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Original Research Paper

The effect of national disease-modifying therapy subsidy policy on long-term disability outcomes in people with multiple sclerosis

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Abstract

Background: Disease-modifying therapies (DMTs) are used to treat people with relapsing-onset multiple sclerosis (ROMS), but our knowledge is largely limited to their short-term effects.

Objective: To determine (1) the impact of national-level DMT subsidy policy on DMT use and health outcomes in people with MS (PwMS) and (2) the long-term effects of DMT on disability and quality of life (QoL; 5-level EQ-5D version (EQ-5D-5L) utility value).

Methods: This observational cohort study compared Australian and New Zealand populations with different levels of DMT availability 10–20 years post-ROMS diagnosis. Between-country differences were assessed using standardised differences. Associations were assessed with multivariable linear regression models.

Results: We recruited 328 Australians and 256 New Zealanders. The Australian cohort had longer DMT treatment duration, greater proportion of disease course treated and shorter duration between diagnosis and starting DMT. The Australian cohort had lower median Expanded Disability Status Scale (EDSS) (3.5 vs 4.0) and Multiple Sclerosis Severity Score (MSSS) (3.05 vs 3.71) and higher QoL (0.71 vs 0.65). In multivariable models, between-country differences in disability and QoL were largely attributed to differential use of DMT.

Conclusions: This study provides evidence for the impact of national-level DMT policy on disability outcomes in PwMS. Where DMTs are more accessible, PwMS experienced less disability progression and improved QoL 10–20 years post-diagnosis.

Keywords: Multiple sclerosis, disease-modifying therapies, health policy

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Introduction

Disease-modifying therapies (DMTs) modify, modulate or suppress the immune system and are commonly used to treat relapsing onset forms of multiple sclerosis (relapsing-onset multiple sclerosis (ROMS), relapsing-remitting MS and secondary progressive MS). DMTs modulate immune system attacks on the central nervous system that are characteristic of MS pathology.[1] There is good evidence that DMTs improve health outcomes in people with MS (PwMS), including disability and relapse rate.[2,3] Furthermore, early treatment with DMTs improves health outcomes compared to treatment that has been delayed.[4–8] Although less certain, there is substantial and growing evidence on relative effects of DMTs showing that DMT selection can significantly affect health outcomes.[9] This suggests that differential access to DMTs may affect health outcomes in PwMS.

Governments that subsidise healthcare costs balance the cost of medication and potential health and economic benefits of treatment when making reimbursement decisions.[10] National policy in countries with universal healthcare determines funding for treatment and consequently which treatments are accessible to most PwMS. This is particularly true for DMTs, which cost the Australian government AU$15,000 per year per person, on average,[11] with costs increasing

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over time.[12] However, while they improve health outcomes in PwMS, DMTs can have important adverse effects.[13] Further complicating things is the fact that, in general, higher efficacy second- and third-line DMTs have a greater risk of adverse effects than first-line DMTs.

The high cost and risk of serious adverse effects complicate DMT risk–benefit and cost-effectiveness calculations. Consequently, different nations have chosen different approaches to subsidise DMTs. But comparing national policies presents methodological challenges; it is difficult to quantify the effect of policy decisions because they cannot be assessed in randomised trials. Observational cohort studies, in which differences in treatment are determined by sociopolitical or economic factors rather than participant-related factors, present a unique opportunity to explore the effects of DMT treatment through a public health lens.[14,15] Such studies allow for the evaluation of policy and other health system factors.

We compared disability and health-related quality of life (HRQoL) between cohorts of PwMS in Australia and New Zealand (NZ). Both countries have a similar population composition[16] and universal healthcare. However, historically, DMTs have been significantly more accessible in Australia. To assess the impact of differential national DMT subsidy policy between Australia and NZ on DMT use and health outcomes in PwMS, we examined: (1) whether there were differences in DMT usage and health outcomes between countries and (2) whether differences in health outcomes between countries were attributable to differences in DMT usage.

Methods

In this study (the CompANZ study), we collected data from two extant cohorts, one in NZ and one in Australia. All participants gave their informed consent to participate in this study.

Australia and NZ are demographically and politically similar, but have differed in DMT availability. The Australian Pharmaceutical Benefits Scheme began funding DMTs in 1996 and has gone on to fund all DMTs approved for use by people with ROMS with minimal restrictions. NZ's equivalent body, the Pharmaceutical Management Agency, started funding DMTs in 1999 with greater limits on DMT access than Australia; restrictions were related to disability level, relapse and magnetic resonance imaging (MRI) results.[17] For more details, see Appendix 1.

NZ cohort

The NZ cohort comprised participants from the 2006 NZ MS Prevalence Study (NZMSPS). The NZMSPS surveyed approximately 97% of PwMS and included neurologist-assessed disability level (Expanded Disability Status Scale (EDSS)).[18] The NZ multiregional ethics committee approved the NZMSPS. This study included NZMSPS participants with ROMS diagnosed between 1 January 1996 (year DMTs were first subsidised in Australia) and 31 December 2006 (to allow $\geqslant$10 years of follow-up).

