Original research

Multiple sclerosis mortality in New Zealand: a nationwide prospective study

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ABSTRACT

Background Mortality data from Europe and North America show a shorter life expectancy for people with multiple sclerosis (MS). It is not known if a similar mortality risk exists in the southern hemisphere. We analysed the mortality outcomes of a comprehensive New Zealand (NZ) MS cohort, 15 years postrecruitment.

Methods All participants of the nationwide 2006 NZ MS prevalence study were included and mortality outcomes were compared with life table data from the NZ population using classic survival analyses, standardised mortality ratios (SMRs) and excess death rates (EDRs).

Results Of 2909 MS participants, 844 (29%) were deceased at the end of the 15-year study period. Median survival age for the MS cohort was 79.4 years (78.5, 80.3), compared with 86.6 years (85.5, 87.7) for the age-matched and sex-matched NZ population. The overall SMR was 1.9 (1.8, 2.1)). Symptom onset between 21 and 30 years corresponded to an SMR of 2.8 and a median survival age 9.8 years lower than the NZ population. Progressive-onset disease was associated with a survival gap of 9 years compared with 5.7 years for relapsing onset. The EDR for those diagnosed in 1997–2006 was 3.2 (2.6, 3.9) compared with 7.8 (5.8, 10.3) for those diagnosed between 1967 and 1976.

Conclusions New Zealanders with MS have a median survival age 7.2 years lower than the general population and twice the mortality risk. The survival gap was greater for progressive-onset disease and for those with an early age of onset.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mortality outcomes in multiple sclerosis (MS) have been calculated from a small number of northern hemisphere cohorts but very little data have been published from the southern hemisphere.

WHAT THIS STUDY ADDS

⇒ New Zealanders with MS have an increased mortality risk and survival gap compared with the general population that is similar to northern hemisphere cohorts. This study provides further evidence that progressive-onset disease and early age of symptom onset are negative prognostic factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study presents recent MS mortality data from a comprehensive nationwide southern hemisphere cohort. This analysis, which quantifies the increased mortality risk and survival gap that currently exists for people with MS, can be used to inform decisions on healthcare improvements, resource allocation and to compare contemporary cohorts in the era of high-efficacy treatments.

INTRODUCTION

Multiple sclerosis (MS) mortality rates calculated from large population-based registries in Europe and North America have estimated that people with MS (PwMS) have a life expectancy 6–14 years less than the general population and a mortality risk 2–3 times higher.[1–6] Few mortality data from the southern hemisphere exist and the last nationwide Australian mortality study was published in 1989.[7] In that study, the MS age-standardised mortality rate (SMR) dropped from 0.74 per 100 000 person years in the 1950s to 0.53 in the 1970s.[7] However, only those with MS listed as the underlying cause of death were included and the frequency of MS at death was likely underestimated.[7]

Mortality outcomes have been difficult to compare between studies due to differing methodology and background populations.[8] Recent studies have used a combination of classic survival analyses (Kaplan-Meier curves and Cox regression) with SMRs as well as excess death rates (EDRs).[1–6 8–10]

SMRs are the ratio of observed mortality in the study population to the expected age-matched and sex-matched mortality of the general population.[3] An SMR greater than 1 indicates an excess risk of mortality in the cohort compared with the general population.[3] SMRs tend to reduce with increasing age as there are more competing causes of death.[2]

EDRs are calculated by subtracting the expected number of deaths per 1000 person-years from the observed number of deaths.[9] EDRs vary with age but are accepted as a better method of comparing mortality over different periods than SMRs.[8]

Overall, studies indicate that mortality rates have decreased and life expectancy of PwMS has increased relative to, but not as yet reaching, the levels of the general population.[4 6 10 11] Several key factors have been associated with a higher mortality risk and shorter survival. Those with a younger age of onset have shorter survival from birth compared with older onset PwMS and a higher mortality risk compared with the general population.[3 4 6 10]

Progressive-onset disease has been found to be a negative prognostic factor in most studies, but one recent paper reported a similar survival age for relapsing remitting MS and primary progressive MS.[3 6 12] There have been conflicting reports on the impact of sex on MS survival, complicated by changing sex ratios in MS over time.[8] A recent meta-analysis showed a survival disadvantage for females with MS, with higher SMRs than males.[5]

