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MS prevalence in New Zealand, an ethnically and latitudinally diverse country

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Abstract

Background: The prevalence of multiple sclerosis (MS) is not uniform, with a latitudinal gradient of prevalence present in most studies. Understanding the drivers of this gradient may allow a better understanding of the environmental factors involved in MS pathogenesis.

Method: The New Zealand national MS prevalence study (NZMSPS) is a cross-sectional study of people with definite MS (DMS) (McDonald criteria 2005) resident in New Zealand on census night, 7 March 2006, utilizing multiple sources of notification. Capture–recapture analysis (CRA) was used to estimate missing cases.

Results: Of 2917 people with DMS identified, the crude prevalence was 72.4 per 100,000 population, and 73.1 per 100,000 when age-standardized to the European population. CRA estimated that 96.7% of cases were identified. A latitudinal gradient was seen with MS prevalence increasing three-fold from the North (35°S) to the South (48°S). The gradient was non-uniform; females with relapsing–remitting/secondary-progressive (RRMS/SPMS) disease have a gradient 11 times greater than males with primary-progressive MS ($p < 1 \times 10^{-7}$). DMS was significantly less common among those of Māori ethnicity.

Conclusions: This study confirms the presence of a robust latitudinal gradient of MS prevalence in New Zealand. This gradient is largely driven by European females with the RRMS/SPMS phenotype. These results indicate that the environmental factors that underlie the latitudinal gradient act differentially by gender, ethnicity and MS phenotype. A better understanding of these factors may allow more targeted MS therapies aimed at modifiable environmental triggers at the population level.

Keywords

ethnicity, gender ratio, latitude, multiple sclerosis, prevalence

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Introduction

One of the most striking features of the epidemiology of multiple sclerosis (MS) is the significant variability in prevalence and incidence seen throughout the world.[1,2] This geographical distribution is thought to be driven by two main factors: genetics and the environment acting at the population level.[3–6] MS is predominantly a disease of persons of Northern European origin although it is recognized in almost all ethnic groups around the world.[2] In admixed populations the rates of MS differ, with the coexisting European population always having a higher prevalence.[2]

The most notable geographical variation described is the latitudinal gradient of MS prevalence seen in genetically susceptible populations. This has been demonstrated in Australia,[7] USA,[8] France,[9] and New Zealand.[10] However, other studies in Sardinia[11] and

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Patagonia[12] have not supported this observation. Others[13] have suggested that the latitudinal gradient is largely due to a failure to standardize prevalence rates by age, or lack of ethnic stratification of the populations being studied.[2] A recent meta analysis of incidence studies[14] has documented a consistent incidence latitudinal gradient with some reduction in strength since 1980. Causative environmental factors that have been postulated and extensively studied include decreased winter ultraviolet radiation (UVR)[15,16] and subsequent decreased vitamin D levels,[17] and geographical variation in late onset Epstein Barr virus infections.[18]

A national study of MS prevalence can be used to better understand this geographical variation and the contribution of factors such as ethnicity, clinical variables and environmental exposures acting at the population level. New Zealand (NZ) is ideally suited to such a study as it is latitudinally diverse, extending from 35°S to 48°S with a widely dispersed population, largely of Northern European origin. The NZ health system is highly developed with equitable access to neurological care throughout the country. In addition significant ethnic minorities are present including people of Polynesian origin, principally NZ Māori and Pacific Island peoples, allowing for the study of the role of ethnicity in the development of MS in an admixed population in an environment associated with a high risk of MS.[10] In addition, there is a significant awareness of MS in the NZ healthcare system and the general population, due to the well established high prevalence of the disorder.[10] A national MS prevalence study in NZ was therefore undertaken with the specific aims of:

- Measuring the crude, and age and sex adjusted prevalence (ASP) of DMS in NZ
- Determining if a latitudinal gradient of DMS is present in NZ.
- Determining whether a latitudinal gradient is influenced by age, gender, MS phenotype, or ethnicity.

Methods

The NZ national MS prevalence study (NZMSPS) was jointly funded by the NZ Health Research Council and the National MS Society of NZ. It was established with the specific aims of determining the national prevalence of MS in NZ on census day, 7 March 2006. Ethical approval for this study was obtained from the NZ multi-regional ethics committee. All persons who provided a questionnaire response signed an informed consent form. All other data was de-identified.

