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Why does the north–south gradient of incidence of multiple sclerosis seem to have disappeared on the Northern hemisphere?

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ABSTRACT

The traditional view, based on numerous early studies and reviews, is that MS is particularly prevalent in temperate zones both on the northern and southern hemisphere. This uneven distribution of MS can be attributed to differences in genes and environment and their interaction. Diagnostic accuracy and case ascertainment are sources of error and have their shares in the geographical and temporal variations, and improvements in diagnostic accuracy and case ascertainment influence incidence- and prevalence rates. In addition the prevalence also depends on survival. With this meta-analysis we have focused on the trend in the incidence and sex ratio of MS through the last five decades, and we have analyzed the latitudinal distribution of MS incidence, based on a recent literature search. Our findings indicated that the prevalence and incidence rates had increased in almost all areas, but the previously reported latitudinal gradient of incidence of MS in Europe and North America could not be confirmed even when restricting the search to surveys published before 1980 or 1970. Conversely, the latitudinal gradient of prevalence rates seemed to be preserved. This apparent discrepancy can be explained by the circumstance that incidence estimates only depend on complete ascertainment for a relative short recent period of time, whereas reliable prevalence rates presuppose complete ascertainment decades back in time. A contributory explanation for the missing latitudinal gradient for incidence may be changes in environmental factors, levelling out differences in habits of life across Europe and North America, and, not least, that the interpretation of a latitudinal gradient in Europe was based primarily on prevalence studies and reviews.
In addition, we observed in most regions a profound increase in female incidence of MS. The last observation should prompt epidemiological studies focusing on change in female life style.

1. Introduction

One of the most striking epidemiological characteristics of MS is the apparent uneven distribution of the disease across the world. The traditional view, based on numerous early studies and reviews, is that MS is particularly prevalent in temperate zones and, conversely, less common in subtropical zones, and uncommon in tropic zones [1]. Hence, both on the northern and southern hemisphere the characteristic pattern have been increasing prevalence towards the poles, although deviations from this pattern can be seen both on in Europe and North America as well as in Australia and New Zealand. This distribution suggests that interplay between three factors, which are not easily separated, is in effect: the genetic composition in a population, geographically determined environmental factors, and socio-economic structure, including access to medical facilities.

As a population gene pool is stable apart from what could be caused by migration and selection, short-term marked changes in incidence of MS, if true, will have to be caused by changes in etiologic environmental factors and/or socio-economic aspects.

The availability of medical service has a profound impact on the diagnostic accuracy and ascertainment probability, and these factors have improved in most parts of the world and have been more uniform throughout the last three to four decades.

As the incidence of MS peaks at about 35 years and the prevalence about 50 years of age the crude incidence and prevalence rates also depend on the population's age distribution. In recent decades, adjustment of rates by standardization to a hypothetical standard population has been more common in incidence- and prevalence studies. A recent study indicated that the latitudinal effect on adjusted prevalence has weakened, and that the latitudinal effect on incidence could not survive standardization [2], seriously challenging a latitudinal effect on the northern hemisphere within the latitudinal range studied (40–60° N).

In this review we have focused on the changes in incidence, prevalence, and sex ratio through the last decades and discuss whether the established north–south latitudinal gradient on the northern

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hemisphere truly has disappeared and the possible causes for this change in geographical distribution.

2. Methodological considerations

From articles retrieved from PubMed, published since 1965 in English language with the terms multiple sclerosis and incidence or prevalence in title or abstract, supplemented by the authors' personal archives, we selected 228 original articles, in which the words incidence or prevalence referred to the frequency of the disease. Only papers using approved diagnostic criteria, applied by their authors or by other neurologists, were included in graphs and analyses.

Incidence and prevalence figures are liable to stochastic variation, differences of diagnostic criteria, inclusion of possible MS cases, ascertainment errors, selection bias, and age and sex adjustment. The stochastic variation depends on the number of cases included in a study. Many of the surveys have been rather small and have lacked statistical power. Hence, we excluded prevalence studies with less than 20 prevalent cases and incidence studies with less than 10 incident cases because of the high variance of these estimates. Accordingly, studies in which numbers of prevalent or incident cases were not shown were also excluded.

Incompleteness of ascertainment may play an important role in studies based on hospital records. Selection bias can occur if an *a priori* impression of the prevalence and incidence is anticipated, or if the studied samples have not been population-based. Also lack of age and sex adjustment to a common standard population may introduce bias that, however, in most cases insignificant or even negligible.