In this study, we analysed the mortality rates and survival of New Zealanders with MS over 15 years, following a comprehensive nationwide prevalence cohort collected in 2006 with 97% ascertainment of all MS cases. We hypothesised that MS mortality in New Zealand (NZ), assessed using this unique cohort, would be similar to that seen in other countries with advanced healthcare systems and would provide information for future health economic and service provision and to assess the impact of health interventions including the increasing use of high efficacy disease modifying agents. We examined the effect of sex, disease type at onset (relapsing vs progressive), age at onset and diagnosis, and epoch of onset and diagnosis on survival age and mortality rates. We compared the mortality outcomes of New Zealanders with MS with the general NZ population.

METHODS

MS cohort and study design

The NZ MS Prevalence Study (NZMSPS) was conducted with a census day of 7 March 2006 and aimed to recruit all people living in NZ with clinically definite MS.[13 14] Multiple sources were used to identify participants and capture-recapture analysis demonstrated an ascertainment rate of 97%.[13] Clinically definite MS was defined by the McDonald criteria 2005[14] and the diagnosis of all participants was confirmed by the study neurologists.[13 14] Data collected for the NZMSPS included sex, date of birth, ethnicity, age of onset and diagnosis, disease course at onset (relapsing vs progressive onset) and level of disability at entry to the study.[13] All data from participants were stored using a unique identifier number (UIN).[15]

In this study, we analysed the 15-year mortality outcomes for the NZMSPS group. The study period was from the date of enrolment on 7 March 2006 to 7 March 2021.

All 2917 participants in the NZMSPS were included. The NZMSPS UINs were linked to national health index (NHI) numbers, which were used to search electronic records to identify which participants were deceased as of 7 March 2021 and to confirm the dates of death. For those participants in the NZMSPS who did not provide consent for use of their NHI number, their UIN was submitted back to the original referring neurologist who was asked to confirm if the person was alive and if not, their date of death. Once the dates of death were linked to the UINs, the NHIs and other personal identifying information were removed.

Mortality outcomes in the NZMSPS group were compared with the NZ population using national cohort life tables (as revised in 2021).[16] A synthetic age-matched and sex-matched control sample was created using the median life expectancy and variance from the NZ life tables. A hypothetical individual was matched to each person in the MS group based on the cohort life table for a person of their year of birth and sex, conditional on having reached the age that person was at the study census date in 2006. Using this as the conditional age was important to account for the survivorship bias of the MS group having already reached that age. A year of death was then simulated for each synthetic individual by iterating up from the matched MS person's age at census. At each year of age, a random number was generated (uniformly distributed between 0.0 and 1.0). If that number was less than the life table probability of such a person dying within the next year, the age was incremented, and the simulation continued for that individual. If the random number exceeded the probability, then the current age was assigned as the synthetic person's age of death. The control sample was randomly simulated seven times and the one with the median mortality was used as the comparison against the MS group. The expected mortality in the control group was relatively stable across the 7 simulations, varying from 15% to 16%.

Statistical analysis

Survival age

Median survival age for the MS group was compared with the generated age-matched and sex-matched NZ control population. Survival age for both groups was calculated from 2006, using Kaplan-Meier curves, and compared with the log-rank test. The same method was used to compare the survival of subgroups.

Standardised mortality ratios

SMRs and corresponding 95% CIs were calculated to compare the mortality in the MS group and subgroups to the NZ population.

Cox proportional hazards model

A Cox proportional hazards model was used to test whether there was a differential impact of sex on mortality in MS, relative to the substantially earlier mortality of males in the general population.

Excess death rates

EDRs were used to compare the mortality rates of different periods of symptom onset and diagnosis. Periods of onset and diagnosis were divided into 10-year intervals, apart from the earliest cases, which were combined into a longer interval due to small numbers.

All computation was done in R V.4.1.3 and particularly the survival package.[17 18] The creation of the synthetic matched sample from the cohort life tables was done via a publicly available custom R package (msnz).[19] Cls around SMR and EDR values were calculated using the R package PHEindicatormethods.[20]

To investigate possible survivorship bias within this prevalence cohort, the analyses were repeated after excluding those with symptom onset prior to 1990.