From March 2017 to February 2018, we followed up NZMSPS participants meeting the inclusion criteria who had consented to participate in future research using contact details provided during the NZMSPS. Those whose contact details were outdated or whom we were unable to contact directly were contacted using details associated with their National Health Index (NHI) number. All contact details were tried at least once.

Australian cohort

The Australian cohort was recruited from the Australian MS Longitudinal Study (AMSLS), an ongoing longitudinal cohort study of >2500 participants. The University of Tasmania Health and Medical Human Research Ethics Committee approved the AMSLS. Every year, participants in the AMSLS are invited to complete surveys. Those with ROMS diagnosed between 1 January 1996 and 31 December 2006 completing surveys online were invited to complete the CompANZ survey.

Measurements

Data were collected from the NZ cohort in a single questionnaire that took approximately 45 minutes to complete. NZ participants were given the choice of completing the survey over the phone or online. The AMSLS had already collected most of the data from the Australian cohort via its regular surveys, primarily in 2016–2017 (Supplementary Table 1). The CompANZ survey captured data not yet collected, including DMT treatment history before 2010 and current disability. The Australian CompANZ survey took approximately 10 minutes to complete and was administered online from October 2017 to February 2018.

Most of the questions asked in both cohorts were standard questions and scales (see below). Where questions were not standard, the NZ questionnaire was modelled on AMSLS surveys, using the same language and structure.

Outcomes. Our outcome measures were disability (EDSS and Multiple Sclerosis Severity Score (MSSS), both 0–10 scales) and HRQoL (5-level EQ-5D version (EQ-5D-5L) utility value). The CompANZ survey queried the year of MS diagnosis to determine disease duration, measured current EDSS via the web-EDSS[19] (a validated online version of the tool) and thus calculated the MSSS, a relative measure of disease progression.[20] The CompANZ study evaluated HRQoL using the EQ-5D-5L, which is a −0.5 to 1 scale.[21]

Disease-modifying therapy. We queried DMT use, including the history of DMT treatment and participation in DMT trials where treatment allocation was known. The NZ cohort was presented with a list of DMTs and reported the total number of months of use for each. In the Australian cohort, total DMT duration was calculated by summing the duration of use of all DMTs. Post-2010 DMT use was calculated from the 2015–2016 AMSLS surveys (participants gave treatment name, start and end dates of use). Pre-2010 DMT use was reported as total months of use for a particular DMT, rather than start and end dates. We also collected self-reported time between diagnosis and first DMT use from both cohorts.

From the above information, we derived four DMT variables: *time to first DMT, total DMT duration, ever used DMT* and *DMT treatment fraction. Ever used DMT* was a binary variable; all participants who reported using a DMT for ⩾1 month were categorised as a DMT user. *DMT treatment fraction* was a measure of relative DMT use defined as the number of months of DMT treatment divided by months of MS duration (from the year of diagnosis).

In both cohorts, implausible DMT exposure values (i.e. those that exceeded the amount of time DMT had been available) were excluded from analyses of *total DMT duration* and *DMT treatment fraction*, but these participants were still categorised as DMT users for the *ever used DMT* variable (six participants, three from Australia and three from NZ). Similarly, implausible disease duration values (⩾300 months, exceeding possible duration with diagnosis 1996 or later) were excluded.

Other measures. We collected data on age, sex, relationship status, education level, weight and height, physical activity (International Physical Activity Questionnaire (IPAQ)–Short Form),[22] smoking status and number of cigarettes smoked, vitamin D supplement use, fatigue (Fatigue Severity Scale (FSS)),[23] anxiety and depression (Hospital Anxiety and Depression Score (HADS)).[24] Body mass index (BMI) was calculated from self-reported height and weight using the formula weight (kg)/height (m)^2.

Primary predictor and outcome variables

The primary predictor variables for our analyses were country of residence and *DMT treatment fraction*. The primary outcomes of interest were EDSS and MSSS, and HRQoL (EQ-5D-5L utility value).

Analysis

Cohort representativeness. The representativeness of the NZ cohort was determined by comparing the characteristics of (1) NZMSPS participants who met our inclusion criteria and could be contacted (invited) with those who were not contactable (not invited) and (2) invited people who completed the survey (completers) with those who did not (non-completers). The representativeness of the Australian cohort was determined by comparing the characteristics of those who were eligible but did not complete the CompANZ survey (non-completers) with those who did (completers). Comparisons were made using standardised differences (Cohen's *d*, phi coefficient and Cramer's *V*). The phi coefficient is used to compare categorical variables between two groups; values range from −1 to 1, with values between −0.3 and 0.3 generally considered as showing no association. Cramer's *V* is used to compare categorical variables in more than two groups; values range from 0 to 1, with values near 1 demonstrating an association. Cohen's *d* calculates effect sizes for the difference between means in two groups. We used guidance from Cohen and Sawilowsky to evaluate results.[25,26]

Comparison of study cohorts

Baseline characteristics of the NZ and Australian cohorts were compared using standardised differences. Primary predictor variables and outcomes of interest were compared using chi-square tests and Wilcoxon rank-sum (Mann–Whitney) tests of equal medians. *Time to first DMT* was assessed using the Kaplan–Meier method and differences between countries were compared using a log-rank test.

