RESEARCH PAPER

Latitude continues to be significantly associated with the prevalence of multiple sclerosis: an updated meta-analysis

Steve Simpson, Jr.,[1,2] Wendy Wang,[3,4] Peter Otahal,[2] Leigh Blizzard,[2] Ingrid A F van der Mei,[2] Bruce V Taylor[2]

ABSTRACT

Objectives Previous studies have demonstrated a strong latitudinal gradient in multiple sclerosis (MS) prevalence. Herein, we present a meta-analysis of the latitudinal gradient of MS prevalence including studies published since our 2011 review, seeking to assess the latitudinal gradient and whether it has changed since our previous analysis.

Methods Studies published up to December 2018 were located via Embase, Web of Knowledge and PubMed, using standardised search terms; data were extracted from peer-reviewed studies and these studies added to those from our previous analysis. Where age-specific data were available, prevalence estimates were age-/sex-standardised to the 2009 European population. Prevalence estimates were adjusted for study prevalence year and ascertainment methods. The latitudinal association with MS prevalence was assessed by meta-regression.

Results A total of 94 studies met inclusion criteria, yielding 230 new prevalence points and 880 altogether with those from the prior study. There was a significant positive gradient in time-corrected MS prevalence with increasing latitude (5.27/100 000 per degree latitude), attenuating slightly to 4.34/100 000 on age-standardisation, these associations persisting on adjustment for ascertainment method. Of note, the age-standardised gradient was consistently significantly enhanced from our previous study, regardless of whether it was as-measured, time-corrected or adjusted for ascertainment methods. Certain areas, such as the Scandinavian and Atlantic Coast/Central Europe regions, showed changes in MS prevalence gradient over time, but other regional gradients were similar.

Conclusions This new meta-analysis confirms that MS prevalence is still strongly positively associated with increasing latitude and that the gradient is increasing, suggesting that potentially modifiable environmental factors, such as sun exposure, are still strongly associated with MS risk.

INTRODUCTION

There is a strong association between increasing multiple sclerosis (MS) prevalence and distance from the equator. While this latitudinal gradient has been well documented, it is unclear how the magnitude of this gradient is changing with time and what implications this has for the risk factors and pathogenesis of MS. Our previous meta-analysis published in 2011 examined the worldwide pattern of MS prevalence and confirmed the existence of a robust latitudinal gradient for MS prevalence.[1]

Latitude is perhaps the most basic indirect evidence in support of a link between vitamin D and sun exposure and MS. The latitudinal variation of MS has been long recognised,[2 3] and is strongly suggestive of environmental factors, particularly sun/vitamin D, in MS aetiology, alongside direct behavioural and biomarker studies. While some studies have suggested that this latitudinal variation is associated with variation in Epstein-Barr virus (EBV) exposure,[4–6] smoking[7] or genetics,[8–10] the consistency of the latitudinal gradient in both hemispheres, and in regions as diverse as Europe,[7 8 11] Australia[12 13] and New Zealand,[14] the Americas[15 16] and elsewhere, does indicate a more unifying explanation, of which ambient ultraviolet (UV) is the most obvious.[17 18] There are a plethora of studies supporting a role for sun exposure and vitamin D in MS onset and progression.[19 20] This is not to exclude the potential for other factors in contributing to local variation in MS, but the general consistency globally suggests that the sun and/or vitamin D are likely to be the primary drivers for the worldwide latitudinal gradient. Both vitamin D and sunlight/UV rays (UVR) exposure have been found to have independent immunomodulatory effects,[21 22] and while vitamin D lies on the same or overlapping pathway with the sun/UVR, it is important to acknowledge that UVR effects need not solely be via vitamin D.

Beyond questioning potential mechanisms underlying the latitudinal gradient, others have questioned its existence altogether, suggesting it to be due to methodological artefact due to failure to age-standardise and account for different population age/sex structures,[23] temporal variation in prevalence stymying efforts to compare successively measured populations,[24] or due to differences in case ascertainment.[24] Moreover, some authors have pointed to disparities from the general positive gradient, including prevalences lower than expected from a simple linear gradient in the Scandinavian region and higher than expected prevalences in the Mediterranean, including Sicily and Sardinia, which they proposed as proof that the gradient was artefactual.