RESULTS

MS cohort

Of the 2917 participants enrolled in the NZMSPS, 2909 were included in the mortality analysis. Eight patients were excluded: three were unable to be identified and five were ineligible due to either a change in diagnosis or duplicate entry. The baseline characteristics of the NZMSPS group are presented in table 1.

Ethnicity data were recorded for 2004 (69%) of the study participants. Of those, 1817 (91%) reported their ethnicity as NZ European. Other ethnicities included 54 (3%) Māori, 14 (0.8%) Asian and 3 (0.2%) Pasifika.

MS cohort mortality

At the end of the 15-year study period, 844 (29%) of the MS cohort were deceased. The observed mortality compared with the expected numbers in the population group is shown in table 2.

Table 1 New Zealand multiple sclerosis (MS) cohort characteristics

MS cohort characteristics	N
Total	2909 (100.0%)
Sex	
Female	2184 (75.1%)
Male	725 (24.9%)
Disease type	
Relapsing onset	2386 (82.0%)
Progressive onset	459 (15.8%)
Unknown	64 (2.2%)
Age at 2006 study census (years)	
1–20	11 (0.4%)
21–30	157 (5.4%)
31–40	481 (16.5%)
41–50	782 (26.9%)
51–60	839 (28.8%)
61–70	416 (14.3%)
71–80	196 (6.7%)
81–90	26 (0.9%)
91–95	1 (0.0%)
Age at onset (years)	
0–20	251 (8.6%)
21–30	876 (30.1%)
31–40	937 (32.2%)
41–79	803 (27.6%)
Unknown	42 (1.4%)
Disease duration at 2006 study census (years)	
0–10	1197 (41.1%)
11–20	830 (28.5%)
21–30	500 (17.2%)
31–40	241 (8.3%)
41–50	77 (2.6%)
51–65	22 (0.8%)
Unknown	42 (1.4%)
Period of symptom onset	
1941–1966	130 (4.5%)
1967–1976	292 (10.0%)
1977–1986	541 (18.6%)
1987–1996	933 (32.1%)
1997–2006	971 (33.4%)
Unknown	42 (1.4%)

The median duration of survival from symptom onset for the whole cohort was 45.4 years (95% CI (44.0 to 47.7)). For the relapsing onset group, median survival was 48.7 years (95% CI 47.4 to 50.1) from symptom onset and for the progressive onset group it was 34.6 years (95% CI 31.2 to 36.8).

Mortality risk relative to the NZ population

Standardised mortality ratios

The MS group had approximately twice the mortality risk of the general NZ population (SMR 1.9, 95% CI (1.8 to 2.1)). The SMRs for relapsing and progressive-onset disease compared with the NZ population were similar (1.8 (95% CI 1.7 to 2.0) and 2.2 (95% CI 2.0 to 2.5)), as were the SMRs for males and females compared with the NZ population (2.0 (95% CI 1.8 to 2.3) and 1.9 (95% CI 1.7 to 2.1)) (table 2).

MS symptom onset between 21 and 30 years was associated with the highest mortality risk, almost three times the general population (table 2). Those diagnosed with MS in the same age range had 3.5 times the mortality risk of the NZ population (table 2). An age of onset or diagnosis below 21 years was also associated with high mortality rates but the numbers were smaller and the confidence intervals wide (table 2).

The overall SMR was 2.1 (95% CI 1.9 to 2.4) when MS cases with an onset of symptoms prior to 1990 were excluded.

Cox proportional hazards model

A Cox proportional hazards model testing the interaction effect of sex on age-of-death in MS showed that there were significant hazard ratios associated with having MS (2.27 (95% CI 1.98 to 2.60), $p<0.001$) and with being male in the general population (table 3).

There was, however, no differential impact of sex on age-at-death in MS (HR 1.13 (95% CI 0.88 to 1.46), $p=0.3$) (table 3). A simpler Cox model examining only the effect of having MS produced a very similar HR (2.32 (95% CI 2.07 to 2.61), $p<0.001$).

A test of the proportionality of hazards failed for the comparison of MS versus the population ($\chi^2(1) = 15.1$, $p=0.0001$). This was likely due to the time metric for the model being age-at-death. As shown in the Kaplan-Meier plots, for the first few decades of life, there was little differential mortality: only when a substantial number of cases appeared would there be an impact on survival. Accordingly, this model was repeated with years-since-disease-onset as the survival time metric. On that scale, the two groups begin to diverge almost immediately and the test for proportionality no longer failed ($\chi^2(1) = 2.7$, $p=0.1$). The HR for MS in the duration-at-death model was 2.13 (95% CI 1.90 to 2.40). That is, the non-uniformity of hazard across the life span in the age-at-death model did not materially affect the estimate of the HR.