Inclusion and exclusion criteria

Inclusion criteria:

- Definite multiple sclerosis as defined by the McDonald criteria 2005.[19]
- Resident in NZ on census day (prevalence day).

Exclusion criteria:

- Probable, possible or not MS diagnosis
- Clinically isolated syndromes
- Devic's disease (neuromyelitis optica).
- Deceased before census day.

Recruitment

The NZMSPS recruited cases of MS from multiple sources, including MS societies' databases, hospital databases, NZ government health information statistics services, neurologist databases, MS care providers, and direct advertising through the media. For privacy reasons all cases were assigned by the notifier with a unique identifier number encompassing the person's date of birth, sex and initials. If upon receipt by the study the notification was unique the notifier was asked to contact the patient and invite them to participate. Informed consent was sought at this point including access to medical records. If the person could not be contacted or declined to participate the neurologist involved with the patient's care was asked to complete a de-identified neurological assessment that confirmed the diagnosis of MS including all investigations, year of onset and diagnosis, MS phenotype and current disability level. A neurological assessment form was completed for all unique notifications and the diagnosis of DMS verified by a study neurologist.

If a notified case had not been reviewed by a neurologist within 12 months or the diagnosis of DMS could not be confirmed, they were directly reviewed by a study neurologist to confirm the diagnosis. All cases were confirmed as being resident in NZ on census day by questionnaire or by NZ health information statistics.

Questionnaire

All unique individuals with DMS were sent a questionnaire based on the NZ national census 2006, responses were monitored and if no questionnaire was received the person was contacted by the notifier or, if they had consented, by the study centre. This process was performed at least twice for each case. Where the person was incapacitated relatives were utilized to complete the questionnaire; research staff also completed questionnaires over the phone and in person.

Data entry

All data was dual entered by two independent research assistants and then cross referenced to identify discrepancies, with all detected errors directly corrected from the paper copy.

Ethnicity

NZ is an ethnically diverse society with people of European origin comprising the majority in all regions. Ethnicity was assessed using the same self defined ethnicity question used in the 2006 NZ population census. Prior to this census being undertaken there was a campaign in NZ to declare ethnicity as 'New Zealander' under 'Other' ethnicity. Approximately 10% of respondents took this option, thus the grouping of 'Others' is greater than in previous NZ censuses. Statistics NZ do not provide individual breakdowns by age and sex for 'New Zealanders'; however, their analysis shows that 'New Zealanders' are over represented among males, middle age, and rural and southern regions and that they are more likely to be born in New Zealand and mono-lingual.[20] As the proportion of the population with 'New Zealander' self-defined ethnicity varied throughout the country we consistently took a scenario that would minimize ethnically defined gradients to eliminate any inflationary bias that this ambiguous response may generate.

When describing the 'European' population in NZ many assumptions have to be made, particularly in assuming that the majority of those responding 'Other' should be included as European. Therefore in this study the population defined as Non-Māori/Pacific People is the best approximation to European from those available from the census. The NZNMSPS study participants were asked about ethnicity of all four grandparents, allowing us to define ethnicity by descent and also self reported ethnicity.

Population denominators

All population denominators, including age, gender and ethnicity denominators, were obtained from the national census undertaken on the 7 March 2006 downloaded from Statistics NZ[20] on 22 January 2009.

Analysis and statistical methods

Analysis of latitudinal data. NZ census regions were aggregated into six broad latitudinal regions from North to South (Figure 1). These regions each contain sufficient MS cases to allow meaningful stratification by ethnicity, age, gender and MS phenotype. For each region a population weighted latitude and longitude centroid (PWC) was calculated and this centroid was taken as the latitudinal reference point for that region (Figure 1). The latitude gradient was estimated by calculating ASPs and their confidence intervals for each of the six regions and fitting this to the PWCs.

Capture–recapture analysis. Capture–recapture analysis (CRA) is an established method for assessing population size[21] that has been widely used in the estimation of MS prevalence[22] worldwide and in the estimation of disease incidence and prevalence in NZ.[23] In this study six sources of notification were utilized. These six sources were not totally independent for various reasons. While simple capture–recapture estimates assume list independence, we fitted log-linear models to assess the dependence between lists thus explicitly adjusting for non-independence.[24] Log-linear models were fitted to the national dataset and to the data stratified by region. For each initial model the Akaike Information Criterion (AIC) was used to select the model with the best fit, as it produces less bias and more accurate estimates than competing measures of fit.[25] For the national dataset, models were fitted with and without covariates of age, sex and region. The estimates of the number of missing cases and population totals are based on the model including covariates for age, sex and region with minimum AIC. The large number of possible models prohibited a comprehensive model averaging approach.

