RESEARCH PAPER

# Effects of multiple sclerosis disease-modifying therapies on employment measures using patient-reported data

Jing Chen,[1] Bruce V Taylor,[1] Leigh Blizzard,[1] Steve Simpson Jr,[1,2] Andrew J Palmer,[1] Ingrid A F van der Mei[1]

[1]Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia
[2]Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia

**Correspondence to**
A/Prof. Ingrid A F van der Mei, Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS 7000, Australia; ingrid.vandermei@utas.edu.au

Received 13 February 2018
Revised 1 May 2018
Accepted 28 May 2018

## ABSTRACT

**Background** The direct comparative evidence on treatment effects of available multiple sclerosis (MS) disease-modifying therapies (DMTs) is limited, and few studies have examined the benefits of DMTs on employment outcomes. We compared the effects of DMTs used in the previous 5 years on improving the work attendance, amount of work and work productivity of people with MS.

**Methods** The Australian MS Longitudinal Study collected data from participants on DMTs usage from 2010 to 2015 and whether DMTs contributed to changes in employment outcomes. We classified 11 DMTs into three categories based on their clinical efficacy (β-interferons and glatiramer acetate as category 1; teriflunomide and dimethyl fumarate as category 2; fingolimod, natalizumab, alemtuzumab and mitoxantrone as category 3). Each DMT used by a participant was treated as one observation and analysed by log-multinomial regression.

**Results** Of the 874 participants included, 1384 observations were generated. Those who used category 3 (higher efficacy) DMTs were 2–3 times more likely to report improvements in amount of work, work attendance and work productivity compared with those who used category 1 (classical injectable) DMTs. Natalizumab was associated with superior beneficial effects on patient-reported employment outcomes than fingolimod (RR=1.76, 95% CI 1.02 to 3.03 for increased work attendance and RR=1.46, 95% CI 1.02 to 2.10 for increased work productivity).

**Conclusions** Those using the higher efficacy (category 3) DMTs, particularly fingolimod and natalizumab, reported significant increases in amount of work, work attendance and work productivity, suggesting they have important beneficial effects on work life in people with MS.

## INTRODUCTION

People with multiple sclerosis (MS) often change job roles, reduce working hours and sometimes leave their employment earlier due to MS.[1–3] Indirect costs associated with these productivity losses account for a significant component of total societal costs for MS (48% in Australia[4] and 37% in the USA).[5] Apart from time absent from work, employees with MS could also experience reduced productivity while at work (presenteeism),[6 7] imposing a significant burden on employers and society, as well as indirectly on the individuals.

Although no treatment is currently available to reverse the progressive disability accumulation in MS, clinical trials of disease-modifying therapies (DMTs) have shown positive effects on relapse rate with some also showing decreased rates of short-term disability progression in relapsing-remitting MS (RRMS).[8 9] Few studies have evaluated the effects of DMTs on patient-reported outcomes, such as patient-reported symptom severity or employment outcomes[10 11] (employment status, working hours or work productivity). Demonstrating beneficial effects on these outcomes beyond traditional clinical outcomes of disease activity (disability, relapse and MRI outcomes) is important, as these measures can provide different and meaningful metrics that could improve our understanding of the effectiveness and possibly cost-effectiveness of these expensive therapies.

We have recently shown that the employment rate of Australians with MS has increased from 48.8% in 2010 to 57.8% in 2013.[12] The factors associated with this encouraging improvement are largely unclear but increased availability of more potent DMTs may be an important contributor.[13] However, the differential effects of currently available DMTs on improving work ability for people with MS remains unknown. DMT drug trials generally do not measure employment outcomes nor do the large clinical registries that can do head-to-head comparisons such as MSBase. National observational studies or registries with large sample sizes that can capture a wide range of DMTs and employment outcomes may advance our understanding of the overall effects of DMTs and the effects of individual or groups of DMTs on employment outcomes in the real-world setting and potentially inform clinical practice and future research.

We used a nationally representative sample of people with MS and asked those who used DMTs in the previous 5 years whether their DMTs resulted in any changes in work-related outcomes. The aim of this study was to compare the effects of DMTs on improving the work attendance, amount of work and work productivity.