A more complex Cox proportional hazards model was explored with the additional variables of disease course and age at onset. The model became unstable with the inclusion of age at onset and no additional significant information was gained from adding disease course (online supplemental table 1).

Period analysis using EDRs

The EDR for the group diagnosed most recently (in 1997–2006) was less than half the EDR of those diagnosed between 1967 and 1976 (table 2). A similar reduction in EDR was seen when comparing those with an onset of symptoms in 1997–2006 with the group who became symptomatic in 1967–1976 (table 2).

Survival age relative to the NZ population

The MS group had a median survival age of 79.4 years (78.5, 80.3), compared with 86.6 (85.5, 87.7) in the age-matched and sex-matched NZ population group (figure 1). The survival curves and median survival ages compared with the NZ population for sex and disease type are shown in figures 2 and 3.

Males with relapsing-onset disease had a median survival age 4.8 years lower than the NZ population (77.5 (75.3, 79.5) compared with 82.3 (80.4, 86.2)). Females with relapsing onset lived 5.9 years less than expected (81.0 (80.1, 82.5) compared with 86.9 (85.5, 88.2)). Females with progressive onset had a survival age 9.3 years lower than the NZ population (78.9 (78.0, 82.6) compared with 88.2 (85.5, 89.8)). The largest survival gap was seen for males with progressive onset, surviving 11.6 years less than NZ males without MS (75.0 (72.3, 77.4) compared with 86.6 (81.2, upper limit undefined)) (figure 3).

Median survival age varied by age at symptom onset (figure 4). Symptom onset between 21 and 30 years was associated with the

Table 2 Multiple sclerosis (MS) cohort compared with New Zealand population with standardised mortality ratios (SMR) and excess death rates (EDR)

Group	n	Observed mortality	Expected mortality	SMR	EDR	Patient years
MS cohort	2909	844 (29%)	438 (15%)	1.9 (1.8, 2.1)	4.8 (4.4, 5.3)	83899
Sex						
Female	2184	600 (27%)	316 (14%)	1.9 (1.7, 2.1)	4.4 (3.9, 5.0)	64308
Male	725	244 (34%)	122 (17%)	2.0 (1.8, 2.3)	6.2 (5.2, 7.4)	19591
Disease course						
Relapsing onset	2386	579 (24%)	316 (13%)	1.8 (1.7, 2.0)	3.7 (3.3, 4.2)	70176
Progressive onset	459	232 (51%)	104 (23%)	2.2 (2.0, 2.5)	10.4 (8.7, 12.4)	12266
Unknown	64	33 (52%)	18 (28%)	1.8 (1.3, 2.6)	10.3 (5.8, 17.0)	1457
Age at onset (years)						
0–20	251	61 (24%)	24 (10%)	2.5 (1.9, 3.3)	3.9 (2.8, 5.4)	9459
21–30	876	193 (22%)	70 (8%)	2.8 (2.4, 3.2)	4.3 (3.6, 5.1)	28595
31–40	937	240 (26%)	133 (14%)	1.8 (1.6, 2.0)	4.0 (3.3, 4.8)	26820
41–79	803	321 (40%)	194 (24%)	1.7 (1.5, 1.8)	6.7 (5.6, 7.9)	19026
Unknown	42					
Age at diagnosis (years)						
1–20	88	20 (23%)	7 (8%)	2.9 (1.7, 4.4)	4.9 (2.6, 8.4)	2653
21–30	586	117 (20%)	33 (6%)	3.5 (2.9, 4.2)	4.8 (3.9, 6.0)	17369
31–40	915	219 (24%)	93 (10%)	2.4 (2.1, 2.7)	4.7 (3.9, 5.6)	26962
41–85	1286	472 (37%)	297 (23%)	1.6 (1.4, 1.7)	4.8 (4.1, 5.6)	36372
Unknown	34					
Period of onset						
1941–1966	130	88 (68%)	62 (48%)	1.4 (1.1, 1.7)	3.6 (2.3, 5.2)	7279
1967–1976	292	157 (54%)	78 (27%)	2.0 (1.7, 2.4)	6.0 (4.8, 7.5)	13072
1977–1986	541	204 (38%)	111 (21%)	1.8 (1.6, 2.1)	4.8 (3.9, 5.9)	19390
1987–1996	933	232 (25%)	106 (11%)	2.2 (1.9, 2.5)	5.0 (4.1, 5.9)	25430
1997–2006	971	134 (14%)	64 (7%)	2.1 (1.8, 2.5)	3.7 (2.9, 4.7)	18728
Unknown	42					
Period of diagnosis						
1945–1966	33	23 (70%)	18 (55%)	1.3 (0.8, 1.9)	2.7 (0.9, 6.3)	1848
1967–1976	140	94 (67%)	44 (31%)	2.1 (1.7, 2.6)	7.8 (5.8, 10.3)	6377
1977–1986	402	203 (50%)	107 (27%)	1.9 (1.6, 2.2)	6.1 (5.0, 7.5)	15614
1987–1996	844	279 (33%)	139 (16%)	2.0 (1.8, 2.3)	5.3 (4.5, 6.3)	26304
1997–2006	1456	229 (16%)	122 (8%)	1.9 (1.6, 2.1)	3.2 (2.6, 3.9)	33214
Unknown	34					