We evaluated associations between the measures of DMT use, country of residence, demographic and lifestyle factors, and primary outcomes using linear regression models adjusted for age. Because outcomes were markedly skewed, these were transformed to reduce heteroskedasticity; we used Box–Cox regression to identify transformation theta

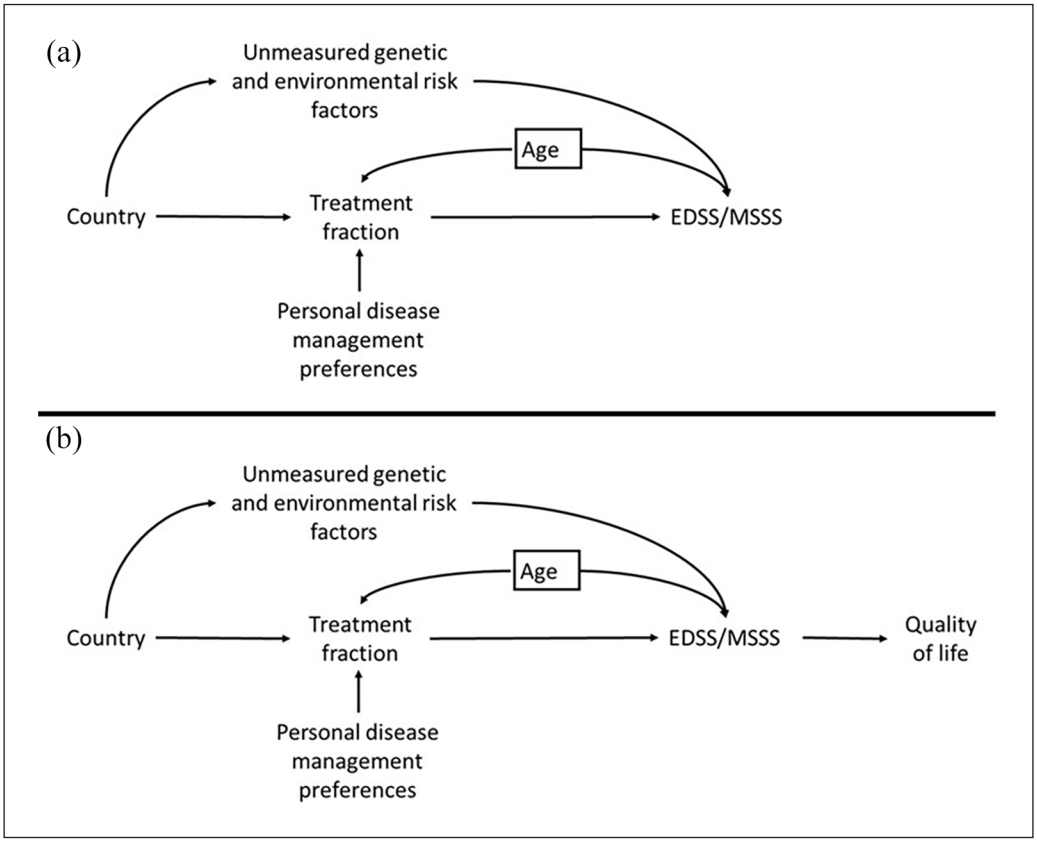

Figure 1. Direct acyclic graph (DAG) of the association between (a) country and disability outcomes and (b) country, disability outcomes and quality of life. The assumed causal relationships suggest that the association between country and disability may be mediated through DMT exposure and that the relationship between country and quality of life may be mediated through DMT exposure and disability. Boxes indicate conditioning in multivariable models.

coefficients. All coefficients were back-transformed at the mean of model covariates.

Based on the outcomes of the adjusted analyses enriched with expected associations (illustrated with a directed acyclic graph (DAG; Figure 1), we developed multivariable models that were used to evaluate associations between country of residence, *DMT treatment fraction* and disability, adjusted for age. Similarly, we developed a multivariable model to evaluate associations between country of residence, *DMT treatment fraction* and HRQoL, adjusted for age.

A single measure of DMT exposure, *DMT treatment fraction*, was included in the multivariable models to avoid multicollinearity. In multivariable models assessing HRQoL, measures of disability were excluded, as disability falls on the same pathway as *DMT treatment fraction* in our DAG.

All analyses were carried out in Stata/SE 16 (StataCorp, College Station, TX, USA).

Results

Cohort recruitment

Of the 2917 NZMSPS participants, 869 met inclusion criteria (Figure 2). Of these, 7 were excluded due to change in diagnosis, 46 were deceased, and we could not contact 395. This left 421 contactable eligible participants. Of these, 93 (22.1%) declined to participate, and 50 (11.8%) were contacted but did not begin the survey (failed follow-up). Two hundred and eighty-eight people began the survey. Eleven withdrew (counted among those that declined), and 25 partially completed the survey. Of these, 22 participants were excluded because they did not provide both EDSS and DMT treatment data.