We previously described the latitudinal variation of MS prevalence[1] and importantly were able to dispel not merely the methodological arguments

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[1]Melbourne School of Population & Global Health, The University of Melbourne, Melbourne, Victoria, Australia
[2]Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia
[3]Department of Neurology, Royal Hobart Hospital, Hobart, Tasmania, Australia
[4]The Alfred Hospital, Monash University, Clayton, Victoria, Australia

Correspondence to
Dr Steve Simpson, Jr., Melbourne School of Population & Global Health, The University of Melbourne, Melbourne, Victoria 3053, Australia; steve.simpson@utas.edu.au; steve.simpson@unimelb.edu.au

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against the latitudinal gradient hypothesis, but also explain some of the disparities from the gradient. First, our study made active efforts to acquire age-specific prevalence data, or estimate this from available census and case number data, so as to allow age-standardisation of much of our data set. We applied a novel time-correction regression function to account for and minimise the increase in prevalence with time, thus allowing for the inclusion of multiple prevalence estimates from the same locations. Finally, we endeavoured to account for case ascertainment methods, both in terms of the diagnostic criteria used and cases included (definite/probable/possible), thus accounting for the impacts of these study characteristics. In this analysis, we found a potent positive latitudinal gradient for much of the latitudinal range, substantiating its global reach among European-descent populations, as well as explaining the aberrations from the gradient previously pointed out in the Scandinavia and the Italian regions. In that study, 321 peer-reviewed studies were analysed, including 650 prevalence points in 59 countries between 1923 and 2009, finding a significant increase in age-adjusted prevalence per degree-latitude (1.04/100 000 ($p<0.001$)), which strengthened on correcting for prevalence year (2.60/100 000 ($p<0.001$)). Given the large number of prevalence studies that have been undertaken in the intervening years, including a large number in the Middle East, we sought to examine whether the latitudinal gradient has changed. Our aims were to quantify the association of latitude and prevalence and, particularly, to see whether the magnitude of this association has changed since the previous study.

METHODS

Literature search

Search methods used were the same as those in our previous MS prevalence study.[1]

Studies published between 2010 and 2018 were located via Embase (http://www.embase.com), Web of Knowledge (http://www.isiknowledge.com) and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), using search terms 'multiple sclerosis AND prevalence' OR 'multiple sclerosis AND epidemiology'. We also sourced studies from article references. In addition, reviews published since our previous meta-analysis drew our attention to studies in the Middle East and Asia/Pacific regions from prior to 2010 that we had not included in the original study.[25–28]

Inclusion criteria

Included studies contained crude data and/or breakdown of prevalence estimates by age, with or without sex. A defined area, source population and study period were also required. Authors were contacted regarding missing information and the included studies were published in English or relevant tables and text were translated as necessary using Google Translate (http://translate.google.com), including one in Bosnian, two in Russian and one in Spanish. Only complete, peer-reviewed articles were included in this analysis, that is, conference abstracts were not included.

Data collection

Extracted data from studies included the area involved (including the latitude of the municipality for discrete areas or, if for a region/province/country, the mean of the highest and lowest latitude of the specified area was used to estimate the midpoint latitude), the study prevalence year or final year of a period-prevalence study, the diagnostic criteria used, the source and study populations plus the crude and, if obtainable, the age-/sex-specific prevalence data.

HLA analysis

HLA (Human leukocyte antigen)-DRB1 allele frequencies for Europe were obtained from the online database, http://www.allelefrequencies.net, or individual publications.

Statistical analysis

Crude prevalence

The number of prevalent cases obtained from each study divided by the number of persons in a defined population yielded a crude prevalence value. Where population size was not provided, data were obtained from regional statistical sources. Additionally, population sizes were calculated from studies that reported total prevalent cases and crude prevalence.

Age and sex standardisation

In studies where age-specific and sex-specific prevalence data were available, prevalence values were age-/sex-standardised to the 2009 European population to allow comparison with our previous study.

Statistical analysis

Methods here are as described previously.[1] First, the new prevalence estimates were combined with those from the original study. Prevalence estimates were log-transformed and weighted with the inverse of the variance, or the inverse of the case number, as appropriate. Given high heterogeneity, random effects meta-regression was used using STATA/SE V.15.0. Models were adjusted for prevalence year, diagnostic criteria and whether studies included possible cases alongside probable/definite MS. Turn points (the threshold value in the figure where the linear function up to that latitudinal point is replaced to include quadratic term to reflect the curved nature of the function beyond that point) in the bubble plots in figure 1, estimated using segmented analysis, were the same as those described previously, as the turn points did not materially differ from the original study (data not shown), also allowing greater ease of comparison with the original study's results.

Time-corrected analysis

For the bubble plots and region-specific estimates, all prevalence estimates (both original and new prevalence points) were predicted for what they would have been in 2009 and 2018, using methods described previously.[1] Results were generally consistent whether time-correction was to 2009 or 2018. Both are presented so as to allow ease of comparison with the previous study's results.

Adjustment for HLA-DRB1

As described previously,[29] regional gradients in Europe were adjusted for population frequencies of several key MS-associated HLA-DRB1 alleles (HLA-DRB1*15, *11, *01, *03 and *14).