largest survival gap compared with the NZ population, of 9.8 years (77.6 (75.1, 80.3) compared with 87.4 (84.5, 88.9)).

When those with symptom onset prior to 1990 were excluded from the analysis, the MS group had a median survival age of 78.5 years (77.4, 81.9), compared with 86.5 (83.8, 91.7) in the age-matched and sex-matched NZ population.

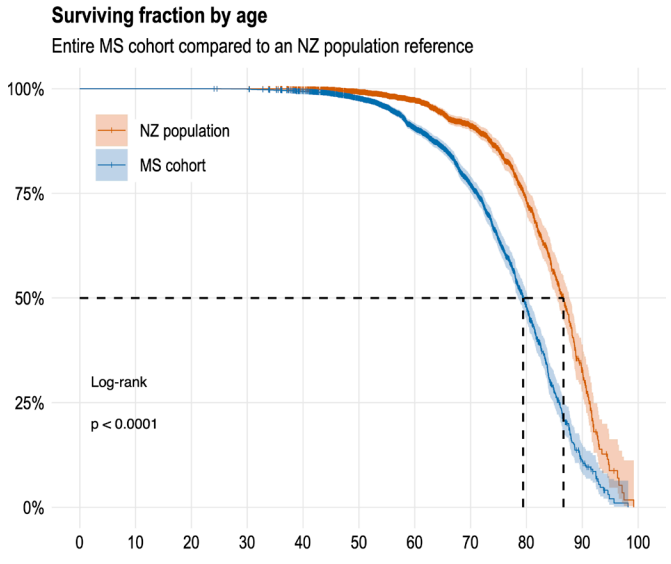
Table 3 Cox proportional hazards model testing differential impact of sex on multiple sclerosis (MS) mortality

Characteristic	HR	95% CI	P value
Sample			
NZ population	—	—	
MS cohort	2.27	1.98 to 2.60	<0.001
Sex			
Female	—	—	
Male	1.41	1.14 to 1.73	0.001
Sample×sex			
MS cohort×male	1.13	0.88 to 1.46	0.3

NZ, New Zealand.

DISCUSSION

To our knowledge, this is the first nationwide MS mortality study to be conducted in the southern hemisphere in the last 30 years. These data reflect the most recent 15-year mortality outcomes for New Zealanders with MS. New Zealanders with MS had a median survival age 7.2 years lower than the general population and twice the overall mortality risk. These results are similar to recent studies of Canadian and European MS cohorts, which found a difference in life expectancy of 6–9 years and a mortality risk 2–3 times higher than their general populations.[3–6 9–11] The median duration of survival from symptom onset was 45 years, which is comparable to other contemporary MS cohorts and much longer than a reported median survival in 1969 of only 17 years.[3 4 10 11 21] MS survival has increased relative to the general population in the last 30 years.[2 6 10 11] This may be due to improved general medical care for PwMS, use of disease modifying therapy, treatment of complications and comorbidities, and provision of disability rehabilitation.[2 6 10 11] It is also thought that there may be more benign MS cases occurring, or simply greater inclusion of benign cases in mortality studies.[2 10 11]



Sample	Cases	Deaths	Median survival
MS cohort	2909	844	79.4 [78.5, 80.3]
NZ population	2909	438	86.6 [85.5, 87.7]

Figure 1 Kaplan-Meier survival curve comparing survival age of multiple sclerosis (MS) cohort to New Zealand (NZ) population.