Therefore, of the 421 contactable eligible NZMSPS completers, 256 (60.8%) were included in analyses (Figure 2(a)). Of these, 50 (19.5%) completed all or part of the survey over the phone. There were few differences between groups. However, as expected, those who completed the survey over the phone were

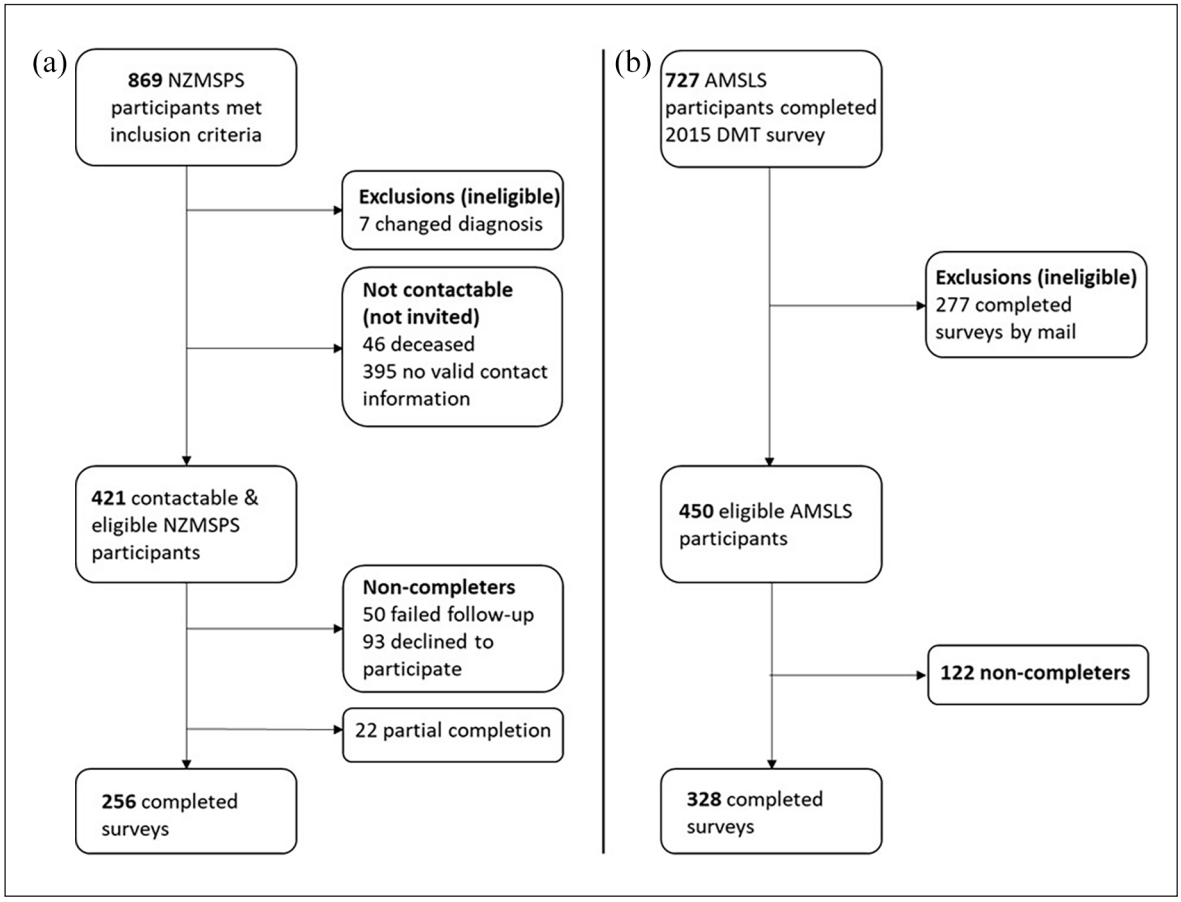

Figure 2. Cohort recruitment flowcharts for (a) New Zealand and (b) Australia.

about 5 years older and had greater disability and lower quality of life (QoL) than those who completed the survey online (data not shown).

Four hundred and fifty AMSLS participants were eligible for this study. Of these, 328 participants completed the online survey (72.9%; Figure 2(b)). Therefore, in total, 584 participants were included in this study.

Cohort representativeness

The invited NZ cohort was broadly representative of the NZMSPS participants who met our inclusion criteria. The invited group did not differ from those who were not invited based on any of the factors assessed (Supplementary Table 2). Similarly, the completers did not differ from the non-completers based on standardised differences.

In the Australian cohort, survey completion was not associated with any of the factors assessed (Supplementary Table 3).

Comparison of Australian and NZ cohorts

Baseline characteristics. The Australian and NZ cohorts did not differ in sex, relationship status, smoking status or education level (Table 1). However, the Australian cohort had a higher prevalence of vitamin D supplementation (71% compared to 34%). Cohen's *d* values suggest that there was no difference by country for BMI, mean FSS or HADS anxiety or depression scores, and only a small difference by age and disease duration (Table 1).