RESULTS

Literature review

For the period of 2010–2017, 62 studies were sourced from Embase, 46 from ISI/Web of Knowledge and 99 via PubMed. This resulted in 126 unique studies, of which 94 met our inclusion criteria, yielding 230 new prevalence points. Details of these studies are shown in online supplementary table 1. Regional

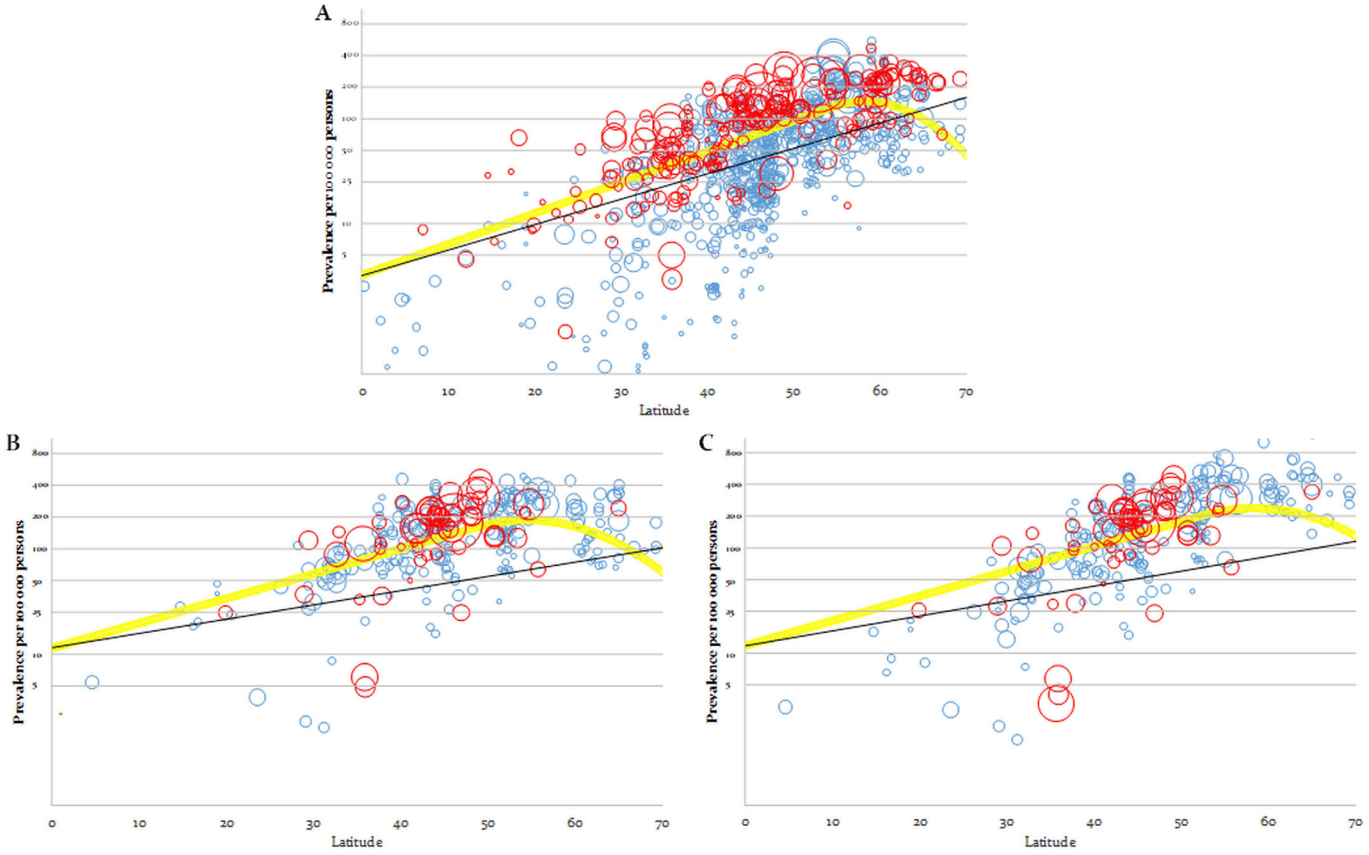

Figure 1 Plot of time-corrected prevalence against latitude. Points in blue are the prevalence points from the original study, while those in red are those from the present study. Size of bubbles is proportionate to the inverse of the sample variance. (A) All crude prevalence estimates; (B) Crude prevalence estimates restricted to those with age-specific data and (C) Age-standardised prevalence estimates. All fit lines are from all available data points.

distribution of included studies and number of prevalence estimates are presented in table 1, and shown graphically in figure 2.

Regions that had the largest numbers of new studies included were Western Europe and the Middle East/Africa: 180 new prevalence points in Western Europe (including 51 new prevalence points from the Scandinavia/North Atlantic and 53 from the Atlantic Coast/Central Europe regions) and 63 new prevalence points in the Middle East/Africa regions.

