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

Associations between latitude and the prevalence of multiple sclerosis are well recognised,[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(37.9ºS) to southern (45.8ºS) regions of New Zealand. In addition, the study found that of the 2,422 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 previously published.[5, 7] The study included all persons resident in New Zealand on census day (March 6th 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 previously described methodology.[9]

Latitude data were derived by aggregating New Zealand census regions into six broad latitudinal regions from north (35^{0}S) to south (48^{0}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 5 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 2,917 persons with multiple sclerosis were identified. Disability and residential data were available for 2,422 (1,824 females and 598 males), of whom 2,023 (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 5 regions from 37.9°to 45.8°; Figure 1A), 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 1B). When the Auckland region 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 1A&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 be obtained in about 17% subjects, this proportion was similar in all regions and the missing cases should therefore not 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 proportions of telephone to clinical EDSS assessments were uniform throughout the country, thus avoiding latitudinal bias in the type of disability assessments.

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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