All models and analysis were done using version 2.8.1 of the R language for statistical computing. Confidence intervals for modeled parameters use the profile likelihood method; confidence intervals for the two list analysis are by goodness of fit.

Results

Notifications and response rates

The NZNMSPS received a total of 13,803 notifications for 5901 unique individuals from which 2917 cases of DMS were identified as resident in NZ on prevalence day. Table 1 displays the notification data for all cases and response rates.

Capture–recapture analysis

Table 2 shows the best fitting models for the national dataset, with and without covariates and for the regionally stratified datasets, with the statistically 'best model' estimating that 91 cases (95% confidence interval [CI] 34–147) were missed, bringing the MS population to 3008 (95% CI 2951–3064). The predicted breakdown by gender, age and region is shown in Table 3, indicating that the missed cases were evenly distributed by region, age group and gender. Tables 2 and 3 illustrate

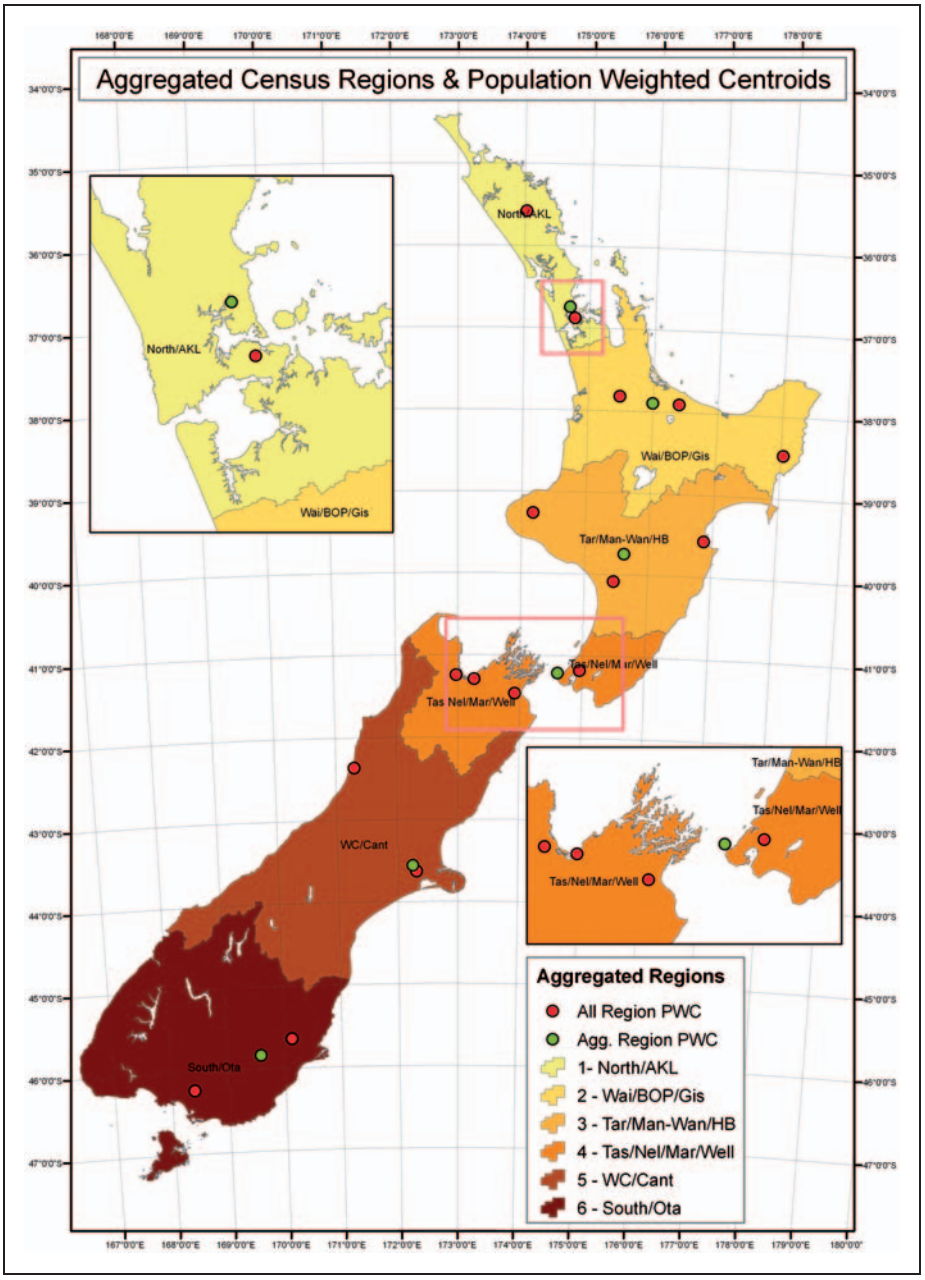

Figure 1. Aggregated census regions for New Zealand (NZ), all region population weighted centroids (PWCs) refer to the NZ statistical regions; aggregated PWCs refer to the combined regional PWCs as defined by the NZNMSPS.

that the chosen model produces estimates representative of models with good fit even though it may not be the 'true' model.

National age and sex standardized prevalence rates

The NZNMSPS identified 2917 cases of DMS amongst the NZ population of 4,027,950 on census day giving a crude MS prevalence of 72.4 per 100,000 population. When age-standardized to the standard European population this gives a prevalence of 73.1 per 100,000 population (CI 70.5–75.8). Figure 2 demonstrates the age and sex breakdown of DMS cases in NZ when compared with the overall NZ population.

Ethnicity and MS prevalence