DMT. The Australian and NZ cohorts differed in all measures of DMT exposure (Table 2). The Australian cohort had a higher prevalence of DMT exposure (*ever used DMT*; 94% compared to 50%), a far higher median *total DMT duration* (148 vs. 0 months) and 87.5% shorter median *time to first DMT* (3 vs. 24 months). Consequently, the Australian cohort had a far greater median *DMT treatment fraction* (0.86 vs. 0).

Disability and HRQoL. The NZ cohort had a higher median EDSS than the Australian cohort (Table 2, 4.0 ± 3.5 vs 3.5 ± 3.25, $p = 0.0018$). To account for

Table 1. Baseline characteristics of the Australian ($n = 328$) and New Zealand ($n = 256$) cohorts (total $N = 584$).

Characteristic	Australian cohort, *n* (%)	New Zealand cohort, *n* (%)	phi coefficient
Sex, $n = 584$			
Female	267 (81.4)	203 (79.3)	0.001
Male	61 (18.6)	53 (20.7)	
Relationship status, $n = 504$			
Partnered	179 (72.2)	185 (72.3)	0.001
Unpartnered	69 (27.8)	71 (27.7)	
Vitamin D supplementation, $n = 505$			
No	73 (29.3)	170 (66.4)	0.371
Yes	176 (70.7)	86 (33.6)	
Smoking status, $n = 509$			
No	231 (91.3)	233 (91.0)	0.005
Yes	22 (8.7)	23 (9.0)	
Education level, $n = 581$			Cramer's *V*
Secondary school or less	52 (15.9)	94 (37.2)	0.253
Occupational diploma[a]	121 (36.9)	83 (32.8)	
Bachelor's degree or greater	155 (47.3)	76 (30.0)	
Characteristic	Australian cohort mean (SD)	New Zealand cohort mean (SD)	Cohen's *d*
Age at survey start, $n = 584$	53.5 (12.6)	55.3 (9.7)	0.154
Disease duration, $n = 555$	15.5 (2.9)	15.9 (3.4)	0.144
BMI, $n = 503$	26.9 (6.5)	27.5 (10.3)	0.066
Fatigue and mental health			
Mean FSS, $n = 550$	4.54 (1.59)	4.66 (1.66)	0.079
HADS anxiety score, $n = 582$	6.32 (3.93)	6.32 (3.68)	0.000
HADS depression score, $n = 582$	4.94 (3.61)	5.07 (3.50)	0.036

BMI: body mass index; FSS: Fatigue Severity Score; HADS: Hospital Anxiety and Depression Score.
[a]Occupational diploma: occupational or national certificate or diploma or associate degree.

the marginal between-country difference in disease duration, we also evaluated MSSS; the NZ cohort had a higher median MSSS (3.79 ± 4.02 vs 3.05 ± 3.45, $p = 0.010$). NZ participants also reported a lower HRQoL than Australian participants (Table 2; EQ-5D-5L utility value of 0.65 ± 0.40 vs 0.71 ± 0.42, $p = 0.0085$).

Multivariable models of disability

Models adjusted for age showed significant associations between country of residence and disability, with the Australian cohort having, on average, 0.560 lower EDSS and 0.557 lower MSSS scores compared to the NZ cohort (Table 3). *DMT treatment fraction* and *total DMT duration* were also associated with disability (Table 3), with every 0.10 increase in treatment fraction associated with a 0.081 lower EDSS score and 0.073 lower MSSS score, and every year increase in total DMT use associated with a 0.048 lower EDSS and 0.047 lower MSSS score. A longer *time to first DMT* and *ever* (vs never) *use of DMTs* were not associated with disability levels.

We next included both country of residence and *DMT treatment fraction* in the model, adjusted for age. In this model, country was no longer associated with EDSS or MSSS; its effect sizes were reduced by 74% and 35%, respectively (Table 3), suggesting that a substantial part of the difference between the countries was attributable to the difference in *DMT treatment fraction.*

Multivariable models of HRQoL

Similar patterns were observed for HRQoL. Adjusted for age, country of residence was associated with HRQoL, with the Australian cohort having, on average, a 0.066 higher utility value than the NZ cohort (Table 4). *DMT treatment fraction* was also associated, with every 0.10 increase in *DMT treatment fraction* associated with a 0.006 higher utility value. *Total DMT*

Table 2. Differences in DMT variables and health outcomes between the Australian ($n=328$) and New Zealand (NZ; $n=256$) cohorts (total $N=584$).

	Australian cohort	NZ cohort	Chi square coefficient	*p*-value
DMT variables				
Ever used DMT, *n* (%), *n* = 584			144.5	**<0.0001**
No	20 (6.1)	127 (49.6)		
Yes	308 (93.9)	129 (50.4)		
Time to first DMT (months),[a] median (IQR), *n* = 548	3 (11)	171 (NA)[b]	331.5	**<0.0001**
	Median (IQR)	Median (IQR)	*z*-value	*p*-value
Total DMT duration (months), *n* = 576	148.0 (87.5)	0.0 (72.0)	−14.3	**<0.0001**
DMT treatment fraction,[c] *n* = 559	0.86 (1.0)	0.0 (0.39)	−14.3	**<0.0001**
Disability				
MSSS, *n* = 555	3.05 (3.45)	3.79 (4.02)	2.6	**0.010**
EDSS, *n* = 584	3.50 (3.25)	4.00 (3.50)	3.1	**0.0018**
Health-related quality of life				
EQ-5D-5L utility value, *n* = 502	0.71 (0.42)	0.65 (0.40)	−2.6	**0.0085**

DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Score; IQR: interquartile range; EQ-5D-5L: 5-level EQ-5D version.
[a]Time between diagnosis and first DMT treatment; medians calculated using the Kaplan–Meier method and *p*-value derived from a log-rank test.
[b]IQR could not be calculated because the NZ cohort final survival proportion does not reach 0.25.
[c]Treatment fraction = number of months of DMT treatment/number of months disease duration (from diagnosis).
p-values <0.05 are in bold.

duration was marginally associated ($p=0.05$), and again, no associations were seen for *time to first DMT* or *ever use of DMTs*.

When we included both country of residence and *DMT treatment fraction* in the model, country was no longer associated with EQ-5D-5L; its effect size reduced by 24%, suggesting that a part of the between-country difference was attributable to the difference in *DMT treatment fraction*.

Discussion

In this study, we found that PwMS in NZ and Australia, two countries with different national-level DMT subsidy policies, differed significantly in DMT use and, consequently, in disability and HRQoL. In Australia, DMT exposure was markedly greater than in NZ, with a mean proportion of time treated since MS diagnosis of 74% compared to 22%. The mean EDSS score was a half-step lower and MSSS was a half-decile lower than in NZ. These results represent clinically meaningful differences in MS-related disability and disease severity 10–20 years post-diagnosis and were largely driven by differences in DMT exposure. Furthermore, HRQoL was significantly higher among Australian participants, an association that was partially driven by greater DMT exposure.

We compared two populations with similar genetic,[16] economic and environmental characteristics that differed in the national-level DMT funding policy, both historically and at present. Australia, which has been more permissive than NZ, had much more rapid DMT access and far greater DMT exposure. In our study, 93.9% of the Australian cohort had been treated with DMT, compared to 50.4% of the NZ cohort.

The unique circumstances that allowed for this study also provide insight into the long-term effects of DMT treatment. We evaluated the association between DMT exposure and disability and HRQoL using multivariable models. The results are likely to underestimate the strength of association, as this work is susceptible to treatment indication bias, which tends to reduce the chance of finding differences between groups.[27] Despite this, we found that DMT usage was associated with disability and HRQoL, and the results suggest that differences in DMT use underpin the observed clinically significant differences in disability outcomes. This agrees with previous work demonstrating the effects of DMT treatment on health outcomes in PwMS, including disability and relapse,[3] and differences in disability among PwMS in NZ and Australia.[28] Furthermore, the effect sizes that we observed, with greater amounts of DMT treatment resulting in a half-step decrease in EDSS over

Table 3. Associations between country and DMT variables on EDSS score and MSSS.

	EDSS		MSSS	
	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)
Country: Australia (*reference: New Zealand*)	**−0.560 (−0.915 to −0.204)**	−0.147 (−0.420 to 0.126)	**−0.557 (−0.977 to −0.136)**	−0.364 (−0.885 to 0.157)
p-value	**0.002**	0.291	**0.009**	0.171
DMT variables				
DMT treatment fraction[c] (per 0.10 increase)	**−0.081 (−0.124 to −0.039)**	**−0.039 (−0.072 to −0.007)**	**−0.073 (−0.123 to −0.023)**	−0.049 (−0.111 to 0.013)
p-value	**<0.001**	**0.019**	**0.004**	0.124
Total DMT duration (months) (per year)	**−0.048 (−0.072 to −0.012)**	–	**−0.047 (−0.073 to −0.020)**	–
p-value	**0.002**		**0.001**	
Time to first DMT (months)	0.003 (−0.002 to 0.008)	–	0.0007 (−0.005 to 0.006)	–
p-value	0.217		0.808	
Ever used DMT: Ever used (*reference: Never used*)	−0.254 (−0.678 to 0.171)	–	−0.149 (−0.653 to 0.354)	–
p-value	0.242		0.561	

DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Score; CI: confidence interval.
[a]Model 1: Individual variables adjusted for age.
[b]Model 2: Multivariable model including country, treatment fraction and age.
[c]DMT treatment fraction = number of months of DMT treatment/number of months of disease duration (calculated from year of diagnosis).
Results with *p*-values <0.05 are in bold.

10 years, are similar to previous work showing the prevention of 1 EDSS point increase for every 11.6 years of interferon beta or glatiramer acetate treatment.[29]

Our results suggest that the difference in HRQoL between the NZ and Australian cohorts was significant and at least partially driven by the disparity in DMT access.[30] This agrees with previous research demonstrating the strong association between disability and HRQoL.[31] Overall, our results agree with previous work showing that DMT treatment improves health outcomes in PwMS over long-term follow-up periods.[32–34] However, unlike previous studies, we did not find a clear association between the time to first DMT use and long-term health outcomes, likely because of indication bias.