We plotted prevalence- and incidence rates against latitude and year and analysed the effect of latitude and time on the prevalence and incidence estimates using weighted linear regression analysis with the square root of number of cases as weight. For incidence surveys, time was defined as the midpoint of an incidence period. Latitude was determined using Google Earth. The software SPSS v. 19 was used for the calculations. The results presented in this article are mainly based on a meta-analysis published in 2010 by the present authors [3] with addition of a few recently published epidemiological studies [4,5]. A full list of references for the studies included in the meta-regression analyses will be available at the journal web site.

3. Geographical distribution

3.1. Prevalence rates

Fig. 1 shows the prevalence estimates in studies from Western Europe, (Panel A), North America (Panel B), and Australia and New Zealand (Panel C) plotted by geographical latitude. The weight

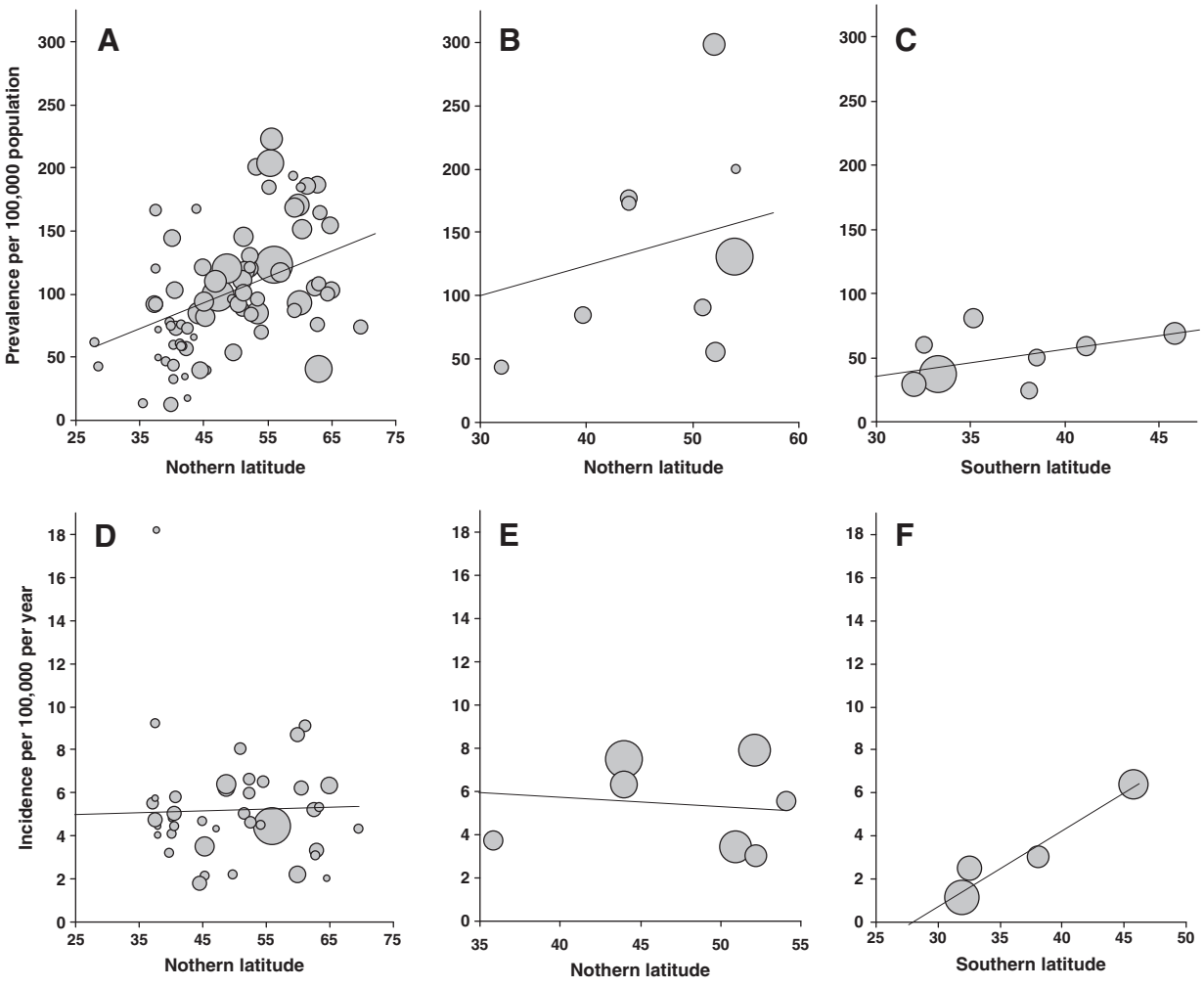

Fig. 1. Variation of prevalence and incidence with latitude in three continents. The areas of the bubbles are proportional to weight (square root of number of cases). Weighted regression analyses and regression lines. A: Prevalence by latitude in Western Europe. $R^2 = 0.147$; prevalence increase 0.70 per 100,000 per degree latitude; $p = 0.001$. B: Prevalence by latitude in North America. $R^2 = 0.129$; prevalence increase 3.44 per 100,000 per degree latitude; $p = 0.31$. C: Prevalence by southern latitude in Australia and New Zealand. $R^2 = 0.291$; prevalence increase 2.08 per 100,000 per degree latitude; $p = 0.17$. D: Incidence by latitude in Western Europe; $R^2 = 0.001$; incidence increase: 0.009 per 100,000 person years per degree latitude; $p = 0.79$. E: Incidence by latitude in North America. $R^2 = 0.009$; incidence increase: -0.035 per 100,000 person years per degree latitude; $p = 0.84$. F: Incidence by southern latitude in Australia and New Zealand. $R^2 = 0.93$; incidence increase: 0.352 per 100,000 person years per degree southern latitude; $p = 0.024$.

of each result is illustrated by the sizes of the bubbles (proportional to the square roots of number of cases). It appears that the latitudinal effect is modest in Europe and North America while prevalence did not vary significantly with latitude in Australia and New Zealand ($p = 0.17$; Fig. 1 panel C).: In Europe and North America linear regression meta-analyses for the two continents together, including prevalence year and weighted by the square root of number of cases in the individual surveys, resulted in a