Prevalence rates by ethnicity are displayed in Table 4. Table 5 gives the ethnic breakdown of the NZ population as determined by the self reported ethnicity question in the census. This data is divided into the six NZNMSPS geographical regions. In the NZNMSPS

Table 1. New Zealand national MS prevalence study demographics

Unique notifications	13,803			
Unique individuals	5901			
Mean notifications per individual	(Mean 2.5 + range 1–9, SD 1.5)			
Confirmed DMS cases	2917/5901 (49.4%)			
Not included reasons	2984/5901 (50.4%)			
Not confirmed/located	547 (9.3%)			
Deceased before census	1086 (18.4%)			
Possible MS	173 (2.9%)			
CIS	393 (6.7%)			
Not in NZ on census day	62 (1.1%)			
Diagnosed post census	24 (0.4%)			
Not MS	699 (11.8%)			
Questionnaire response rates (*n*, %)	2073, 71.1%			
Gender ratio M:F	728:2189 1:3			
Age	**Mean**	**Max**	**Min**	
Overall	51.74	93	9	
Male	51.14	82	16	
Female	51.94	93	9	
MS clinical phenotypes and disability levels	***N***	**Mean age**	**M : F ratio**	**Mean Expanded Disability Status Scale**
RRMS	1541	48.6	1:3.6	2.5
SPMS	918	59.6	1:4.5	6.4
PPMS	458	69.7	1:1.47	6.3

MS, multiple sclerosis; DMS, definite MS; NZ, New Zealand; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS; PPMS, primary progressive MS.

Table 2. Capture–recapture analysis log-linear modelling

								List interaction terms		
Region	*n*	95% CI	*N*	AIC	Deviance	*df*	Zeros	2way	3way	4way
National										
Saturated model	336	(–,–)	3253	405.9	0	0	2	15	20	15
Best model	64	(33,117)	2981	383.9	15.5	19	2	15	16	6
Best model with age, sex and region	91		3008	2669.2	857.1	1388	1013	14	12	4
Regional stratification (best model)										
R1	45	(23,82)	864	273.5	49.4	38	17	12	6	0
R2	17	(10,45)	351	192.5	52.5	48	30	8	0	0
R3	2	(0,8)	281	204.0	3.4	23	26	15	16	2
R4	45	(27,71)	550	235.3	31.5	43	14	10	3	2
R5	4	(1,11)	602	231.2	21.5	37	18	14	5	2
R6	44	(23,79)	426	203.0	24.9	39	23	12	5	6
Total	157	(84,296)	3074							

n, estimated number of cases missed; CI, confidence interval; *N*, population; AIC, Akaike Information Criterion; *df*, degrees of freedom.