Global analysis

Latitude was consistently and significantly associated with MS prevalence in all analyses: the time-adjusted latitudinal gradient was 5.27/100 000 per degree latitude, attenuating slightly to 4.27/100 000 on restriction to those with age-specific data and persisting on age-standardisation. In the fully adjusted model, adjusted for ascertainment methods used, and on age-standardisation, the latitudinal gradient persisted as 3.64/100 000.

While the overall latitudinal gradient for crude studies did not significantly differ from that found in our 2011 study, on restriction to studies with age-specific and on standardisation, the latitudinal gradient was significantly increased in all analyses, both unadjusted (p=0.005), time-corrected (p=0.016) and adjusted for ascertainment methods (p=0.021; table 2).

Table 3 presents a pattern of increasing MS prevalence with latitude that reached statistical significance at all points, excepting the turn-point, showing the strong positive association up to the turn-point, before declining and becoming a negative association above 55°. These global trends are graphically depicted in figure 1, showing consistency between crude and age-standardised analyses with the strong positive latitudinal gradient up to the higher latitudes, whereupon it becomes negative. Time correction to 2009 or 2018 did not materially impact on the results, as regardless there is an obvious jump in the gradient on inclusion of the new studies (online supplementary figure 1).

Regional analyses

Analyses by region, as summarised in table 4, show that many of the trends found in the original study persist in the current analysis; as in the original study, there was a strong and significant positive gradient in Australasia, the UK/Ireland and North America, while the Italian region again had a significant inverse gradient and the Eastern Europe, Latin America and Middle East/Africa results were not materially altered from our previous study. Appreciable differences were seen elsewhere; however, the negative gradient in the Scandinavia/North Atlantic region was markedly reduced to a non-significant inverse gradient, and the Atlantic Coast/Central Europe region went from having a weak positive gradient in the original study to a gradient on par with that of the UK/Ireland region, while the Asia/Pacific gradient largely abrogated. The change in the Asia/Pacific region was due to influential prevalence points, however. For instance, the attenuation in the Asia/Pacific regional gradient was a function of the new prevalence points in the Republic of Korea (median latitude 35.9°N, small prevalence 3.62/100 000 and large sample size n=1658) and in the Shandong Province in northeast China (median latitude 35.9°N, small prevalence 5.3/100 000 and large sample size n=5038) markedly impacting on the overall regional gradient.

Table 1 Regional distribution of the original study and the 2010–2018 studies between brackets and number of prevalence estimates, overall and those with age- and sex-specific data

	Studies	Prevalence estimates	Age-standardised prevalence estimates	Sex-specific, age-standardised prevalence estimates
Australasia	17 (+1)	32 (+1)	28 (+1)	27 (+1)
Western Europe				
UK/Ireland	40 (+4)	56 (+9)	23 (+2)	23 (+2)
Scandinavia/North Atlantic	52 (+11)	152 (+51)	42 (+1)	18 (+0)
Atlantic Coast and Central Europe	60 (+12)	183 (+53)	47 (+27)	44 (+26)
Italian region	69 (+14)	82 (+16)	43 (12)	40 (+10)
Eastern Europe	51 (+12)	159 (+15)	57 (+9)	19 (+3)
North America	47 (+4)	62 (+4)	32 (+2)	15 (+2)
Latin America and Caribbean	20 (+10)	33 (+12)	5 (+1)	4 (+0)
Middle East and Africa	39 (+23)	83 (+63)	19 (+8)	14 (+5)
Asia and Pacific	22 (+6)	38 (+6)	8 (+2)	5 (+1)
Total	407 (+94)	880 (+230)	304 (+65)	213 (+50)

One study (Visser *et al*, 2012) crosses regions (one point in the UK region and two in Scandinavia/North Atlantic region) so total number of new studies exceeds actual total (n=53). Also, note that another study (Ha-Vinh, 2016) crosses regions, including 22 in the Atlantic Coast/Central Europe region, 3 in South America and 1 in the Middle East/Africa region.