statistical significant but weak association between prevalence and latitude with a regression coefficient of 2.114/100,000 per degree latitude ($r^2 = 0.118$; $p = 0.001$:;) which is in accordance with a recent review [6]. Prevalence rates exceeding 200/100,000 were seen in some studies at high latitudes (>55° N), [7–10] but even values than 50/100,000 have been found in single cases north to 55° N. [10] Examples of aberrant prevalence rates are Samis in northernmost Norway [11], in whom only a couple of cases has been diagnosed, far fewer than expected from the MS prevalence in the local Caucasian population, and the paucity of MS cases among the Maori population of New Zealand [12].

Prevalence rates invariably increased with repeated surveys in the same area for several reasons. One reason may be "first survey under ascertainment": The first survey may have missed cases diagnosed decades earlier, whereas the new survey has included new cases accumulated with time, making the effect of missing old cases, some of which may have died, less important, and the new figures will approximate a true prevalence. Prevalence as well as incidence estimates have also increased as a result of better access to medical facilities in most countries. New diagnostic criteria provide the diagnosis at an earlier time in the disease course, and in particular the revised McDonald diagnostic criteria [13] may have led to earlier diagnosis. A true increase in prevalence or incidence must surpass these trends to be recognized as a true increase in frequency. A main reason for increase in prevalence rates is the increased life-expectancy for people with MS.[14] Hence, as prevalence rates are inflated by longer survival, a true increase will not necessarily reflect a higher risk of the disease, making incidence is a better parameter to identify increase in population disease risk.

In Western Europe and North America, prevalence rates, observed in recent years, indeed tend to be higher than rates observed decades ago (Fig. 2, panel A). The correlation of prevalence with time is rather weak albeit statistical significant, weighted regression coefficient: 1.29/100,000 per year ($r^2 = 0.12$; $p < 0.001$), at least for the reasons stated above. However, latitude seemed to confound the correlation negatively, as correlation between prevalence and time was more pronounced when analysed for high and low northern latitudes separately: Below 52° N the weighted regression line slope was 1.53/100,000 per year; $r^2 = 0.12$; $p = 0.006$;:; at or above 52° N: regression coefficient: 1.99/100,000 per year; $r^2 = 0.28$; $p < 0.001$.).