Table 3. Missing cases as estimated by capture–recapture analysis by NZMSPS defined region (R1–R6), age and gender

		Estimate of missing cases						
Sex	Age	R1	R2	R3	R4	R5	R6	Sum
F	(0,60)	16.02	5.98	3.97	12.21	4.13	11.00	53.30
M	(0,60)	7.00	2.61	1.73	5.33	1.80	4.80	23.28
F	(60,100)	3.12	1.16	0.77	2.38	0.80	2.14	10.37
M	(60,100)	1.14	0.42	0.28	0.87	0.29	0.78	3.78
Sum		27.27	10.17	6.75	20.78	7.02	18.72	90.72

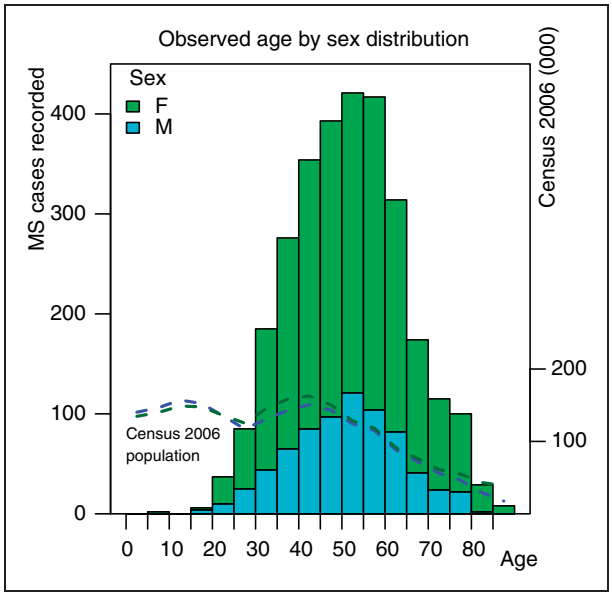

Figure 2. Age and sex breakdown of multiple sclerosis (MS) cases in New Zealand (NZ) compared with standardized population percentages from NZ census.

only one respondent listed 'New Zealander' as their ethnicity.

Table 4 demonstrates that the ASP of MS in NZ differs significantly between ethnic groups. Most notably persons who define themselves ethnically as Māori have a significantly lower prevalence of MS than the European population. Similarly, a low MS prevalence is seen in those of Pacific and Asian origin with a combined 15 cases identified. Due to low numbers no further analysis was undertaken on these two groups. Prevalence rates by ethnicity were not affected by region (data not shown).

MS prevalence variation by latitude and ethnicity

Using the defined six latitudinal regions of NZ (Figure 1) MS prevalence was plotted against the latitude of the population weighted centroid of each region. Figure 3 demonstrates that there is a clear increase in MS prevalence with increasing latitude south of 37°. To assess the relationship between MS prevalence and latitude a linear model has been fitted to the southern five regions. The linear model has not been fitted to the northernmost region as it appears to go against the linear trend. The northernmost centroid includes Auckland, the largest city in NZ, with around one-quarter of the total population and the highest concentration of recent migrants. The increase in cases of MS found in Auckland compared with the neighboring region, Waikato, could be due to a number of factors, including ethnic mix, internal migration, external migration and availability of services and personal support. While Waikato has the largest population of Māori in NZ this is not the determining factor in the Auckland/Waikato difference as seen by the prevalence for the Māori and non-Māori/Pacific People groups. Similarly when the Northern region is split into its smaller constituents Northland and Auckland, Northland has the same prevalence as the Waikato region. This would indicate that the elevated prevalence in Auckland is due to local factors as outlined above.

MS prevalence for the total population increases by 10.7 ± 0.9 per 100,000 population per degree of latitude south of 37°S ($p < 0.002$). There is no difference in prevalence gradients between the total and non-Māori/Pacific People's populations, supporting the assertion that the non-Māori/Pacific People's group best represents the European population in this study. In the Māori population there is no evidence for a latitude gradient in the North Island; however, in the South Island the latitude gradient is similar to the total population (but not statistically significant due to low numbers), at 11.7 ± 1.4 increase in prevalence per degree of latitude ($p = 0.07$).