Australasia (including Australia and New Zealand); **UK region** (including the United Kingdom of Great Britain and Northern Ireland (England, Northern Ireland, Scotland and Wales), Ireland, and the Orkney Islands (UK)); **Scandinavia and North Atlantic** (including Denmark, Finland, Iceland, Norway, Sweden, the Faroe Islands (Denmark), and the Shetland Islands (UK)); **Atlantic and Central Europe** (including Austria, Belgium, the Czech Republic, France, Germany (as well as the countries formerly known as East Germany and West Germany), the Netherlands, Portugal, Spain (continental, the Balearic Islands and the Canary Islands), and Switzerland); **the Italian region** (including Peninsular and Insular Italy, and San Marino); **Eastern Europe** (including Albania, Bosnia-Herzegovina, Bulgaria, Croatia, Estonia, Greece, Hungary, Kosovo, Moldova, Poland, Romania, Russia, Serbia, and the country formerly known as Yugoslavia); **North America** (including Canada and continental and insular USA); **Latin America and the Caribbean** (including Argentina, Brazil, Chile, Colombia, Ecuador, Panama, and Peru, as well as overseas departments of France, including French Guyana and the French West Indies); **the Middle East and Africa** (including Egypt, Iran, Israel, Jordan, Kuwait, Libya, Malta, Qatar, South Africa, Turkey, and the United Arab Emirates, as well as the overseas department of France, Réunion); **Asia and Pacific Islands** (including Fiji, India, Japan, the People's Republic of China, the Republic of China (Taiwan), and the Republic of Korea).

Of note, in keeping with our previous findings, adjustment of the regional gradients for the frequencies of HLA-DRB1 genotypes wholly accounted for the inverse gradient seen in the Italian region, while other regional gradients within Europe were largely independent of HLA-DRB1 allele frequencies (table 5). We were unable to assess the impact of HLA-DRB1 frequencies in other global regions, however, as there was insufficient allele frequency data (data not shown).

Figure 2 Global distribution of prevalence points in analysis. Those in blue are the prevalence points from the original 2010 study, while those in red are the new prevalence points in the current study.

Table 2 Estimated change in prevalence per 100 000 persons per degree of latitude, unadjusted, adjusted for year of study and further adjustment for use of systematic diagnostic criteria and inclusion of possible cases

		Prevalence estimates with age-specific data		
		All crude (n=880) Slope* (95% CI)	Crude (n=304) Slope* (95% CI)	Age-standardised (n=304) Slope* (95% CI)
Unadjusted	Original	1.55 (1.28 to 1.83)	0.81 (0.34 to 1.27)	0.99 (0.47 to 1.50)
	Current	1.98 (1.68 to 2.27)	1.01 (0.46 to 1.57)	1.25 (0.65 to 1.86)
	Difference from adding new prevalence points	*p=0.10*	*p=0.012*	*p=0.005*
Adjusted for prevalence year	Original	4.64 (3.63 to 5.65)	3.31 (1.79 to 4.83)	3.60 (1.97 to 5.24)
	Current	5.27 (4.48 to 6.05)	4.27 (2.71 to 5.82)	4.34 (2.74 to 5.95)
	Difference from adding new prevalence points	*p=0.86*	*p=0.037*	*p=0.016*
Fully adjusted model	Original	4.09 (3.13 to 5.06)	2.41 (1.16 to 3.66)	2.68 (1.30 to 4.07)
	Current	5.03 (4.25 to 5.81)	3.55 (2.19 to 4.90)	3.64 (2.22 to 5.05)
	Difference from adding new prevalence points	*p=0.77*	*p=0.047*	*p=0.021*

Time adjustment is to the year 2018, in contrast to 2009 as in the previous paper.
Italicised figures are p-values for tests for difference between original and updated analyses.
*Slope is the prevalence increase per 100 000 population per degree of latitude increase.

DISCUSSION

This current meta-analysis, using new data for 230 prevalence points from 94 studies found in our present literature search, confirms the latitudinal gradient in MS prevalence. The overall global magnitude of this gradient has increased, the fully adjusted, age-standardised prevalence increasing significantly from 2.68/100 000 per degree latitude to 3.64/100 000. As previously,[1] while the overall gradient was linear throughout much of the latitudinal range, there was a downturn in the higher latitudes above 55° encompassing the Scandinavian countries. While many of the general trends observed in the original study persisted here, some differed notably, including a marked attenuation in the inverse gradient in the Scandinavia/North Atlantic and an increase in the Atlantic Coast/Central Europe regional gradients.

Latitude's association with MS prevalence was again evident in all the European-descent areas assessed, excepting Latin/South America. The significant positive gradients in Australasia, the UK/Ireland and North America found previously were again evident, as was the potent inverse gradient in the Italian region. Some gradients, however, were markedly altered, most notably the inverse gradient in the Scandinavia/North Atlantic region, which attenuated appreciably, while the weak positive gradient in the Atlantic Coast/Central Europe region found previously was now markedly enhanced, now on par with that seen in the UK/Ireland region. The Atlantic Coast/Central Europe change was influenced by the additional prevalence points in the 2016 Pivot study from France,[30] since despite its covering a similar range to the 2007 Vukusic study[31] included in the previous paper (roughly 42°–50°), the Pivot study prevalence estimates were on average twice as high (74.4/100 000 vs 150.5/100 000). These results, in combination with a number of studies conducted in the Iberian Peninsula, thus manifest in a markedly enhanced gradient in this region. On the other hand, in the Scandinavia/North Atlantic region, the 2011 Ahlgren study in Sweden[11] and 2014 Berg-Hansen study in Norway,[32] with their fairly consistently high prevalence across broad latitudinal ranges (56°–67.2° and 59.5°–66.4°, respectively), served to significantly attenuate

