Letters to the Editor

An investigation of the relationship between latitude and multiple sclerosis severity in New Zealand

Keywords: Multiple sclerosis, disability, prevalence, latitude, New Zealand

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Associations between latitude and the prevalence of multiple sclerosis are well recognized,[1–3] although the association is not seen in some geographical regions.[4] The 2006 New Zealand National Multiple Sclerosis Prevalence Study (NZMSPS)[5] reported a three-fold increase in multiple sclerosis prevalence with increasing latitude from northern (37.9°S) to southern (45.8°S) regions of New Zealand. In addition, the study found that of the 2422 subjects assessed, 60% had moderate to severe disability (Expanded Disability Status Score (EDSS)[6] score 3.5 to 9.5). There has been little previous investigation of whether disease severity is related to latitude. We therefore investigated, using data acquired in the NZMSPS, whether latitude is associated with disease severity in New Zealand.

A full description of the NZMSPS methodology has been published previously.[5,7] The study included all persons resident in New Zealand on census day (6 March 2006) with a confirmed diagnosis of multiple sclerosis.[8] Clinical data included type of disease at onset (relapsing or progressive), disease duration and EDSS.[6] A Multiple Sclerosis Severity Score (MSSS) was derived for each patient using a previously described methodology.[9]

Latitude data were derived by aggregating New Zealand census regions into six broad latitudinal regions from north (35°S) to south (48°S). For each region a population weighted latitude and longitude centroid was calculated, and this centroid was taken as the latitudinal reference point for analysis, as described earlier.[5] The northernmost centroid includes Auckland, the largest city in New Zealand, with around one quarter of the total New Zealand population. The Auckland population differs from the rest of the country, with more than 40% of residents having immigrated from outside of New Zealand. Therefore, this region was excluded in the models investigating the relationship of latitude with prevalence (as previously reported[5]) and with disease severity (reported below). The relationship between latitude and disease severity in the five remaining latitudinal regions was examined using a generalized additive model, as previously described,[5] in R version 3.0.2 (Vienna, Austria).

A total of 2917 persons with multiple sclerosis were identified. Disability and residential data were available for 2422 (1824 females and 598 males), of whom 2023 (83.5%) had a relapsing onset and 399 (16.5%) a progressive onset disease. The mean (SD) age at onset of symptoms was 35 (10.7) years and mean disease duration 17.2 (11.8) years. The mean EDSS score was 4.4 (2.6). Disease severity of the cohort was remarkably similar to that of the original cohort of 11,867 subjects with MS in whom MSSS data was derived,[9] with distributions of the expected MSSS and of the measured MSSS of our MS population being almost identical (data not shown).

In striking contrast to the threefold increase in prevalence of relapse onset MS with increasing latitude (for the five regions from 37.9°s to 45.8°s; Figure 1(a)), disease severity actually slightly decreased over the same latitudes, albeit by only 0.07 MSSS units per degree (95% CI: 0.02–0.12; $p = 0.005$) (Figure 1(b)). When the Auckland region (35°S) was included in the model, there was no longer any relationship of latitude with disease severity (p=0.69). In progressive onset MS there was less difference, with prevalence increasing slightly and disease severity decreasing slightly with increasing latitude (Figure 1(a) and (b)).

New Zealand has an advanced health care system, with equitable access to neurological services throughout the country, and any minor differences in regional services could not account for the marked latitudinal gradient of prevalence that occurs in relapse onset disease. Reasons for the minor inverse gradient of disease severity with latitude when the Auckland region was excluded are unknown, but they are of such a small degree that they would not seem to be clinically or biologically meaningful.

Notable strengths of this study are that it is based on a nationwide MS prevalence cohort,[5] and that the New Zealand population extends over a wide latitude. Although MSSS scores were not obtained in about 17% of subjects, this proportion was similar in all regions, and the missing cases should, therefore, not