3.2. Incidence rates

The incidence rates for Western Europe are shown in Fig. 1, (Panel D). The latitudinal effect is apparently non-existing with a zero regression coefficient ($r^2 = 0.001$; $p = 0.79$). Including year in the analyses gave an insignificant effect of 0.037/100.000/degree latitude ($r^2 = 0.19$; $p = 0.26$).

In North America (Fig. 1, panel E), r^2 and the regression coefficient was close to zero with $p = 0.84$ and it did not change when time was included.

On the southern hemisphere (Fig. 1, panel F) most of the observations stem from New Zealand and Australia. There is a clear trend that incidence increases with southern latitude both in New Zealand and in Australia. These studies are particularly important, as the Caucasian populations in New Zealand and in Australia are quite homogenous with the same British ancestry when leaving aside the Maoris and Aboriginals, in whom the rates were low. The incidence rates varied significantly with rather high regression coefficient of 0.36 per 100,000 per year per degree southern latitude; $p = 0.02$; $r^2 = 0.96$. This strong latitudinal trend on the southern hemisphere is also supported by an incidence study from New Zealand [15] showing a marked increase of incidence over the just 13 degrees of latitude which the country spans over. This study was not included in the meta-analysis because it lacked detailed information on number of cases. A recent study from the east coast of Australia [16] showed a significant increase of incidence of a first demyelinating event (clinically isolated syndrome (CIS)) with degree of southern latitude. The increase was estimated at 9.5% per degree southern latitude. As CIS not necessarily is leading to MS we did not include this study in the meta-regression analysis.

We found only one incidence study from South America [17], showing an incidence rate of 1.76 per 100,000 per year in a selected sub-population, and no data on a latitudinal gradient of the incidence are available, but a recent study showed a strong latitudinal gradient in prevalence of the disease [18].

As well as prevalence, incidence also increased with time. For Western Europe and North America combined the increase in

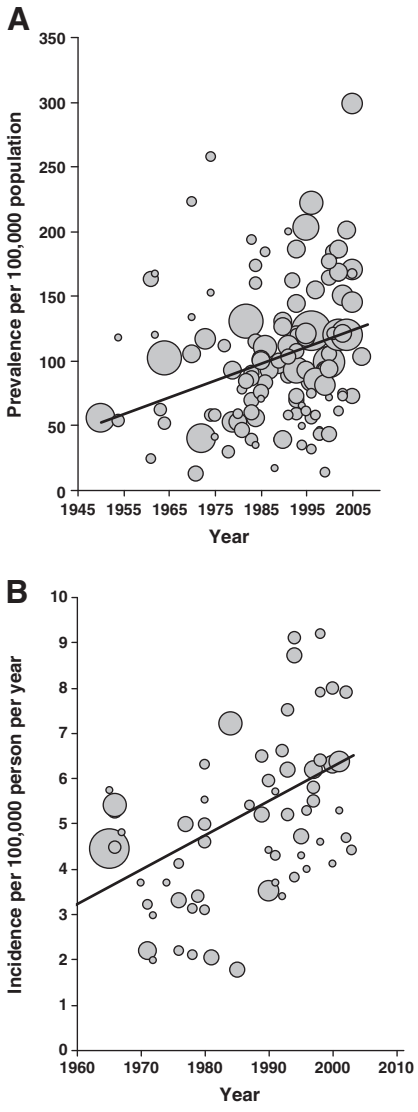

Fig. 2. Variation of prevalence and incidence with time. The areas of the bubbles are proportional to weight (square root of number of cases). Weighted regression analyses and regression lines. A: Prevalence by year in Western Europe and North America. $R^2 = 0.12$; prevalence increase per year: 1.29 per 100,000; $p < 0.001$. B: Incidence by year in Western Europe and North America. $R^2 = 0.19$; Incidence increase per year: 0.076 per 100,000; $p < 0.001$.

incidence per year: was 0.076 per 100,000; $r^2 = 0.19$, $p < 0.001$ (Fig. 2, panel B). Inclusion of latitude in the regression analysis made little difference. (Fig. 2, panel B).

We examined 24 cases of incidence studies that had been repeated after some years or decades in the same population. Leaving aside unsystematic random fluctuations, the incidence increased in all of them except in Orkney [7, 19], Shetland [7, 20], and Gothenburg, Sweden [21].