Table 3 Estimated change in prevalence per 100 000 persons per degree latitude at 5-unit increments of latitude, estimated at 2018

	All crude	Crude restrcited to those w/ age-specific data	Age-standardised
0	**0.28 (0.23 to 0.34)**		
5	**0.40 (0.33 to 0.47)**	**0.59 (0.41 to 0.78)**	**0.58 (0.39 to 0.77)**
10	**0.56 (0.47 to 0.65)**	**0.79 (0.57 to 1.01)**	**0.76 (0.54 to 0.99)**
15	**0.79 (0.68 to 0.90)**	**1.04 (0.78 to 1.31)**	**1.01 (0.74 to 1.28)**
20	**1.11 (0.97 to 1.24)**	**1.38 (1.05 to 1.71)**	**1.34 (1.01 to 1.67)**
25	**1.55 (1.37 to 1.74)**	**1.83 (1.40 to 2.26)**	**1.77 (1.34 to 2.21)**
30	**2.18 (1.92 to 2.45)**	**2.43 (1.85 to 3.01)**	**2.35 (1.76 to 2.94)**
35	**3.07 (2.67 to 3.47)**	**3.22 (2.40 to 4.04)**	**3.11 (2.28 to 3.94)**
40	**4.31 (3.69 to 4.94)**	**4.26 (3.07 to 5.46)**	**4.12 (2.91 to 5.33)**
45	**6.06 (5.08 to 7.05)**	**5.65 (3.88 to 7.42)**	**5.45 (3.67 to 7.23)**
50	**8.52 (6.95 to 10.10)**	**7.49 (4.86 to 10.11)**	**7.22 (4.57 to 9.86)**
55	**13.00 (10.23 to 15.79)**	**10.51 (6.40 to 14.61)**	**10.09 (5.96 to 14.21)**
60	–1.93 (–5.76 to 1.90)	**2.61 (0.20 to 5.02)**	**3.05 (0.53 to 5.57)**
65	**–14.84 (–19.91 to –9.76)**	**–6.96 (–11.42 to –2.49)**	**–5.83 (–10.37 to –1.29)**
70	**–14.39 (–16.71 to –12.07)**	**–12.22 (–17.07 to –7.38)**	**–11.27 (–16.32 to –6.22)**

Slope (95% CI) represents change in prevalence per 100 000 persons per degree latitude at specified latitude. Results in boldface denote statistical significance (p<0.05). All analyses adjusted for prevalence year, use of systematic diagnostic criteria and inclusion of possible cases. Values at 0 latitude not calculated for crude and age-standardised analyses where age-specific data required, as there were no such prevalences at this latitude to allow estimation.

Table 4 Region-specific latitudinal gradients, in original and current study

	Age-standardised prevalence estimates	Midpoint latitude*	Original data set, slope in 2009 (95% CI)	Current analysis, slope in 2009 (95% CI)	Current analysis, slope in 2018 (95% CI)
Australasia	28	35.67	**8.38 (5.77 to 10.98)**	**7.97 (4.97 to 10.98)**	**11.05 (5.96 to 16.15)**
Western Europe	155	47.88	**8.11 (3.85 to 12.35)**	**2.75 (1.04 to 4.46)**	**3.77 (1.28 to 6.25)**
UK/Ireland	23	53.43	**19.81 (7.11 to 32.51)**	**16.86 (5.93 to 27.78)**	**19.60 (6.80 to 32.40)**
Scandinavia/North Atlantic	42	62.75	**–4.29 (–7.59 to –0.99)**	–1.39 (–4.01 to 1.23)	–1.41 (–4.17 to 1.34)
Atlantic Coast/Central Europe	47	43.93	**2.82 (0.42 to 5.21)**	**13.12 (7.40 to 18.83)**	**17.59 (8.51 to 26.67)**
Italian region	43	41.56	**–11.59 (–20.17 to –3.02)**	**–10.33 (–17.48 to –3.17)**	**–15.58 (–26.90 to –4.26)**
Eastern Europe	57	51.44	–0.76 (–4.67 to 3.15)	–0.20 (–5.06 to 4.66)	–0.27 (–6.86 to 6.33)
North America	32	43.84	**15.35 (6.37 to 24.32)**	**13.98 (7.67 to 20.30)**	**17.80 (8.60 to 26.99)**
Latin America and Caribbean	5	16.25	0.06 (–1.56 to 1.68)	0.12 (–0.46 to 0.70)	0.03 (–0.26 to 0.31)
Middle East and Africa	19	32.12	1.62 (–4.26 to 7.50)	0.93 (–2.40 to 4.25)	0.86 (–2.07 to 3.79)
Asia and Pacific	8	33.55	0.90 (–3.24 to 5.03)	**0.37 (0.34 to 0.40)**	**0.08 (0.06 to 0.09)**