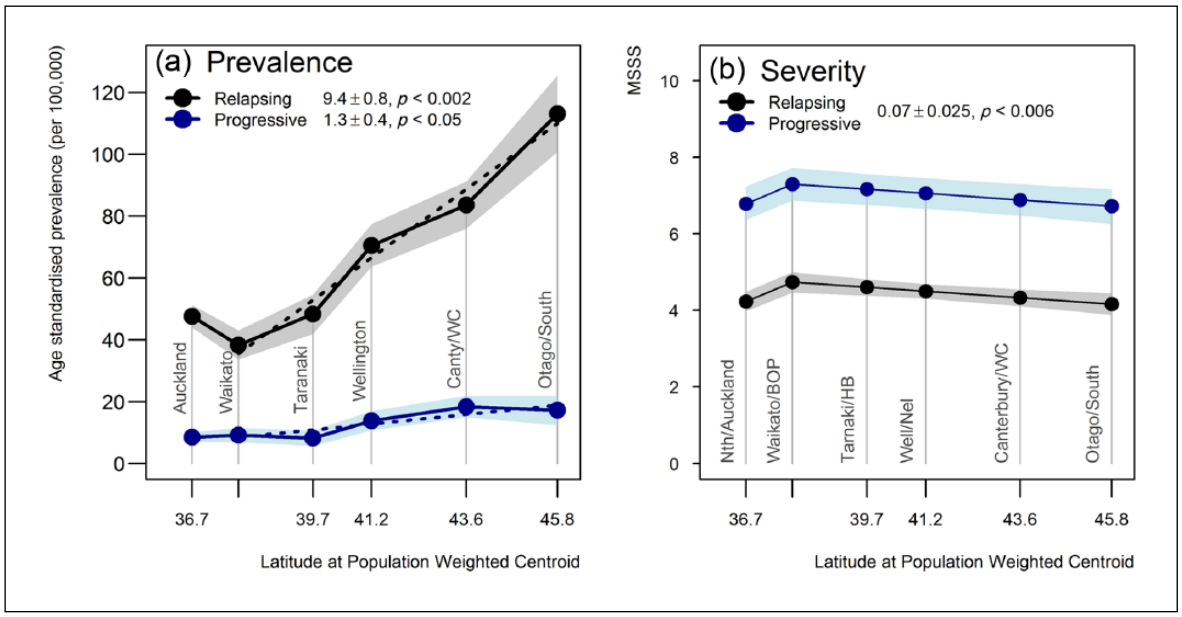

Figure 1. (a) Multiple sclerosis prevalence by latitude in New Zealand. (b) Disease severity by latitude in New Zealand. Legends gives gradient for the five latitudinal regions (excluding Auckland) in the final model, shading shows 95% confidence interval for the mean.

influence our findings. A potential limitation is that assessment of disability was obtained by telephone EDSS in 75% of cases[10] (the remaining 25% were obtained by clinical examination). However, the telephone EDSS is a well-validated tool to assess disability in multiple sclerosis, and a high correlation (Pearson's $r = 0.95$) has been reported with clinical EDSS assessment.[10] Indeed, we observed a high correlation (Pearson's $r = 0.96$) between telephone and clinical EDSS in a subgroup of 400 patients of our New Zealand cohort who had both assessments (B Taylor, unpublished). Furthermore, the proportion of telephone to clinical EDSS assessments was uniform throughout the country, thus avoiding latitudinal bias in the type of disability assessment.

In conclusion, the contrast between the strong and direct relationship of latitude with prevalence, and its weak inverse relationship with disease severity, suggests there are important differences in the factors influencing MS susceptibility and severity in relapsing onset MS in New Zealand. Further research would be of interest to elucidate factors associated with the prevalence and severity of MS in New Zealand.

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Conflict of Interest

None declared.

Contributors

SA analysed the data and wrote the first and last draft of the manuscript. JFP assisted in study design and analysed the data. RR analysed and interpreted the data. GC conducted the study and analysed the data. BVT designed the study, supervised the project and edited the manuscript. DHM interpreted the data and reviewed the manuscript. AR, DAA, EW and CES designed the study and edited the manuscript. DFM designed the study, supervised the project and edited the manuscript.

Ethical approval

Ethical approval for this study was obtained from the New Zealand multi-regional ethics committee.

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Comment on "Fingolimod effects on left ventricular function in multiple sclerosis" *Mult Scler* 2015

To the editor: We would like to comment on the design/analysis aspects of the recent study published in your journal by Racca et al. that concluded that fingolimod reduces left ventricular function in multiple sclerosis patients.[1] Also, we wish to inform the readers that left ventricular ejection fraction (LVEF) has been previously assessed in a sub-study of the Safety and Efficacy of Fingolimod in Patients with Relapsing–Remitting Multiple Sclerosis (FREEDOMS II) trial with fewer limitations and a different conclusion.[2]

Racca et al. have summarized their study limitations, e.g. open-label design, observational nature, non-blinded assessments. Coupled with these, the relatively small and unequal treatment groups (53 fingolimod, 25 natalizumab) not concurrently studied at initiation of the respective therapies, and not followed up for comparable durations (12 months fingolimod, six months natalizumab), substantially hinder interpretation of the results. Moreover, the statistical procedure of comparing one time point to another within treatment arms is unable to address the scientific question of a between-treatment effect, and it increases the chance of false positive findings due to multiple statistical tests/comparisons.

As mentioned above, echocardiographic measurements were included in a sub-group of patients within the randomized, double-blind, placebo-controlled, 24-month FREEDOMS II study. A total of 136 patients contributed to the analysis (fingolimod 1.25 mg, $n = 45$, fingolimod 0.5 mg, $n = 44$, and placebo, $n = 47$). At all post-baseline time points (months 3, 12 and 24), and in all treatment groups, the mean absolute change from baseline in LVEF was within ±

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