## METHODS

### Study population and data collection

Individuals included in this study were participants in the Australian MS Longitudinal Study (AMSLS), which is an ongoing research project established



**To cite:** Chen J, Taylor BV, Blizzard L, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2018-318228

**Table 1** Characteristics of participants of Australian MS Longitudinal Study who reported using at least one DMT in the past 5 years and impacts of DMTs on their employment

| Characteristics | N=874 |
|---|---|
| Mean age, years (SD) | 49.7 (9.7) |
| MS duration since diagnosis, years (SD) | 11.5 (6.4) |
| Female sex, n (%) | 717 (82.0) |
| Education level, n (%) | |
| Primary school or secondary school | 169 (19.4) |
| Occupational certificate or diploma | 292 (33.5) |
| University bachelor's degree | 241 (27.6) |
| University postgraduate degree | 171 (19.6) |
| MS phenotype, n (%) | |
| Primary progressive MS | 19 (2.3) |
| Relapsing remitting MS | 711 (81.5) |
| Secondary progressive MS | 76 (8.7) |
| Progressive relapsing MS | 15 (1.7) |
| Unsure | 51 (5.9) |
| Employment status, n (%) | |
| Full-time employed | 225 (26.4) |
| Part-time employed | 288 (33.8) |
| Self-employed | 96 (11.3) |
| Unemployed but seeking work | 34 (4.0) |
| Not in the labour force* | 151 (17.6) |
| PDDS, median (IQR) | 1 (0–3) |
| FSS, median (IQR) | 4.3 (2.9–5.6) |
| HADS depression, median (IQR) | 5 (2–8) |
| HADS anxiety, median (IQR) | 7 (4–10) |
| Number of participants currently using a DMT, n (%) | 792 (90.6) |
| Number of participants who had used more than one DMTs since 2010, n (%) | 476 (54.5) |
| Reported effects of DMT on amount of work | |
| No real change observed | 659 (80.1) |
| Increased working hours with the same or different employer/decision to return to work | 88 (10.8) |
| Reduced working hours with same or different employer/ decision to stop working | 71 (8.7) |
| Reported effects of DMT on work attendance | |
| No real change observed | 619 (80.3) |
| Missed less hours from work | 76 (9.9) |
| Missed more hours from work | 76 (9.9) |
| Reported effects of DMT on work productivity | |
| No real change observed | 609 (75.8) |
| Increased ability to perform work duties | 144 (17.9) |
| Decreased ability to perform work duties | 50 (6.2) |

*Included those retired, home management and unemployed but not seeking a job.
DMT, disease-modifying therapies; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; MS, multiple sclerosis; PDDS, Patient Determined Disease Steps.

in 2002 with a representative sample of Australians with MS.[14] Currently, there are more than 3000 active participants in AMSLS, of whom approximately 96% have been diagnosed with definite MS according to the McDonald criteria.[15 16] All participants provided informed consent.

In November 2015, the AMSLS conducted a survey to assess disease outcomes and DMT use of participants. Invitation were sent to all 3208 active participants (2185 online surveys, 1023 paper surveys) and 1985 (61.8%) participants completed this survey (1459 online, 526 paper). As we aim to assess effects of DMTs on employment outcomes, the inclusion criteria of participants were people with MS who had used DMTs and who had been employed in the study period. Thus, we excluded those who did not use a DMT between 2010 and the time of survey (n=556) and those who answered 'Not applicable' to the relevant questions (n=324) or who did not answer the questions (mostly because they were not applicable) (n=226). Lastly, we excluded those whose duration of DMTs use was <30 days (n=5). This left 874 participants for our analysis.

## Study outcomes and other assessments

### DMT use from 2010 to 2015

Respondents reported their past and current DMT use since 2010, including month and year they started and stopped a DMT. If they stopped a DMT, the reasons why they stopped were queried, including: (1) lost effectiveness indicated by neurologist or other treating doctor, (2) developed contraindications (eg, detected antibodies to β-interferon, John Cunningham virus positivity, cardiac problems or allergic reaction), (3) side effects (eg, flu-like symptoms, injection-site reactions, reactions after injection or other effects/abnormalities), (4) pregnancy or breastfeeding reasons and (5) personal reasons (eg, tired of injections, do not believe it is working or difficulty with treatment access, etc).