Slope (95% CI) represents change in prevalence per 100 000 persons per degree latitude at specified latitude. Results in boldface denote statistical significance (p<0.05). All analyses adjusted for prevalence year, use of systematic diagnostic criteria and inclusion of possible cases. Study prevalence estimates time-corrected to 2009.
*Midpoint latitude estimated as the mean of the maximum and minimum latitude of the prevalence points within the specified region.

the inverse gradient in that region. Indeed, in contrast to the potent inverse gradient above 60° in the original study, for the new studies, this gradient is completely flat, serving to dampen the inverse gradient for this region. Areas where the latitudinal gradient change, although of less dramatic extent, may instead be attributable to more classic methodological reasons, are those seen in the Middle East/Africa and Asia/Pacific regions, where influential prevalence points markedly impacted on the gradients in those regions, as described in the Results section. These results would seem to suggest that, while gradients are manifestly evident in most of the regions studied, there are some intraregional variations even over a relatively short timeframe. In some of these, like the Middle East/Africa and Asia/Pacific regions, these may simply reflect influential data points, and given as the gradients in these regions are of low magnitude, the general conclusions are likely to be consistent with the previous study.

The changes in the Atlantic Coast/Central Europe and Scandinavia/North Atlantic regions, however, may speak to more genuine change. While there is a notable difference in the study populations in the French studies—the Vukusic study utilising an insurance scheme of French farmers, while the Pivot study was more broadly based—there is nonetheless an appreciably greater increase in the prevalence of locations at the higher latitudes of this region. In the Scandinavia/North Atlantic region, on the other hand, we see a flattening of the inverse gradient we demonstrated in the previous study, the nationwide studies in Sweden and Norway conducted by Berg-Hansen and Ahlgren and their fairly even distribution of MS prevalence across a broad latitudinal range, potentially suggesting an attenuation in the protective dietary behaviours underlying the downturn in the prevalence gradient suggested previously.[33] These changes are more likely to reflect the impact of changes in some modifiable lifestyle factors, of which sun exposure and/or vitamin D are prime candidates. The reasoning for this is twofold. First, the area is quite homogenous in terms of medical infrastructure, access to care and is not as affected by socioeconomic divides that may preclude seeking out medical care for chronic conditions. Thus, it is not expected that changes in these regions' gradients would be attributable to changes in case ascertainment that would not be evident in other areas in the European region, or indeed in other European-descent nations, such as in North America or Australasia. In addition, since these areas had been comprehensively assessed across the regional latitudinal ranges and repeatedly over a long time course, they are less likely to be affected by large and influential data points that could have skewed the gradient trendline. The alternative interpretation, then, is that some aspect of the underlying risk structure has changed, leading to an increase in the frequency of disease commensurate with latitude. As previously, dietary intake of vitamin D has been suggested as a mode by which the latitudinal gradient in the far north of Scandinavia is attenuated,[33] since dietary vitamin D

Table 5 Region-specific latitudinal gradients, in original and current study

	Current analysis, slope in 2009 (95% CI)			Current analysis, slope in 2018 (95% CI)		
	Main model	Restricted to those with HLA genotype data	Adjusted for HLA-01 genotypes	Main model	Restricted to those with HLA genotype data	Adjusted for HLA-01 genotypes
UK/Ireland	**16.86 (5.93 to 27.78)**	**16.86 (5.93 to 27.78)**	13.88 (–4.23 to 31.99)	**19.60 (6.80 to 32.40)**	**19.60 (6.80 to 32.40)**	16.16 (–4.56 to 36.88)
Scandinavia/ North Atlantic	–1.39 (–4.01 to 1.23)	–5.07 (–13.35 to 3.22)	–6.22 (–17.17 to 4.73)	–1.41 (–4.17 to 1.34)	–6.34 (–18.17 to 5.48)	–6.98 (–20.71 to 6.75)
Atlantic Coast/ Central Europe	**13.12 (7.40 to 18.83)**	**10.69 (5.40 to 15.99)**	**15.08 (4.03 to 26.13)**	**17.59 (8.51 to 26.67)**	**14.12 (6.16 to 22.09)**	**20.46 (3.37 to 37.54)**
Italian region	**–10.33 (–17.48 to –3.17)**	**–10.33 (–17.48 to –3.17)**	6.82 (–70.81 to 84.44)	**–15.58 (–26.90 to –4.26)**	**–15.58 (–26.90 to –4.26)**	11.17 (–115.68 to 138.03)
Eastern Europe	–0.20 (–5.06 to 4.66)	0.26 (–5.44 to 5.97)	–0.40 (–13.69 to 12.90)	–0.27 (–6.86 to 6.33)	0.37 (–7.65 to 8.39)	–0.59 (–20.21 to 19.03)