Strengths and limitations

The main strength of this study is its unique historical and sociopolitical context, which has allowed us to compare similar populations in similar political and healthcare systems with different DMT subsidy policies. Although our methodology was robust, there are five important limitations to this study. First, the representativeness of the study cohort is limited in some respects. Although we sought to enrol all NZMSPS participants meeting our inclusion criteria, we only achieved a 29.5% participation rate. Similarly, although the AMSLS is a representative community-based cohort of PwMS, participants voluntarily enrol in the study. In both cases, non-responders may have had significantly more severe or milder disease course than responders, possibly impacting their ability or desire to take part in this study. It is noteworthy that both cohorts had MSSS scores below the fifth decile suggesting that both had lower levels of disability than expected in a typical MS population. These factors generally reduced the magnitude of differences in disability when comparing countries. Second, the Australian cohort had far higher vitamin D supplementation than the NZ cohort. However, previous work has demonstrated that vitamin D supplementation may not significantly affect MS disease activity and is therefore unlikely to influence our results.[35] Third, there was some variance in survey methods between countries and differences in timing for outcome evaluation. Fourth, the self-reported outcomes used in this study may be susceptible to recall bias. Fifth, the study is subject to treatment indication bias. Access to DMT in NZ

Table 4. Associations between country and DMT variables on participant health-related quality of life, assessed by the EQ-5D-5L utility value.

	Model 1[a]		Model 2[b]	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Country: Australia (*reference: New Zealand*)	**0.066 (0.019 to 0.114)**	**0.006**	0.050 (−0.011 to 0.111)	0.107
DMT variables				
DMT treatment fraction[c] (per 0.10 increase)	**0.006 (0.000 to 0.012)**	**0.040**	0.003 (−0.005 to 0.010)	0.501
Total DMT duration (months) (per year)	*0.000 (0.000 to 0.001)*	*0.050*	–	
Time to first DMT (months)	0.000 (−0.001 to 0.000)	0.287	–	
Ever used DMT: Ever used (*reference: Never used*)	−0.025 (−0.080 to 0.030)	0.374	–	
Disability variables				
EDSS	**−0.101 (−0.110 to −0.091)**	**< 0.001**	–	
MSSS	**−0.082 (−0.090 to −0.075)**	**< 0.001**	–	

DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Score; CI: confidence interval; EQ-5D-5L: 5-level EQ-5D version.
[a]Model 1: Individual variables adjusted for age.
[b]Model 2: Multivariable model including country, treatment fraction and age.
[c]DMT treatment fraction = number of months of DMT treatment/number of months of disease duration (calculated from year of diagnosis).
Results with *p*-values < 0.05 are in bold. Marginal results ($p = 0.05$) are italicised.

required significantly more evidence of disability accrual and/or higher relapse activity compared to Australia. As discussed above, treatment indication bias tends to reduce the chances of finding differences between groups,[27] as those most likely to respond to therapy are targeted appropriately and those with mild disease do not receive therapy. Thus, our results are likely to underestimate the effects of DMT use on health outcomes in PwMS.[14]

Conclusion

In conclusion, in this study, we have shown that more permissive national-level DMT funding policy is associated with markedly greater DMT use and lower disability, slower rate of disability accrual and higher HRQoL in people with ROMS. Furthermore, it suggests that greater DMT utilisation may mediate the association of country with disability outcomes 10–20 years post-diagnosis. These results are important for understanding the effects of DMT funding policy and the long-term outcomes of DMT treatment, as these outcomes are not assessed by clinical trials and are only partially assessed by long-term extensions of such trials. These factors may also be important where DMT access is governed by health insurance status or other socioeconomic factors. Due to the period evaluated, this study largely evaluates the impact of first-generation injectable DMTs. Future work should determine the effect of higher-efficacy therapies and continue to explore disparities in treatment access and health outcomes between nations.