There were 11 approved DMTs available and publicly subsidised for use in Australia presented as a list in the survey. They were interferon β-1b (Betaferon), interferon β-1a (Rebif), interferon β-1a (Avonex), pegylated interferon β-1a (Plegridy), glatiramer acetate (Copaxone), natalizumab (Tysabri), fingolimod (Gilenya), teriflunomide (Aubagio), dimethyl fumarate (Tecfidera), alemtuzumab (Lemtrada) and mitoxantrone (Novantrone).

To reduce the number of categories of DMTs in subsequent regression analysis, we classified the 11 DMTs into three broad categories based on their recognised clinical efficacy from pivotal clinical trials[9 13 17 18] and route of administration. The category 1 DMTs included β-interferons (Betaferon, Rebif, Avonex and Plegridy) and glatiramer acetate, which are the classical injectable DMTs; the category 2 DMTs included the oral therapies, teriflunomide and dimethyl fumarate and the category 3 DMTs included the putative higher efficacy DMTs, fingolimod, natalizumab, alemtuzumab and mitoxantrone, which are all given by infusion except for fingolimod. We also undertook direct comparisons between the most commonly used DMTs.

### Employment outcomes

Three outcome variables characterised patient-reported effects of DMTs use on employment. In separate questions, we asked whether the use of a DMT contributed to a change at any time point in the last 5 years in the amount they worked with an employer (no real changes observed, increased working hours or contributed to decision to return to work, reduced working hours or contributed to decision to stopping working), a change in attendance at work (no real changes observed, missed less hours from work, missed more hours from work) and a change in productivity in performing work duties (no real changes observed, increased ability to perform work duties, reduced ability to perform work duties). Lastly, we asked participants to identify which DMTs contributed to the above changes they reported and they could report more than one DMT. If a DMT had not been identified, we assumed that DMT had not contributed to any change in employment outcomes.

### Participants characteristics

We utilised information on age, sex and MS diagnosis year collected in previous AMSLS surveys. In the 2015 survey,

**Table 2** Characteristics by DMT categories in the repeated-measures data set of 1384 DMT observations with p values for differences by DMT categories

| | Category 1 DMTs | Category 2 DMTs | Category 3 DMTs | |
|---|---|---|---|---|
| | N=706 | N=187 | N=491 | P values |
| DMT characteristics | | | | |
| DMT type, n (%) | | | | – |
| Interferon β-1b (Betaferon) | 191 (27.1) | – | – | – |
| Interferon β-1a (Rebif) | 121 (17.1) | – | – | – |
| Interferon β-1a (Avonex) | 136 (19.3) | – | – | – |
| Pegylated interferon β-1a (Plegridy) | 30 (4.3) | – | – | – |
| Glatiramer acetate (Copaxone) | 228 (32.3) | – | – | – |
| Teriflunomide (Aubagio) | – | 47 (25.1) | – | – |
| Dimethyl fumarate (Tecfidera) | – | 140 (74.9) | – | – |
| Fingolimod (Gilenya) | – | – | 294 (59.9) | – |
| Alemtuzumab (Lemtrada) | – | – | 18 (3.7) | – |
| Natalizumab (Tysabri) | – | – | 174 (35.4) | – |
| Novantrone (Mitoxantrone) | – | – | 5 (1.0) | – |
| DMTs that had been ceased, n (%) | 440 (62.3) | 46 (24.6) | 132 (26.9) | **<0.001** |
| Reasons for ceasing a DMT | | | | |
| Lost effectiveness indicated by neurologists or treating doctor | 174 (39.6) | 18 (39.1) | 39 (29.6) | 0.111 |
| Developed contraindications | 18 (4.1) | 6 (13.4) | 65 (49.2) | **<0.001** |
| Side effects | 128 (29.1) | 27 (58.7) | 18 (13.6) | **<0.001** |
| Pregnancy or breastfeeding reasons | 18 (4.1) | 0 (0.0) | 7 (5.3) | 0.289 |
| Personal reasons | 132 (30.0) | 19 (19.6) | 9 (6.8) | **<0.001** |
| Participants characteristics when starting a DMT | | | | |
| Mean age when initiating the DMT assessed in the study, years (SD) | 42.4 (10.1) | 48.6 (10.2) | 44.1 (9.7) | **<0.001** |
| Mean MS duration since diagnosis when initiatingthe DMT assessed in the study, median (IQR) (years) | 1 (0–4) | 9 (5–14) | 7 (3–11) | **<0.001** |
| Duration of DMT use, median (IQR) (months) | 68 (30–127) | 18 (7–24) | 31 (17–51) | **<0.001** |
| Female sex, n (%) | 585 (82.9) | 151 (80.8) | 401 (81.7) | 0.752 |
| Education level, n (%) | | | | 0.915 |
| Primary or secondary school | 126 (17.9) | 36 (19.3) | 97 (19.8) | |
| Occupational certificate | 232 (32.9) | 68 (36.4) | 163 (33.3) | |
| University bachelor's degree | 213 (30.2) | 51 (27.3) | 142 (29.0) | |
| University postgraduate degree | 135 (19.1) | 32 (17.2) | 88 (18.0) | |