MS prevalence variation by latitude, gender and MS phenotype

There were highly significant differences in the latitudinal gradient of MS prevalence by gender ($p < 0.00007$,

Table 4. Prevalence age-standardized to European standard population for major ethnic groups in New Zealand

Ethnic group	Population	MS cases	Prevalence	ASP	ASP CIs
Total	4,027,950	2917	72.4	73.1	70.5–75.8
Māori	565,323	90	15.9	24.2	18.9–29.5
Non-Māori	3,462,606	2827	81.6	78.7	75.7–81.6
Non-Māori/ Pacific Peoples	3,215,667	2823	87.8	82.4	79.4–85.5
European	2,609,586	2699	103.4	101.9	98–105.8

MS, multiple sclerosis; ASP, age and sex adjusted prevalence; CI, confidence interval.

Table 5. Ethnic breakdown of the NZ population by self report from the NZ national population census 2006

Ethnicity responses for total ethnic groups (Thousands (000))(%) by region							
Ethnicity	R1	R2	R3	R4	R5	R6	NZ
European	792(54.6)	445(65.0)	332(70.0)	404(69.8)	417(75.4)	219(76.8)	2610(64.8)
Māori	181(12.5)	164(24.0)	92(19.3)	66(11.5)	40(7.2)	23(8.0)	565(14.0)
Other	115(7.9)	76(11.1)	59(12.3)	66(11.4)	75(13.6)	40(14.1)	431(10.7)
Asian	237(16.3)	27(3.9)	14(2.9)	39(6.7)	30(5.3)	9(3.1)	355(8.8)
Pacific Peoples	182(12.5)	20(2.9)	13(2.6)	36(6.3)	11(2.0)	5(1.6)	266(6.6)
Peoples NEI	77(5.3)	32(4.6)	16(3.3)	19(3.3)	15(2.7)	9(3.2)	168(4.2)
MELAA	19(1.3)	3(0.5)	29(0.4)	6(1.0)	3(0.6)	1(0.5)	35(0.9)
Total stated	1375(94.7)	653(95.4)	458(96.7)	560(96.7)	538(97.3)	276(96.8)	3860(95.8)
Total	1452	685	474	579	553	285	4028

NZ, New Zealand; NEI, no ethnicity indicated; MELAA: Middle Eastern Latin American African.

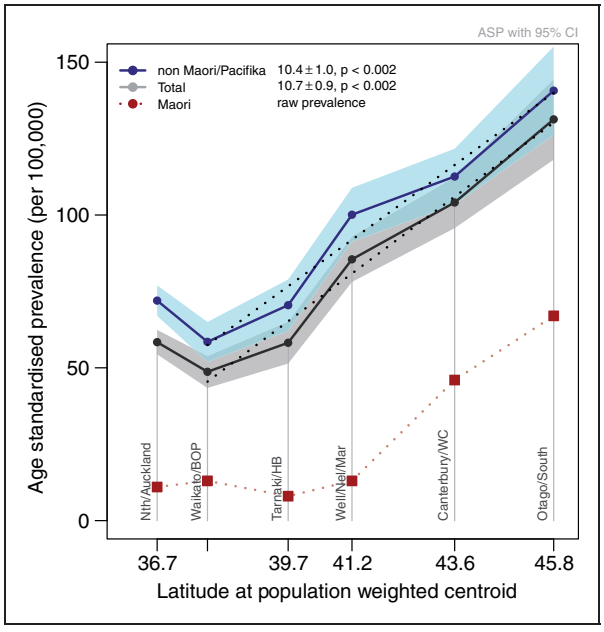

Figure 3. Multiple sclerosis (MS) prevalence by latitude and major ethnic groups in New Zealand (NZ), MS prevalence by region age-standardized to the NZ population with 95% confidence intervals is shown for the total and Non-Māori/Pacific Peoples populations. Raw prevalence is shown for the Māori population as there are insufficient numbers of cases for a valid age standardization.

Figure 4a) and by MS clinical course phenotype (relapsing–remitting/secondary-progressive MS [RMS/SPMS] and primary-progressive MS [PPMS]) ($p < 0.0001$, Figure 4b) and when combined (Figure 4c). ANOVA of a linear model of prevalence with independent slopes and intercepts for each of the four groups shown in Figure 4c, RRMS/SPMS (M or F) and PPMS (M or F), shows evidence for different gradients ($p < 1 \times 10^{-7}$) and that this difference in gradients is driven by the female RRMS/SPMS population.

