well as habits of tobacco smoking and use of alcohol. Our studies mainly focus on the temporal development of w/m ratio of patients with MS in Sweden.

Sex ratio

The sex ratio in MS has been reported in several recent prevalence and incidence studies showing an increasing predominance of women (1-3). There are, however, some problems when comparing these sex ratios studies because of variations over time in diagnosis procedures, accessibility to medical equipment and furthermore, the representation of different periods in time.

In 2006, Orton et al presented a study of Canadian MS patients, with a focus on the sex ratio analysed by the patient's year of birth (4). They showed a significant increase in the w/m ratio ranging from 1.9 to 3.2 from birth cohort 1931 to 1980. This study attracted much attention and has been cited in many articles.

At this time, our research group had recently published data from a prevalence study of MS-patients in the Swedish county of Värmland (5). The data was collected through medical files from all hospitals and primary health care centres in the county. On the prevalence day of 31st December 2002 there was a total of 465 patients. Subsequently, we could calculate a very crude estimate of w/m ratio by year of birth. We did not find any increase of the w/m ratio that supported the Canadian findings (data not published).

We wanted to take this further by analysing the Swedish national sex ratio - both by year of birth and by year of onset. To do this, we used the possibility to take data from the Swedish National MS patient register (SMSreg). This register eventually developed into a web-based data base. The register developed from the larger MS clinics in Sweden but within a decade it reached an impressive coverage in the country. For the analysis of the sex ratio by year of birth, all persons registered until April 2010 were included. This was altogether 8834 patients, 6271

women and 2563 men, born during the time period 1931 to 1985. For the calculation of sex ratio by year of onset the study covered the time period 1946 to 2005 involving 9098 patients, of which 6452 were women. This national study did not find any increase of the w/m ratio analysed by year of birth or by year of onset (6).

As a control of the validity in MS sex ratio we again used the data from the prevalence study in the county of Värmland⁵ and did a careful analysis of sex ratio by year of birth during the period 1931-1975. No clear increasing trend was seen ($r=0.383$, $p=0.308$, $n=9$) and it could not be observed for the year of onset during the time period 1968-2002 ($r=0.000$, $p=1.000$, $n=8$) either (6).

However, we noticed an increased morbidity of MS in the birth cohorts from 1931 to 1960 for women and from 1931 to 1955 for men and a decreasing trend for the later birth cohorts (6). This is probably due to the fact that persons in the later cohorts (1956 to 1985) still have not got MS.

Since the w/m ratio increased in the birth cohorts 1976-1980 and 1981-1985 one may speculate that there could be a difference in age at onset between the sexes. This question gave us a reason to analyse the age at onset using year of birth and sex. The age at onset showed a decreasing trend from year of birth 1931 to 1985 but equal trends for both sexes. The mean age of onset decreased in women from 39.0 to 20.9 years of age, and for men it decreased from 41.2 to 21.3 (6).

So far all our data from Sweden showed a rather stable sex ratio and did not support the increased w/m ratios reported from Canada (4).

We now started focusing on potential social and biological changes that could have had an impact on the susceptibility to MS, and that may differ between Sweden and the countries reporting an increased w/m ratio. Such changes may, for example, be late childbirth in life, hypothesising that early childbirth may be protective for MS (3). Another study on hormonal factors in MS included women who had used combined oral contraceptives (COC). This study showed a potential influence on the risk of MS where women who used COC had a higher age at onset compared to those not using COC (7).

If hormonal factors have an effect on the susceptibility to MS, it is reasonable to suspect that changes of such factors may influence the proportion affected individuals among the fertile women. For this reason we stratified our national data and added an analysis of age-specific sex

ratio by year of onset (8). The result showed a variation of the w/m ratios in all age groups, but the w/m ratio in Sweden still did not demonstrate any significant changes.