DMT, disease-modifying therapy.

participants reported current MS phenotype, education level and their employment status. The Patient Determined Disease Step Scale (PDDS), a validated and simple tool to measure disability by patient self-assessment[19–22] (scored from 0 to 8) was used. A PDDS score of 0 represents no disability and is equivalent to an Expanded Disability Status Scale (EDSS) score of 0. A PDDS score of 3 reflects gait disability without the need for assistance to walk and is approximately equivalent to an EDSS score of 4.0–4.5. PDDS scores of 4 (early cane), 5 (late cane) and 6 (bilateral support) indicate the need for assistance in walking, which are approximately equivalent to EDSS scores of 6–6.5. Similar to EDSS, score 7 indicates wheelchair users and 8 indicates bedridden.[19] Fatigue was measured by the Fatigue Severity Scale.[23] Depression and anxiety were measured by the Hospital Anxiety and Depression Scale.[24]

### Statistical analysis

Means and SD of continuous variable and percentage and frequencies of categorical variables are reported to summarise the characteristics of participants. To compare the difference in patients' characteristics between treatment groups, analysis of variance and covariance (ANOVA) or $X^2$ test were used. The exposure of interest was type of DMT. Log multinomial regression was used to estimate risk ratios (RR) with SEs adjusted for within-individual variation that arose because these were repeated observations on some individuals. The outcome was one of amount of work, work attendance and work productivity with three categories (decrease, no change, increase) in each case. No change was treated as the base outcome. Observations with missing data of any variable were excluded from regression analysis. A p value $<0.05$ (two-tailed) was considered as statistically significant. All statistical analyses were performed using Stata/SE V.14.

## RESULTS

### Characteristics of respondents

The average age of participants was 49.7 years and 81.8% being female (table 1). The mean MS duration since diagnosis was 11.4 years, and the majority (81%) were of the relapsing-remitting MS phenotype. At the time of survey, 72% of participants were still working, of whom 37% worked full time for an employer. More than half (55%) of participants had used more than one DMT during the preceding 5 years and 90% of the total sample