It is a crucial question whether these observations represent true increases in incidence or better ascertainment and more rapid diagnosis. Three factors may have made an early diagnosis more probable throughout the last decades: First, the use of MRI as a standard tool whenever MS or CIS are suspected; second, disease modifying treatments have made early diagnosis warranted as opposed to earlier times reluctance to give the MS diagnosis in younger people without present disability; third, the use of the more sensitive McDonald criteria for MS during the recent years, which, however, does not seem to have increased the number of MS diagnoses but may have hastened them. Review of diagnosis in epidemiological studies is normally based on scrutinizing existing clinical records without the possibility of making new examinations let alone new MRI. Thus, it is not probable that the new criteria have influenced the incidence- or prevalence estimates to any detectable extent.

Migration might modify trends in incidence. As most immigrants to Europe come from areas with low risk of MS, migration might counteract the general tendency of increasing incidence. However, this effect has not been significant in the previous decades as the number of second-generation immigrants reaching the age of risk has been rather small, and even if it will ever become important, it will level out with time because of adaptation of the risk, shown in several studies.

4. Interpretation of changes in geographical distribution over time

We could not demonstrate the expected latitudinal gradient of incidence rates of MS on the northern hemisphere. There could be several probable explanations for this observation. Table 1 gives an overview of factors that might have contributed with various magnitudes.

The question is whether there has ever been a true north–south gradient of incidence. Even restricting the incidence/latitude meta regression analysis to the time before 1980 or even 1970 did not reveal any latitudinal effect either. If the north–south gradient could not be demonstrated for the incidence rates, the north–south gradient for prevalence can only reflect immigration and differences in survival and the fact that prevalence estimates are more sensitive to incomplete ascertainment of older cases.

One of the physical effects of latitude is influx of ultraviolet radiation that is associated with a lower risk of MS. An important study of regional variations of MS in French farmers confirmed an uneven distribution of MS with latitude [22]. Further analyses of these data showed that the prevalence of MS in France correlated best with the known geographical distribution of solar ultraviolet radiation [23, 24]. Also in Bulgaria an association was found, not with latitude but with regional annual sunshine hours [25]. A Norwegian study indicated that summer outdoor activities in childhood and adolescence were associated with a reduced risk of MS even north of the Arctic Circle [26]. However, exposure to sunlight also varies with cultural habits, *e.g.* Northern Europeans exploiting the scarce sun in the summer at beaches, scantily dressed, or vacationing at the Mediterranean beaches, and, on the other hand, many South Europeans will protect themselves against the sun. These habits could tend to level out a possible radiation effect.

The proposed and apparent effect of ultraviolet radiation may have biological rationales as the production in skin of vitamin D3, which is believed to have immunomodulatory effects in MS. High serum levels of vitamin D3 seem to have a protective effect against MS [27] in accordance with the observation that dietary vitamin D probably has a similar effect. [26, 28] In addition, solar radiation may also act through a direct effect on immune cells in the skin [29].

The study on incidence of a first demyelinating event in Eastern Australia [16] showed that the latitudinal trend was stronger with optic neuritis than with spinal cord symptoms and it was proposed that direct sunlight exposure to the eyes might have an independent protective effect against optic neuritis. In a case-control study [30] using the same patient population, longer exposure to UV radiation and high serum vit-D3, reduced the odds ratio of a first demyelinating event but the two effects seemed to act independently implying a separate protective effect of UV radiation not mediated by vit-D3.

It is difficult to explain the discrepancy between the missing north–south gradient on the northern hemisphere and the apparent well-established gradient in Australia and New Zealand. Studies from Australia and New Zealand are few in number but with high reliability, and they are based on very homogenous populations of British ancestry. In addition to the preserved latitudinal gradient, the present-day descendants of this British source population living in Australia and New Zealand have a much lower risk of MS (incidence rates 2–4 per 100,000 per year) than the descendants living in the UK (incidence rates 5–7 per 100,000 per year). So, these south-hemisphere data are in imperative support of strong environmental influences on the risk of MS.

5. Sex ratio

Since the middle of the 20th century there has been a steady increase in female incidence of MS that have accelerated during the last decades.