There was no significant difference in mortality risk between males and females in our MS population. Both sexes had approximately twice the risk of dying compared with the average New Zealander and the difference in survival age was similar to the 3.5 year sex difference in the general NZ population.[22] By contrast, many studies have found a higher mortality risk for females with MS, despite their longer population life expectancy.[5] The reasons for this are unclear but higher rates

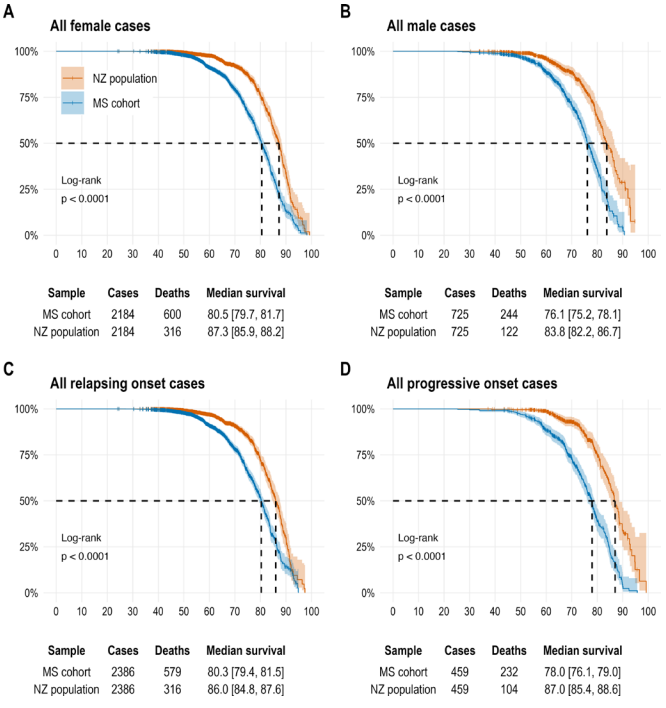


Figure 2 Kaplan-Meier survival curves comparing survival age of multiple sclerosis (MS) cohort subgroups to New Zealand (NZ) population.

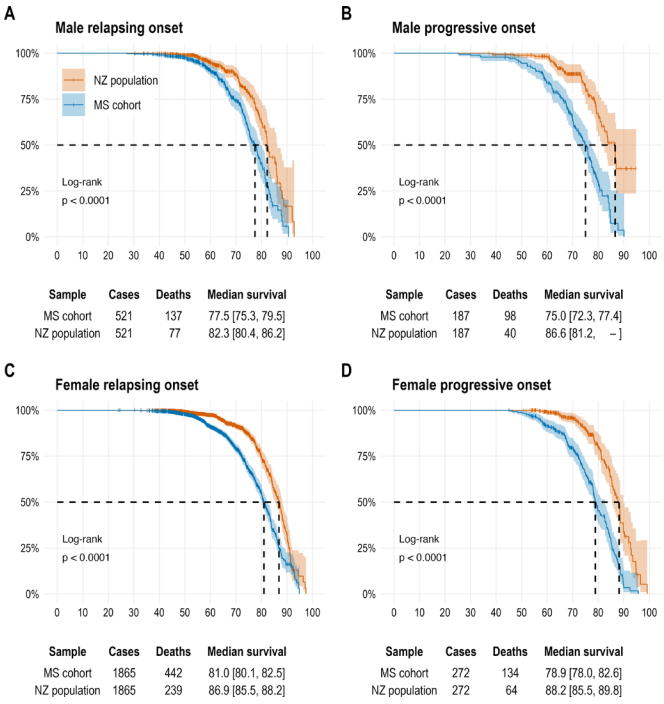
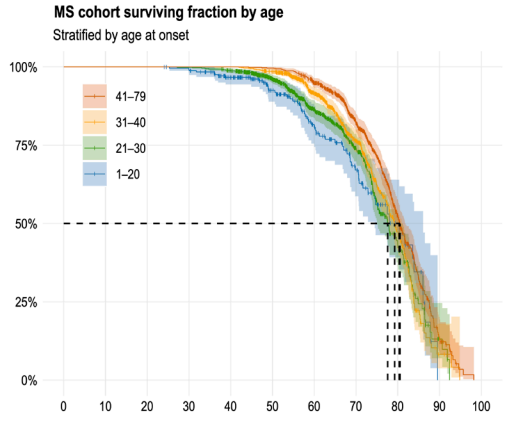