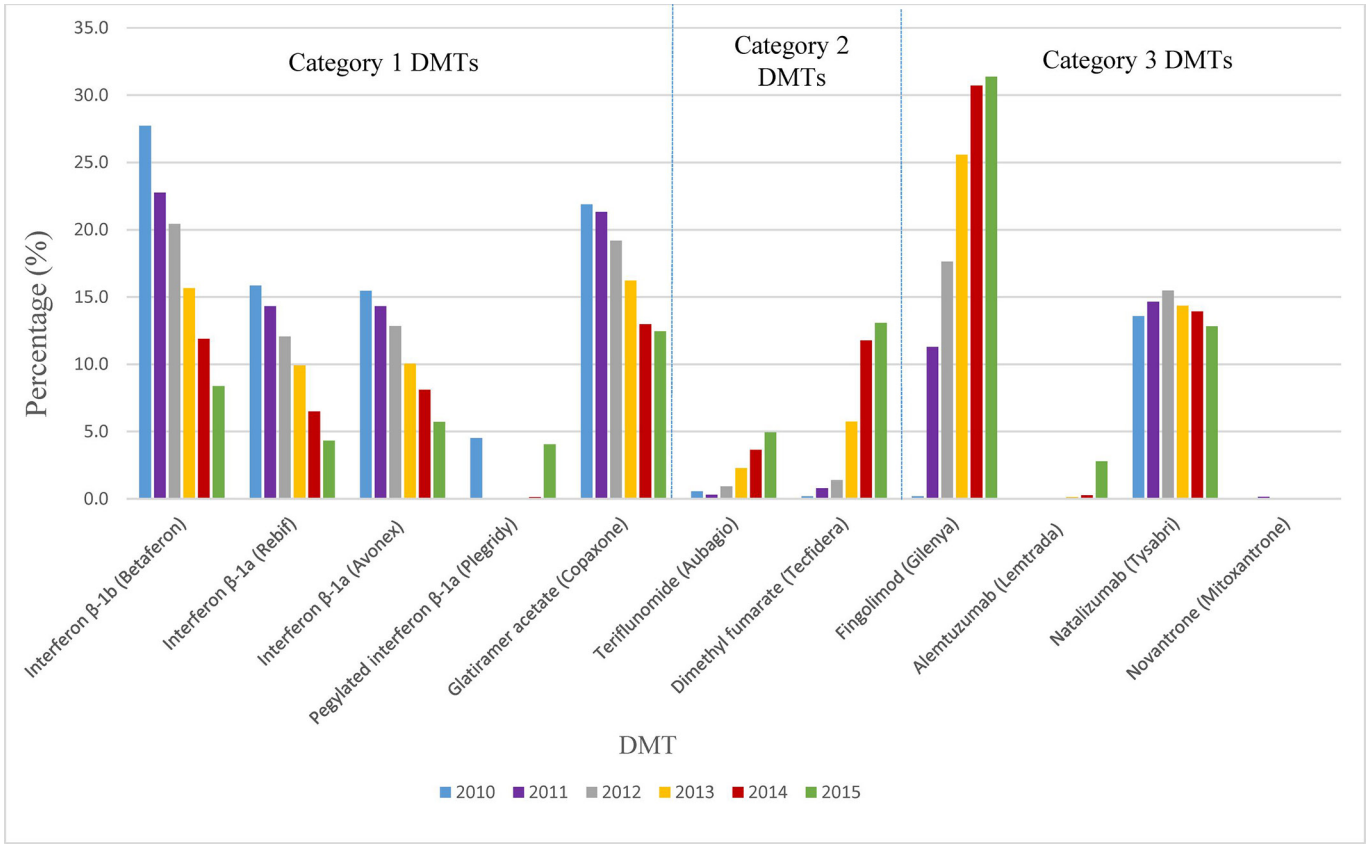


**Figure 1** Percentage of people using disease-modifying therapies (DMTs) by year 2010–2015 among the study population.

were using a DMT at the time of the survey. Overall, 70%–80% of participants reported that DMTs did not change their employment outcomes, with 10%–20% reporting an increase across the three employment outcomes and 6%–10% reporting a decrease.

Compared with non-respondents, the respondents of the survey were slightly older (+2.2 years, p<0.01), had a longer MS duration since diagnosis (+0.58 years, p=0.04) and a slightly higher education level (36% with bachelor or postgraduate degree in respondents vs 31% in non-respondents, p=0.01) but no difference in sex (p=0.47).

## DMT treatment from 2010 to 2015

The repeated measures data set consisted of 1384 DMT observations (table 2). Glatiramer acetate accounted for 32.3% of the total 706 category 1 DMTs observations with the rest being β-interferon formulations. Category 3 DMTs were mainly represented by fingolimod (59.9%) and natalizumab (35.4%).

The reasons for ceasing a DMT differed between DMT categories (table 2). While loss of effectiveness comprised 30%–40% of reasons for ceasing a DMT for all categories, other reasons varied across DMTs types: development of contraindications was the most common reason for discontinuing category 3 DMTs (49.2%), while side effects was the reasoning for over half of category 2 DMTS (58.7%) and personal reasons was the rationale for 30.0% of category 1 DMTs.

The DMT treatment patterns among the study population changed from 2010 to 2015 (figure 1) with the percentage of people using category 1 DMTs reducing (except for pegylated interferon) and the percentage of people using category 2 and category 3 DMTs increasing. Fingolimod experienced the most dramatic increase while natalizumab is merely flat.