Gender ratios and age at onset

Neither gender ratios nor age at onset varied by latitude (data not shown). When sex ratios were calculated by quintennial year of birth as per Orton et al.[26] there was no evidence for an increase in gender ratios, with the F:M ratio remaining at or around 3:1 since birth year, 1940.

Discussion

The NZNMSPS has successfully recruited and acquired neurological information on nearly 3000 people living with MS in NZ on census day, 7 March 2006. This is by

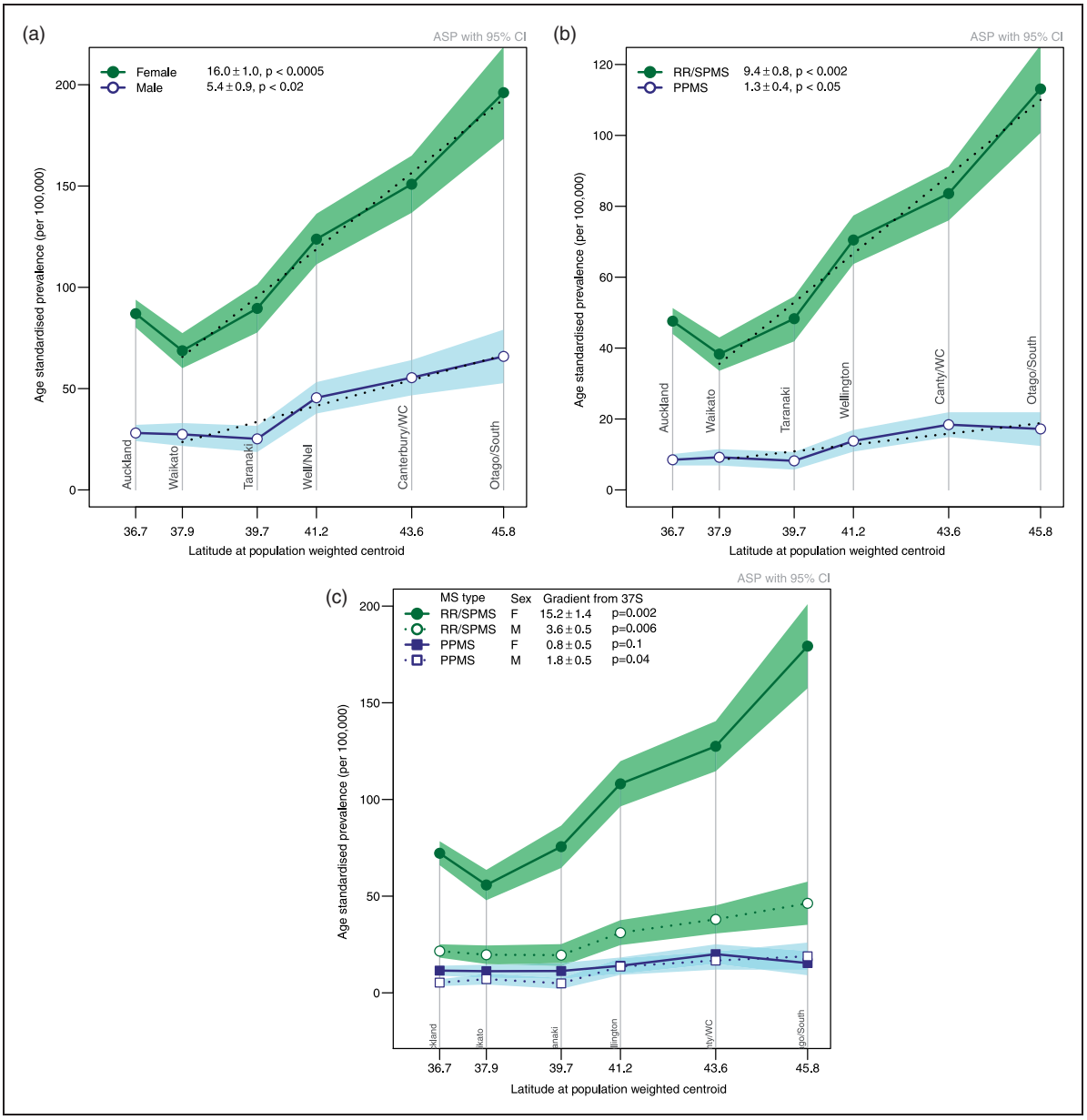

Figure 4. (a) Multiple sclerosis (MS) prevalence latitudinal gradient by gender. A linear model of prevalence on latitude and MS type shows that the gradient for females was about three times that for males ($p < 0.00007$). (b) MS prevalence gradient by clinical course phenotype, a linear model of prevalence on latitude and MS type shows that the gradient for relapsing–remitting (RR)/secondary progressive (SP)MS is 8 ± 0.9 times higher than for primary progressive (PP)MS ($p < 0.0001$). (c) MS prevalence latitudinal gradient by gender and MS clinical course. A linear model of prevalence on latitude, gender and MS type shows that the latitudinal gradient depends on both sex and MS type ($p < 1 \times 10^{-7}$).

far the largest stand-alone cross-sectional MS prevalence survey ever undertaken. CRA indicates that we have detected and phenotyped almost 97% of all individuals with DMS in NZ. The completeness of our data set allows us to undertake detailed analyses of the factors that drive the geographical variability of MS prevalence in NZ, a country ideally suited to research of this type.

The most significant finding from this study is the unequivocal confirmation of a highly significant latitudinal gradient of MS prevalence in NZ, with prevalence increasing threefold between the North and South of the country. The gradient is notable below 37°S. Previous studies have suggested that the factors that drive the latitudinal gradient become significant only above latitude 37°N.[27] In contradistinction to previous

observations[13] the gradient persisted when the population was age and sex standardized. Similarly, ethnic stratification[2] did not influence the latitudinal gradient, with the gradient being strongest amongst those of European origin.

People of Māori origin have a much lower prevalence of MS in NZ: the overall prevalence in people with self defined Māori ethnicity was 30% of that seen in Europeans. No-one with MS and Māori origin had all four Māori grandparents (the majority had one or two Māori grandparents). MS was an uncommon disease among those of Pacific People origin or Asian origin, indicating that these populations may be protected from developing MS. There is, however, a latitudinal prevalence gradient for Māori that mirrors that seen for the European population but appears to start at higher latitudes, indicating that the environmental factors that apply to European populations may also apply to the genetically admixed Māori population.