Figure 3 Kaplan-Meier survival curves comparing survival age of multiple sclerosis (MS) cohort subgroups of sex and disease type to New Zealand (NZ) population.

of cardiovascular disease have been found in females with MS compared with males with MS, and excess mortality due to circulatory disease in females with MS compared with the general population.[6 23]

Both progressive and relapsing-onset groups had approximately twice the mortality risk of the NZ population, however, there was a much larger survival gap seen for progressive-onset disease. When we examined the subgroups of sex and disease type, we found that males with progressive-onset disease had the largest disparity in median survival age, living 11.6 years less than NZ men without MS. This is different from other studies



Onset age	Cases	Deaths	Expected deaths	Median survival	Expected survival
1-20	250	60	24	80.3 [74.5, 86.1]	85.0 [81.8, –]
21-30	876	193	70	77.6 [75.1, 80.3]	87.4 [84.5, 88.9]
31-40	937	240	133	79.2 [78.0, 81.2]	85.5 [82.8, 87.8]
41-79	803	321	194	80.5 [79.4, 81.9]	87.0 [85.9, 88.7]

Figure 4 Kaplan-Meier survival curve comparing survival age of multiple sclerosis (MS) cohort stratified by age of symptom onset to New Zealand population.

where a survival disadvantage for women with progressive-onset MS has been identified.[3] Investigation of the causes of death in these subgroups may provide insight into factors contributing to the poor survival of NZ males with progressive-onset disease.

A younger age of onset of MS has frequently been associated with a higher mortality risk.[3 4 6 10] We found a similar effect, with the highest mortality risk and greatest difference in median survival compared with the general population seen in those with an age of onset between 21 and 30 years. A similar pattern was seen with age of diagnosis, with those diagnosed between 21 and 30 years having an even higher mortality risk compared with the general population. One factor that could contribute to higher SMRs in people with younger onset MS is that there are fewer competing causes of death at younger ages. The stronger effect of age of diagnosis on mortality risk may be confounded by greater severity of disease leading to a younger age of diagnosis. Longer disease exposure over a lifetime also negatively affects survival. Whether this relates to the disease itself, complications or associated risk factors such as cardiovascular disease, is still unknown. It will be important to monitor this effect in the future as to whether increasing exposure to high-efficacy disease-modifying treatments (DMT) has an impact on survival.

This study is different to others recently published, in that a prevalence cohort was used. Prevalence cohorts can lead to left-truncated survival data and survivorship bias.[24] Those born in earlier decades with more severe MS or associated comorbidities may have died before the start of the study period in 2006. To investigate the potential of survivorship bias, we ran the analyses again after excluding those with an onset of symptoms before 1990. Removing the earlier cases resulted in a reduction in survival age by 1 year in the MS group and a small increase in the mortality risk from 1.9 (1.8, 2.1) to 2.1 (1.9, 2.4). This suggests that ascertainment bias is having a small effect on our overall mortality outcomes in that only cases from earlier decades who survived until 2006 were able to be included. This means that the survival age of New Zealanders with MS is likely to be lower than calculated from this cohort. That is, the gap in survival between PwMS and the general population may be larger than what we have estimated.

Recently published longitudinal MS studies have reported a decline in excess death rates in MS over time.[2 6 10 11] This was also seen in our cohort, with those diagnosed most recently having approximately half the EDR of those diagnosed over 30 years ago. Our MS cohort had less exposure to DMT than their contemporaries in countries with similarly advanced healthcare systems.[25] Beta-interferon first became available in NZ in 2000.[26] By 2006, a total of 551 New Zealanders with MS had been approved for treatment with beta-interferon 1a or 1b, or glatiramer acetate (19% of the prevalence cohort).[27] High efficacy DMTs only became available in 2015.[27] This study provides baseline data to compare the effect of high efficacy DMTs on mortality rates in future.