## Association between DMTs and employment outcomes

Compared with users of category 1 DMTs, the probability of reporting increased amount of work (table 3), work attendance (table 4) and work productivity (table 5) was significantly higher in users of category 3 DMTs. The associations strengthened after adjustment for duration of DMT use and age. Sex and education did not confound the associations as they were not significantly associated with DMT type. For example, compared with users of category 1 DMTs, users of category 3 DMTs were 2.84 times more likely to report an increased amount of work, 3.14 times more likely to report an increased work attendance and 2.50 times more likely to report an improved work productivity. In terms of decreased employment outcomes, the probability of reporting decreased work attendance and work amount were slighter higher among category 3 DMTs users but the difference was not statistically significant in the multivariable analysis.

We next compared the effects of individual DMTs that had sufficient observations (glatiramer acetate, fingolimod, dimethyl fumarate and natalizumab) against β-interferon formulations (tables 3–5). Fingolimod and natalizumab consistently exerted significantly greater effects on the perceived improvements in the three employment outcomes with natalizumab showing the largest effect size. Glatiramer acetate and dimethyl fumarate performed equally well compared with β-interferons formulations. The direct comparison between fingolimod and natalizumab (tables 3–5) shows that no significant difference was found in improving work amount but natalizumab users were 1.76 times more likely to report an increase in work attendance and 1.46 times more likely to report an increase in work productivity compared with those used fingolimod. Those using

**Table 3** Patient-reported effects of DMTs on amount of work

| | No. (%) reporting no change | No. (%) reporting increase | No. (%) reporting decrease | Reporting increase versus reporting no change | | Reporting decrease versus reporting no change | |
|---|---|---|---|---|---|---|---|
| | | | | RR | 95% CI | RR | 95% CI |
| Comparing effects between different DMT categories | | | | | | | |
| Univariable model | | | | | | | |
| Category 1 DMTs | 603 (90.1) | 36 (5.4) | 30 (4.5) | 1 (reference) | | 1 (reference) | |
| Category 2 DMTs | 156 (89.7) | 7 (4.0) | 11 (6.3) | 0.75 | 0.35 to 1.60 | 1.41 | 0.72 to 2.77 |
| Category 3 DMTs | 381 (82.5) | 55 (11.9) | 26 (5.6) | **2.21** | **1.47 to 3.32*** | 1.26 | 0.78 to 2.03 |
| Test for trend | | | | | **p<0.001** | | p=0.326 |
| Multivariable model, adjustment for duration of DMT use and age | | | | | | | |
| Category 1 DMTs | | | | 1 (reference) | | 1 (reference) | |
| Category 2 DMTs | | | | 1.46 | 0.62 to 3.43 | 1.28 | 0.65 to 2.55 |
| Category 3 DMTs | | | | **2.84** | **1.90 to 4.25**** | 1.17 | 0.67 to 2.00 |
| Test for trend | | | | | **p<0.001** | | p=0.590 |
| Comparing effects between individual DMTs | | | | | | | |
| Univariable model | | | | | | | |
| β-interferons | 370 (88.5) | 25 (6.0) | 25 (6.0) | 1 (reference) | | 1 (reference) | |
| Glatiramer acetate | 203 (91.9) | 11 (5.0) | 11 (5.0) | 0.83 | 0.40 to 1.73 | 0.58 | 0.26 to 1.29 |
| Dimethyl fumarate | 119 (90.8) | 4 (3.1) | 4 (3.1) | 0.51 | 0.18 to 1.44 | 1.11 | 0.52 to 2.38 |
| Fingolimod | 236 (84.9) | 30 (10.8) | 30 (10.8) | **1.80** | **1.13 to 2.87*** | 0.78 | 0.40 to 1.53 |
| Natalizumab | 126 (78.3) | 22 (13.7) | 22 (13.7) | **2.28** | **1.34 to 3.89*** | 1.47 | 0.79 to 2.72 |
| Multivariable model, adjustment for duration of DMT use and age | | | | | | | |
| β-interferons | | | | 1 (reference) | | 1 (reference) | |
| Glatiramer acetate | | | | 0.92 | 0.43 to 1.96 | 0.53 | 0.24 to 1.20 |
| Dimethyl fumarate | | | | 1.04 | 0.35 to 3.09 | 0.83 | 0.35 to 1.97 |
| Fingolimod | | | | **2.57** | **1.59 to 4.17**** | 0.68 | 0.31 to 1.51 |
| Natalizumab | | | | **2.76** | **1.52 to 4.38**** | 1.21 | 0.61 to 2.40 |
| Head-to-head comparison between fingolimod and natalizumab | | | | | | | |
| Univariable model | | | | | | | |
| Fingolimod | | | | 1 (reference) | | 1 (reference) | |
| Natalizumab | | | | 1.27 | 0.80 to 2.02 | 1.87 | 0.87 to 4.04 |
| Multivariable model, adjustment for duration of DMT use and age | | | | | | | |
| Fingolimod | | | | 1 (reference) | | 1 (reference) | |
| Natalizumab | | | | 1.09 | 0.67 to 1.78 | 1.53 | 0.65 to 3.57 |