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References

1. Reich DS, Lucchinetti CF and Calabresi PA. Multiple sclerosis. *NEJM* 2018; 378: 169–180.
2. Fogarty E, Schmitz S, Tubridy N, et al. Comparative efficacy of disease-modifying therapies for patients with relapsing-remitting multiple sclerosis: Systematic review and meta-analysis. *Mult Scler Relat Disord* 2016; 9: 23–30.
3. Filippini G, Del Giovane C, Vacchi L, et al. Immunomodulators and immunosuppressants for multiple sclerosis in a network meta-analysis (Review). *Cocr Database Syst Rev* 2013; 6: CD008933.
4. Kavaliunas A, Manouchehrinia A, Stawiarz L, et al. Importance of early treatment initiation in the clinical course of multiple sclerosis. *Mult Scler* 2017; 23(9): 1233–1240.
5. Merkel B, Butzkueven H, Traboulsee AL, et al. Timing of high-efficacy therapy in relapsing-remitting multiple sclerosis: a systematic review. *Autoimmun Rev* 2017; 16(6): 658–665.
6. Trojano M, Pellegrini F, Paolicelli D, et al. Real-life impact of early interferonβ therapy in relapsing multiple sclerosis. *Ann Neurol* 2009; 66: 513–520.
7. He A, Merkel B, Brown JWL, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol* 2020; 19(4): 307–316.
8. Brown JWL, Coles A, Horakova D, et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA* 2019; 321: 17587.
9. Trojano M, Tintore M, Montalban X, et al. Treatment decisions in multiple sclerosis – insights from real-world observational studies. *Nat Rev Neurol* 2017; 13(2): 105–118.
10. Drummond M, Brown R, Fendrick AM, et al. Use of pharmacoeconomics information–report of the ISPOR Task Force on use of pharmacoeconomic/health economic information in health-care decision making. *Value Health* 2003; 6: 407–416.
11. Ahmad H, Palmer AJ, Campbell JA, et al. Health economic impact of multiple sclerosis in Australia in 2017. Multiple Sclerosis Research Australia, https://msra.org.au/wp-content/uploads/2018/08/health-economic-impact-of-ms-in-australia-in-2017_ms-research-australia_web.pdf
12. Hartung DM, Bourdette DN, Ahmed SM, et al. The cost of multiple sclerosis drugs in the US and the pharmaceutical industry. *Neurology* 2015; 84: 2185–2192.
13. De Angelis F, John NA and Brownlee WJ. Disease-modifying therapies for multiple sclerosis. *BMJ* 2018; 363: k4674.
14. Sormani MP and Bruzzi P. Can we measure long-term treatment effects in multiple sclerosis. *Nat Rev Neurol* 2015; 11(3): 176–182.
15. Drulovic J, Kostic J, Mesaros S, et al. Interferon-beta and disability progression in relapsing-remitting multiple sclerosis. *Clin Neurol Neurosurg* 2013; 115S: S65–S69.
16. Sawcer S, Hellenthal G, Pirinen M, et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature* 2011; 476: 214.
17. Multiple sclerosis: Managing shades of grey. *Best Practices J* 2013; 38: 54–47.
18. Taylor BV, Pearson JF, Clarke G, et al. MS prevalence in New Zealand, an ethnically and latitudinally diverse country. *Mult Scler* 2010; 16(12): 1422–1431.
19. Leddy S, Hadavi S, McCarren A, et al. Validating a novel web-based method to capture disease progression outcomes in multiple sclerosis. *J Neurol* 2013; 260(10): 2505–2510.
20. Roxburgh RH, Seaman SR, Masterman T, et al. Multiple Sclerosis Severity Score: using disability and disease duration to rate disease severity. *Neurology* 2005; 64: 114451.
21. Kuspinar A and Mayo NE. A review of the psychometric properties of generic utility measures in multiple sclerosis. *Pharmacoeconomics* 2014; 32(8): 759–773.
22. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; 35: 1381–1395.
23. Learmonth YC, Dlugonski D, Pilutti LA, et al. Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. *J Neurol Sci* 2013; 331: 102–107.
24. Marrie RA, Zhang L, Lix LM, et al. The validity and reliability of screening measures for depression and

anxiety disorders in multiple sclerosis. *Mult Scler Relat Disord* 2018; 20: 9–15.

25. Jacob C. *Statistical Power Analysis for the Behavioral Sciences*. Abingdon: Routledge, 1988.
26. Sawilowsky S. New effect size rules of thumb. *J Mod App Stat Meth* 2009; 8: 467–474.
27. Joseph KS, Mehrabadi A and Lisonkova S. Confounding by indication and related concepts. *Curr Epidemiol Rep* 2014; 1: 18.
28. Phyo AZZ, Jelinek GA, Brown CR, et al. Differential multiple sclerosis treatment allocation between Australia and New Zealand associated with clinical outcomes but not mood or quality of life. *Mult Scler Relat Disord* 2019; 30: 25–32.
29. Jokubaitis VG, Spelman T, Kalincik T, et al. Predictors of long-term disability accrual in relapse-onset multiple sclerosis. *Ann Neurol* 2016; 80(1): 89–100.
30. Schmidt S and Jöstingmeyer P. Depression, fatigue and disability are independently associated with quality of life in patients with multiple sclerosis: Results of a cross-sectional study. *Mult Scler Relat Disord* 2019; 35: 262–269.
31. Karatepe AG, Kaya T, Günaydn R, et al. Quality of life in patients with multiple sclerosis: the impact of depression, fatigue, and disability. *Int J Rehabil Res* 2011; 34: 290–298.
32. Palace J, Duddy M, Bregenzer T, et al. Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator. *Lancet Neurol* 2015; 14(5): 497–505.
33. Signori A, Gallo F, Bovis F, et al. Long-term impact of interferon or glatiramer acetate in multiple sclerosis: A systematic review and meta-analysis. *Mult Scler Relat Disord* 2016; 6: 57–63.
34. Kalincik T, Sharmin S, Malpas C, et al. Immunotherapy prevents long-term disability in relapsing multiple sclerosis over 15 years. *BioRxiv*, https://www.biorxiv.org/content/10.1101/735662v1#:~:text=Conclusions%20Continued%20treatment%20with%20multiple,41%25)%20over%2015%20years.
35. McLaughlin L, Clarke L, Khalilidehkordi E, et al. Vitamin D for the treatment of multiple sclerosis: a meta-analysis. *J Neurol* 2018; 265(12): 2893–2905.