The MS prevalence gradient was also non-uniform, with gender and MS phenotype significantly affecting the gradient. RRMS/SPMS cases had a latitudinal gradient 7.2 times greater than PPMS cases ($p < 0.0002$), and females had a gradient three times greater than males ($p < 0.00007$). Multiple regressions analysis indicates that females with RRMS/SPMS are the major drivers of the latitudinal gradient ($p < 1 \times 10^{-7}$).

The finding that the latitudinal gradient is non-uniform with females with RRMS/SPMS being the major drivers indicates that the environmental and/or genetic factor(s) that drive the gradient do not act uniformly on all MS cases. There are two possible explanations for the differential gradients.

If the baseline risk is driven by genetic factors and these factors are influenced by sex, with females being more susceptible, then the baseline genetic risk should not vary with latitude. Therefore the observed gradient indicates that there is either a protective factor operating at lower latitudes or a detrimental factor with higher latitude. If the natural rate of occurrence of MS is that seen at higher latitudes then the protective effect of decreasing latitude exerts a greater influence on females and on the inflammatory forms of MS (RRMS). Conversely the natural incidence may be that seen at lower latitudes and the detrimental factors may influence females and inflammatory forms of MS more with increasing latitude.

There are currently two biologically plausible explanations for the latitudinal gradient: decreased ambient winter UVR and subsequent decreased vitamin D levels, and latitudinal variation in susceptibility to late EBV infection,[18] which have been well discussed elsewhere.[3–5,28]

Of note, the gender ratio did not alter with latitude in NZ and there is no evidence that the gender ratio has changed over time. This is in contradistinction to changes noted in Canada.[26,29] This may reflect the latitudinal differences between the two studies or other environmental or genetic differences between the populations.

The finding of differential gradients of MS prevalence by gender and MS phenotype may open up significant areas of research interest and may assist in the development of therapies and intervention strategies at the population level, aimed at reducing the incidence of MS.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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