Later, a new analysis of sex ratio was performed, by Westerlind et al (9). In this study data from SMSreg and the National Inpatient register (PAR) were used. Data from the Cause of Death Registry was also included. In total 19,510 persons were included in this study, distributed over 13,321 women and 6189 men born in 1931 to 1985. This study showed a distinct increased w/m ratio of MS in Sweden, from 1.70 for patients born in the 1930ies to 2.67 for patients born in the 1980ies. This gave a significant increased w/m ratio, p-value < 0.01, a similar trend to that reported from Canada, see Figure 1 (4). When comparing the coverage of our previous Swedish study⁶ with the latest data, a significantly higher proportion of women were found in the SMSreg in the group born in 1931-1935 (9). A likely explanation to the non-increasing w/m-ratio in the SMSreg is that a higher proportion of men had died before the start of SMSreg, thus resulting in a skewed distribution of the sexes. One may observe that the cohorts born in 1976 - 1985 still are young and because men have a later onset⁶, the sex ratio may change in the future into a lower one.

Environmental factors

The impact of environmental factors on the susceptibility to MS has been highlighted in many studies and smoking is well established as a risk. The Swedish National Institute of Public Health (Folkhälsoinstitutet) has from 2004 yearly presented data of smoking behaviour (10). About 10 % of all women and men in the age group 65-84 years report that they smoke daily, a trend that was stable during the years 2004-2012. In all younger age groups a larger proportion of the women report that they smoke daily. In fact, the largest proportion is in the age group 45-64 years, where in the beginning of the 21st century about 20-25% of the women smoked, compared to 15-17% of the men. After this, there is a decreasing trend for both sexes (see Figure 2). This may theoretically to some extent explain the increase of MS among women, but there is of course need for further studies to analyse the impact of smoking on the increasing w/m ratio.

In the context of an oral presentation about environmental factors relevant to MS in Sweden (11) we used the prevalence (170/100 000) in the county of Värmland to investigate food habits (5). We identified two studies that had investigated food habits in Sweden using questionnaire data, but we were not able to find data for detailed analyses of Värmland. However, for the

nation of Sweden in the end of 90ies (12), the data showed that men had a higher intake of vitamin D and fat, compared to women. For vitamin D, young women (aged 17-24) had an intake of 4.1 microgram/day which is somewhat below the recommended minimum. This is interesting in view of the new findings that lack of vitamin D clearly influences the risk of getting MS (13).

In our latest Swedish national study of sex ratio (9) demonstrating an increase of the w/m ratios we also attempted to analyse if a higher age at the first child birth would explain the increase. We investigated this by calculating the mean age at first childbirth for the female MS patients and compared this to the general population. An increase of this age was seen between the birth cohorts, but as no difference between MS patients and the general population was seen, this can primarily be ruled out as an explanation for the increase in MS in females. A similar finding was also made in studies from Denmark (14).

However, we do not believe that these observations completely rule out an effect caused by hormonal factors and further studies are needed.

An environmental factor related to nutrition is development of body weight. A general investigation by Statistics Sweden (15) (Statistiska Centralbyrån) has shown that the proportion of men with Body Mass Index (BMI) > 25 in the age group 16-84 has increased from 35% to 55% during the years 1980-2011. For women in the same group the increase was somewhat less, from 27% to 40%. This data is very crude and cannot be used to explain an increase in the sex ratio. The EnvIMS study in Norway and Italy (16) showed that obesity is a risk factor for MS but no significant interaction was seen between body size and sex. The same observation was made in a Swedish study where high BMI at age 20 doubled the risk of MS both in men and women (17). In a recent Danish prospective cohort study, the result showed a stronger effect of obesity on the risk of MS in the age group 7–13 years among girls compared to boys (18).

In conclusion the knowledge so far admits us to suspect environmental influences as a cause of the increasing w/m ratio in MS, but these influences have not yet been possible to explain. There is therefore so far no solid ground for interventions. The continuation of research regarding cigarette smoking, hormonal factors and nutrition is important, both in small samples and in national registers.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