The strengths of this study are that it was a nationwide cohort with referrals from multiple sources, leading to an ascertainment rate of 97% of all PwMS in NZ in 2006.[13] Fifteen years later, we had an exceptionally high retention rate with 99% of the original dataset included in this mortality analysis. In addition, when designing the mortality analysis, we recognised that relative survival and life expectancy vary greatly depending on the conditional age used to compare the MS cohort and the general population. While other studies have compared survival from birth or disease onset, we sampled synthetic controls from the population conditional on having reached the much later age-at-study-entry. This took into account the age that each person with MS had lived until 2006. In some previous papers, the population curve shows early divergence from the MS sample due to expected child mortality and other early causes of death in the general population.[4] Not equating the population group for the conditional age at census will tend to reduce apparent differences, as the MS group by definition had survived these earlier periods, simply by virtue of being alive at the study census date.

The majority of our participants who reported their ethnicity identified as being NZ European (91%). The prevalence of MS in the Māori population is known to be much lower than in NZ Europeans (15.9 vs 103.4 per 100 000.)[13] The life expectancy for Māori in the general population is approximately 7 years shorter than for non-Māori New Zealanders and the difference is likely to be even greater for the small number of Māori affected by MS.[28] A longitudinal cohort collecting a larger number of cases is likely needed to accurately investigate the survival of Māori with MS.

We have shown that New Zealanders with MS have a similar reduction in survival to that seen in populations in Europe and Canada. NZ males with progressive-onset MS and those with an age of onset in their 20s had the largest gaps in survival compared with the general NZ population. Although over 50% of MS deaths are thought to be secondary to the disease, PwMS have higher rates compared to the general population of almost all major causes of death except cancer.[2 5] Further investigation into the causes of death and associated comorbidities of PwMS may offer insight into why this gap in survival remains.

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Contributors Study concept and design: RL, DFM, MM, DJM and PJ. Data acquisition: DFM, BVT, RL, PJ and NZMSPS group. Data analysis and interpretation: RL, DFM, MM and DJM. Statistical analysis: MM and DJM. Drafting the manuscript: RL, DFM, MM and PJ. Critical revision of the manuscript for important intellectual content: RL, DFM, BVT, MM, DJM, PJ and NZMSPS group. Funding acquisition: DFM and RL. Study supervision: DFM and BVT. RL is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Health and Disability Ethics Committees of the New Zealand Ministry of Health. Reference: 18/NTA/10. Many participants were deceased and therefore unable to provide consent at the time of the study. The majority of the original NZMSPS 2006 cohort had consented to their data being included in ongoing research. For those who had not consented, deidentified information was obtained from their neurologist, to ascertain whether or not they were deceased and if so, their date of death.

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Data availability statement Data are available on reasonable request. Requests for data should be made to the corresponding author, RL, and will be reviewed by our steering committee.

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Supplemental Table 1: Cox proportional hazards models testing differential impact of sex and disease course on multiple sclerosis mortality

Characteristic	HR[1]	95% CI[1]	p-value
Sample			
NZ population	—	—	
MS cohort	2.08	1.82, 2.39	<0.001
Disease course			
Relapsing onset	—	—	
Progressive onset	0.85	0.68, 1.07	0.2
Sample × Disease course			
MS cohort × Progressive onset	1.52	1.16, 1.99	0.002

[1]HR = Hazard Ratio, CI = Confidence Interval

Characteristic	HR[1]	95% CI[1]	p-value
Sample			
NZ population	—	—	
MS cohort	2.12	1.81, 2.49	<0.001
Sex			
Female	—	—	
Male	1.55	1.20, 2.01	<0.001
Disease course			
Relapsing onset	—	—	
Progressive onset	0.82	0.62, 1.09	0.2
Sample × sex			
MS cohort × Male	0.93	0.68, 1.29	0.7
Sample × Disease course			
MS cohort × Progressive onset	1.39	0.99, 1.95	0.059
Sex × Disease course			
Male × Progressive onset	0.89	0.56, 1.43	0.6
Sample × sex × Disease course			
MS cohort × Male × Progressive onset	1.35	0.76, 2.39	0.3

[1]HR = Hazard Ratio, CI = Confidence Interval