An interesting feature that multiple sclerosis (MS) shares with many other immune-mediated diseases is that susceptibility is higher in females than males.\(^1\)\(^2\) However, the female-to-male ratio (sex ratio) of MS appears to vary significantly in time and space.

A recent meta-analysis of epidemiological studies has shown that the worldwide sex ratio of MS has been substantially increasing over the last century.\(^3\) This increase is particularly clear in large population-based studies from Denmark and Canada.\(^3\)\(^4\) In the latter, the sex ratio of MS patients born in the 1930s was lower than 2 and then increased to more than 3 females for each male patient in the latest birth cohort analysed (1976–1980).\(^4\) This intriguing epidemiological phenomenon warrants particular attention since the sex ratio of MS parallels MS incidence and the increasing frequency of MS among females is a key driver for the worldwide increasing prevalence of this devastating disorder.\(^1\) A change occurring within a century is too short a time for a genetic cause, suggesting that environmental factor/s are at work in a sex-specific manner.

In this issue of the *Multiple Sclerosis Journal*, Boström and colleagues investigate sex ratio trends of MS in Sweden using data from several thousand MS patients identified through the National Swedish MS register. Mean sex ratios were 2.62 in the analysis by year of birth (performed between 1931 and 1985) and 2.57 in the analysis by year of onset (performed between 1946 and 2005). In both cases sex ratio figures appeared stable and no increase with time was observed. While these findings appear to be in conflict with those reported by the studies mentioned above, several considerations are warranted.

First, comparing results obtained from different countries is not always straightforward and when assessing temporal trends the baseline characteristics need to be taken into account. Boström and colleagues report sex ratios which are consistently above 2 while in both the Canadian and Danish data baseline sex ratios were considerably lower. Perhaps the environmental factor driving the increasing sex ratio of MS in Canada and Denmark was already present at baseline in Sweden. Alternatively this putative agent may be less able to increase female incidence in a population in which the latter is already relatively high.

Second, even when baseline levels are similar, inter-country differences should not be too surprising since environmental factors can vary substantially between regions and their effect is likely modified by the genetic background of the population. When studies are well performed and statistically powered like that of Boström et al., conflicting results can actually greatly aid the identification of the environmental agent responsible for the investigated phenomenon.

However, what are the environmental agent/s influencing the sex ratio of MS? An interesting hypothesis comes from a recent Australian study which found that a higher number of offspring was inversely associated with the risk of a first clinical demyelinating event among women but not men.\(^5\) Although other studies have investigated how pregnancy modifies the risk of MS and reported conflicting results,\(^6\)–\(^9\) older age at birth and reduced offspring number could contribute to the increasing sex ratio of MS. Figure 1 shows temporal trends in fertility rates (average number of children that would be born to a woman of reproductive age) in Canada, Denmark and Sweden in the last century obtained from national statistics agencies. The most remarkable increase in MS sex ratio has been observed in Canada starting from the birth cohort 1941–1945.\(^5\) Since these women will be likely to give birth between the 1960s and 1970s, the dramatic increase in sex ratio is parallel to the steep decrease in fertility rates among Canadian women. Similarly in Denmark the increasing sex ratio observed in the second half of the 20th century is associated with a substantial reduction in fertility rates.\(^3\) However, fertility rates have also decreased in Sweden but based on Boström and colleagues there has been no concomitant increase in the MS sex ratio. Whilst reproductive history may well have an influence on female susceptibility to MS, this single factor is unlikely to entirely explain temporal trends in the MS sex ratio.

Vitamin D deficiency, Epstein–Barr virus (EBV) infection and smoking history are known to influence MS risk and therefore represent additional plausible candidates.\(^10\)–\(^14\) Unfortunately sex-specific reliable longitudinal data on both vitamin D deficiency and EBV infection are lacking and it would be extremely useful to investigate their secular trends in those countries in which temporal MS sex ratio figures are available. Interestingly, a recent study has shown how trends in sex ratio of smoking behaviour in both Canada and Denmark strongly correlate with sex ratio.
Multiple Sclerosis Journal 19(1)

changes of MS. However this was mainly driven by a decline of smoking among men and cannot therefore fully explain the increased incidence of MS among females. Further, the smoking trends in Sweden are similar to Denmark and Canada. The sex ratio of MS currently remains an intricate puzzle with no clear solution as yet. Future research is urgently needed to understand the environmental factor/s involved in order to aid disease prevention strategies.

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References

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Figure 1. Changes in fertility rates in Canadian, Danish and Swedish women.