None

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Figures

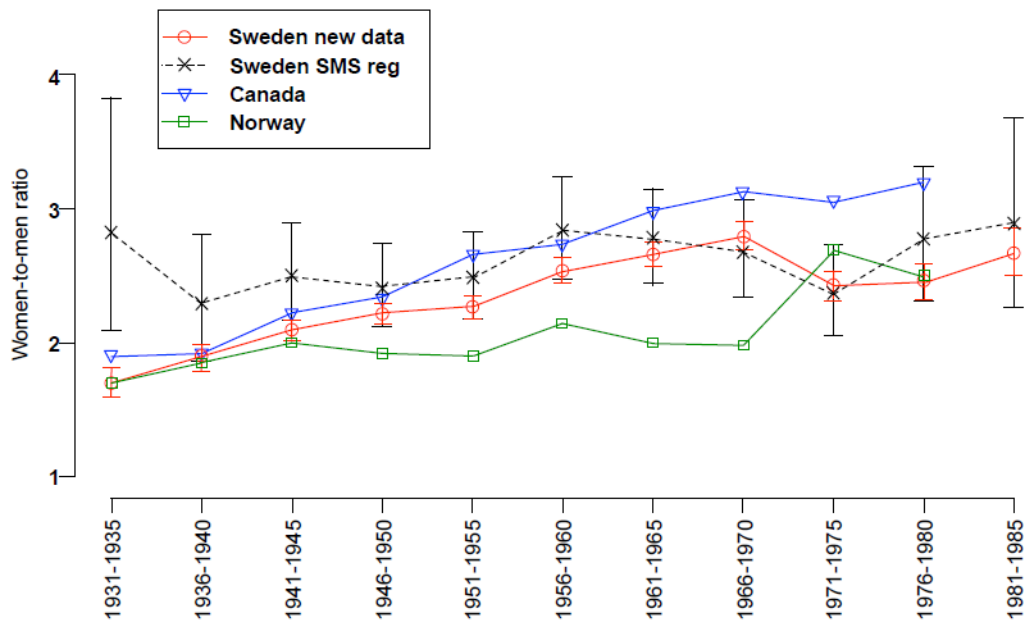


Figure 1. Sex ratios of multiple sclerosis in Sweden, analysed by year of birth from 1931 to 1985 in the previously (6) and the latest Swedish national study of sex ratio (9) and the sex ratios from Canada (4). (Reprinted from Westerlind et al. 2014. Published with permission from Sagepub).

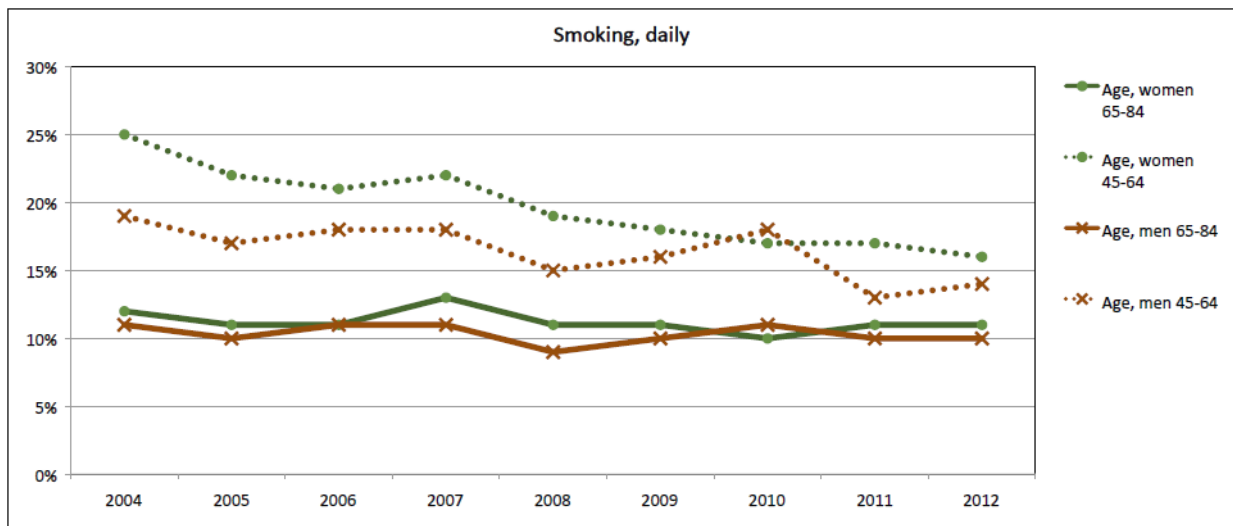


Figure 2. Women's and men's daily smoking behaviour in two age-groups during 2004 to 2012 in Sweden. Figures from The Swedish National Institute of Public Health. Folkhälsoinstitutet (10).