Data in bold indicate statistical significance.
*P<0.05; **P<0.001.
†Base outcome to calculate risk ratio.
DMT, disease-modifying therapy; RR, relative risk.

natalizumab were 3.14 times more likely to experience decreased work attendance.

## DISCUSSION

This large national observational study used employment outcomes as indicators of overall functioning to assess the effects of a wide range of DMTs, providing evidence from the real-world practice. Our findings consistently showed that those who used higher efficacy DMTs (eg, fingolimod and natalizumab) were two to three times more likely to report that DMTs increased their amount of work, work attendance and work productivity compared with patients who used classical injectable DMTs (β-interferons and glatiramer acetate in our study). Our findings are corroborated by the indirect evidence that the increase in use of higher efficacy DMTs since 2010 aligns with the increased employment rates of people with MS in Australia from 2010 to 2013[12]. Taken together, our study suggest that prescribing higher efficacy DMTs to people with RRMS, particularly those of working age, may bring them significant benefits in work productivity and workforce participation compared with the classical first-line injectable DMTs. Our data suggest that the cost-effectiveness of DMTs from a societal perspective may increase once their effects on employment outcomes are taken into account.

To the best of our knowledge, this is the first study that examines the effect of multiple DMTs on employment outcomes, including head-to-head comparisons. For working-aged adults, employment provides income, self-identity and is associated with a higher quality of life. However, people with MS are often challenged in their work performance and may need to retire early due to MS-related symptoms.[3] Consequently, the benefits of DMTs on employment may reflect the efficacy of DMTs on controlling disease activity and symptoms. Our results are matched by the consistency between the transition from injectable DMTs to higher efficacy DMTs and the increased trend of labour force participation in Australians with MS after 2010, which indeed seems to suggest that higher efficacy DMTs may have helped people with MS to manage their disease more effectively. Moreover, DMTs are generally considered to be expensive drugs,[25] and the major direct medical costs in patients with MS arise from DMTs.[26] Our study supports the notion that randomised controlled trials and long-term observational studies