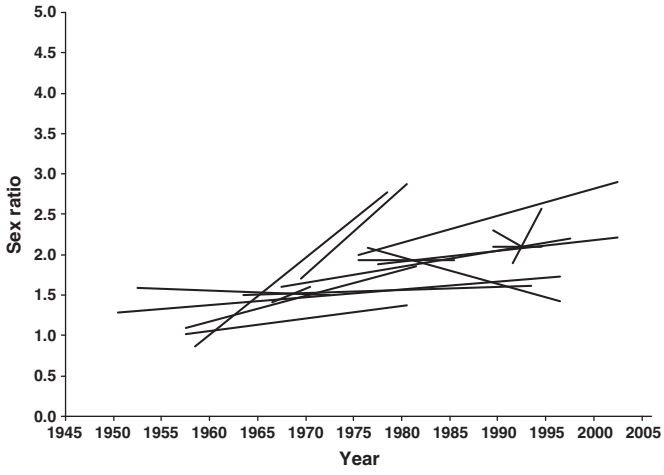

Fig. 3. Change in female:male sex ratio with repeated surveys in the same location.

Table 1
Factors that might have contributed to the apparent disappearance of the north–south gradient in Europe and North America.

1) The north–south gradient has never existed
   - Previous ascertainment errors in southern European countries
   - Selection bias caused by a priori impression of disease frequencies
   - Doubts of the validity of the diagnoses in historical prevalence studies
   - Lack of standardisation to a hypothetical standard population
2) Inflated reported prevalence rates based on estimates or suboptimal methodology in epidemiological surveys
3) Change in genetic composition of the populations
   - Emigration would change the ethnic origin but have probably only played a minor role in Europe
4) Change in environmental factors levelling down north–south differences

Fig. 3 illustrates that sex ratio has a general tendency with few exceptions to increase over time if surveys have been repeated in the same populations years later. In a Canadian study comprising all registered cases in Canada, [31] the female:male sex ratio by year of birth increased from about 1.9 in cases, born in 1936–1940, to almost 3.2 in the latest birth cohort from 1976 to 1980. In Denmark, the incidence rates have been monitored since 1950 through the population-based nationwide Danish MS Registry. [32] The incidence of onset in men has remained virtually constant from 1950 to 2000 apart from a year-to-year stochastic variation, whereas the female incidence of onset has almost doubled since 1970. The female incidence increased for all age groups except teenagers. Recent increase in female incidence of MS has also been reported in Thuringia, Germany, associated with late onset of the disease, [33] in France, [34] in Norway [35], and in Australia [36].

One possible explanation for the increasing sex ratios, indicating an increase of incidence predominantly in women, could be that women in the last decades have been more inclined to seek medical assistance in case of subtle symptoms than men with a more "macho" approach. Another possible explanation could be that benign cases could be more common among women, and that the use of MRI and new diagnostic criteria has identified these benign cases, whereas men having a more severe disease from onset always have had a high probability of an early diagnosis. However, in the Canadian study, showing an increase of female:male ratio, the time from onset to diagnosis did not differ between the sexes, and the Danish incidence figures are based on year of onset rather than year of diagnosis. Hence, in our opinion, this effect could only have a minor share in the female increase, found in Canada, Denmark, or elsewhere. The increasing incidence in females may indicate change in environmental exposure to which only females are susceptible.

A real change in incidence is important, as it will inevitably be attributed to environmental change. However, this change may not be present anywhere and simultaneously and is apparently only true for some of the geographical areas studied. The increase in female:male sex ratio strongly indicates the existence of environmental influence on the risk of MS, but the environmental factors may acti on a population level rather than on the individual level. These observations should prompt epidemiological studies focusing on changes in female life style.

6. Conclusion

The changes in demographic epidemiology of MS through the last decades include an increase in prevalence of MS, predominantly owing to longer survival, a probably true increase in incidence of MS, particularly in women, in many places, and an apparent lack of the latitudinal gradient of incidence in Europe and North America while the latitudinal gradient seemed preserved on the Southern hemisphere. The latter observation is intriguing: if the north–south gradient have existed in Europe and North America, it is difficult to apprehend which changes in genetic or environmental factors that could have levelled down the north–south differences exclusively on the Northern hemisphere. Exposure to sunlight may explain the strong latitudinal gradient in Australia and New Zealand, mediated by skin production of vit-D3, but recent evidence indicates that there is an additional effect of UV exposure independent of vit-D3. Gene–environment interactions may complicate apparently simple epidemiology. Genes may provide differences in susceptibility to environmental factors, but the environment may also influence gene expression. New insight into epistasis and epigenetics has forever made the conception of simple causative associations between genes or environment and MS obsolete.

Conflicts of interest

None.

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