Slope (95% CI) represents change in prevalence per 100 000 persons per degree latitude at regional midpoint latitude. Results in boldface denote statistical significance (p<0.05). All analyses adjusted for prevalence year, use of systematic diagnostic criteria and inclusion of possible cases. Study prevalence estimates time-corrected to 2009.

intake would mitigate the latitudinal variation in winter ambient UV. This behaviour would have been a necessary element of survival for early migration into the far northern latitudes so as to avoid rickets and other hypovitaminosis D effects, but has in recent history has potentially had a beneficial effect on MS risk in this region. That we see in the Scandinavian region, the prevalence for serially measured sites in the south of the region (up to 60°N) is generally flat, while for mid-tier regions (60–65°N) and especially those in the north (≥65°N), prevalence increases much markedly over the period up to 2013, at that point prevalence estimates are largely overlapping. In the absence of concomitant rises in deleterious behaviours in the northern latitudes, such as smoking,[34 35] or in differential rates of infection by EBV, these results suggest that some of the cultural practices, such as diet, which might previously have been protective against MS have become less common, leading to a rise in the vitamin D deficiency in this high latitude area. This is substantiated by work in the Inuit population of Greenland, where there was a marked increase in vitamin D deficiency alongside a decrease in traditional diet, overall[36] and particularly among the younger age groups of the population.[37] Similar results have been seen in the far north of Norway,[38] where diet rich in vitamin D-containing foods was associated with vitamin D status, but this behaviour was less common among younger participants. While substantiation of this hypothesis would require a systematic longitudinal survey of diet behaviours across the Scandinavian region and across its latitudinal range, this would still seem to be the most plausible interpretation, as we suggested in our previous paper.[1]

On the other hand, the continued inverse gradient seen in the Italian region, which we previously suggested might be a function of regional variation in protective and deleterious HLA-DR variants, would provide some credence to this hypothesised explanation for the inverse gradient in this region. As in our previous analysis, we found that the inverse gradient in this region was solely a function of the regional variation in *HLA-DRB1* allele frequencies, whereas other regional gradients in Europe were largely independent of this adjustment.

While there is some potential role for differential case ascertainment, this is not likely to be a potent driver of the changes in gradient observed in the European regions and European-descent populations, given as there have been relatively minor changes to the diagnostic criteria and use of paraclinical evidence over the duration of studies described here. Moreover, the fact that other regions in Western Europe, North America and Australasia were relatively consistent in their gradients, despite having similar medical infrastructure and access to care, would argue against improved case ascertainment being a driver of the changes seen in these regions.

Strengths of our study included consistent data collection and statistical analysis methodologies, which were well-defined and adjusted for variables that could introduce population bias. The data used in our updated meta-analysis were extracted independently and after analysis showed a clear latitudinal MS gradient, similar to our previous paper. Included studies were varied in geographical location and had clear inclusion criteria. Values obtained were age-/sex-standardised, as allowed by available data, and all prevalence estimates were time-corrected to allow comparability of prevalence studies conducted over time, as well as adjusting for diagnostic criteria and population inclusion.

Our study also had some weaknesses. A total of 94 studies that met our inclusion criteria were included, which is a much smaller number of studies compared with our previous analysis. This is, however, a comprehensive audit of the studies conducted over the years since our previous study. Indeed, reviews published since our previous meta-analysis drew our attention to studies in the Middle East and Asia/Pacific regions from prior to 2010 that we had not included previously.[25–28] The fact that there are notable aggregations of prevalence studies in some regions of Western Europe and the Middle East, while other high prevalence regions, such as Australasia and North America, had comparatively few, may hinder our ability to definitely comment on the change, or lack thereof, of the latitudinal gradient in these regions. While publication bias is less a concern for studies of this sort, there being no 'null' finding in a prevalence study, this variability in studies conducted by region could be ascribed to a type of publication bias. We did not grade studies based on perceived study quality, instead endeavouring to constrain analyses to population-based and peer-reviewed epidemiological studies, as well as controlling for study methodological characteristics, such as diagnostic criteria used and inclusion of possible/probable cases in addition to definite MS.

Overall, these results are strongly supportive of the positive relationship of latitude with MS prevalence, though the regional idiosyncrasies, both in terms of local characteristics and the studies conducted, continue to manifest in markedly different regional gradients. While there are potential intraregional effects contributing to the latitudinal variation in MS prevalence, these results and the relative consistency across the whole of the globe continue to provide indirect evidence in support of the role of the sun and/or vitamin D in MS aetiology.

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