**Table 4** Patient-reported effects of DMTs on work attendance

| | No. (%) reporting no change† | No. (%) reporting increase | No. (%) reporting decrease | Reporting increase versus reporting no change | | Reporting decrease versus reporting no change | |
|---|---|---|---|---|---|---|---|
| | | | | RR | 95% CI | RR | 95% CI |
| Comparing effects between different DMTs categories | | | | | | | |
| Univariable model | | | | | | | |
| Category 1 DMTs | 582 (91.2) | 26 (4.1) | 30 (4.7) | 1 (reference) | | 1 (reference) | |
| Category 2 DMTs | 149 (89.8) | 8 (4.8) | 9 (5.4) | 1.18 | 0.57 to 2.47 | 1.15 | 0.52 to 2.57 |
| Category 3 DMTs | 348 (80.62) | 51 (11.8) | 33 (7.6) | **2.90** | **1.83 to 4.86**** | **1.62** | **1.02 to 2.60*** |
| Test for trend | | | | | **p<0.001** | | **p=0.045** |
| Multivariable model, adjustment for duration of DMT use and age | | | | | | | |
| Category 1 DMTs | | | | 1 (reference) | | 1 (reference) | |
| Category 2 DMTs | | | | 1.57 | 0.66 to 3.72 | 0.80 | 0.37 to 1.74 |
| Category 3 DMTs | | | | **3.14** | **1.98 to 5.00**** | 1.46 | 0.89 to 2.41 |
| Test for trend | | | | | **p<0.001** | | p=0.127 |
| Comparing effects between individual DMTs | | | | | | | |
| Univariable model | | | | | | | |
| β -interferons | 360 (90.0) | 17 (4.3) | 23 (5.8) | 1 (reference) | | 1 (reference) | |
| Glatiramer acetate | 196 (93.3) | 9 (4.3) | 5 (2.4) | 1.01 | 0.43 to 2.35 | 0.41 | 0.16 to 1.09 |
| Dimethyl fumarate | 109 (89.3) | 6 (4.9) | 7 (5.7) | 1.16 | 0.47 to 2.88 | 1.00 | 0.43 to 2.30 |
| Fingolimod | 225 (86.9) | 24 (9.3) | 10 (3.9) | **2.18** | **1.25 to 3.82*** | 0.67 | 0.32 to 1.40 |
| Natalizumab | 111 (73.0) | 24 (15.8) | 17 (11.2) | **3.72** | **2.05 to 6.73**** | **1.95** | **1.09 to 3.48*** |
| Multivariable model, adjustment for duration of DMT use and age | | | | | | | |
| β -interferons | | | | 1 (reference) | | 1 (reference) | |
| Glatiramer acetate | | | | 1.03 | 0.43 to 2.49 | **0.35** | **0.13 to 0.94*** |
| Dimethyl fumarate | | | | 1.47 | 0.54 to 3.99 | 0.56 | 0.24 to 1.31 |
| Fingolimod | | | | **2.36** | **1.33 to 4.20*** | 0.50 | 0.23 to 1.09 |
| Natalizumab | | | | **3.91** | **2.16 to 7.10**** | 1.67 | 0.91 to 3.08 |
| Head-to-head comparison between fingolimod and natalizumab | | | | | | | |
| Univariable model | | | | | | | |
| Fingolimod | | | | 1 (reference) | | 1 (reference) | |
| Natalizumab | | | | **1.70** | **1.03 to 2.81*** | **2.90** | **1.35 to 6.18*** |
| Multivariable model, adjustment for duration of DMT use and age | | | | | | | |
| Fingolimod | | | | 1 (reference) | | 1 (reference) | |
| Natalizumab | | | | **1.76** | **1.02 to 3.03*** | **3.14** | **1.48 to 6.70*** |

Data in bold indicate statistical significance.
*P<0.05; **P<0.001.
†Base outcome to calculate risk ratio.
DMT, disease-modifying therapy; RR, risk ratio.

should include employment outcomes, as this would provide a more complete picture of health economic impacts of DMTs.

Our study demonstrated the superior efficacy of natalizumab and fingolimod on patient-reported employment outcomes compared with β-interferons, glatiramer acetate and dimethyl fumarate, which is consistent with the limited evidence of the effects of DMTs on clinical outcome measures. A Cochrane review systematically evaluated the pivotal RCTs of 15 DMTs aiming to rank the associated effectiveness of those DMTs.[9] It revealed that alemtuzumab, natalizumab and fingolimod are more effective than the other DMTs in preventing relapses in people with RRMS. An observational study from France also showed a superior efficacy of fingolimod to injectable DMTs in second-line therapy of RRMS in reducing relapse and slowing EDSS progression.[27] In terms of a head-to-head comparison between natalizumab and fingolimod, our study demonstrated that natalizumab might be more effective in improving employment outcomes than fingolimod, which seems consistent with two recent observational studies.[28 29] An international prospective study using MSBase found that switching to natalizumab was more effective than switching to fingolimod in reducing relapse and short-term disability burden for active RRMS.[29] Similarly, a multicentre study from France showed superior beneficial effects of natalizumab to fingolimod on relapse and MRI outcomes at 1 and 2 years.[28] Currently, few studies have assessed the effects of DMTs on symptoms and employment outcomes. More head-to-head studies using outcomes from the patients' perspective such as employment and symptoms are needed as it would be useful to both guide clinical practice and inform decision makers.

Strengths of our study include the large sample size and the representativeness of the working sample.[14] A limitation is that we asked people to retrospectively report the effects of DMTs on their employment, which may be influenced by the patient's belief in a treatment. It is possible that their belief in a treatment was higher for DMTs that have been shown to have a higher efficacy and adverse risk profile. This effect can only be prevented by using a prospective study design and it may have overestimated our findings. The outcome, work productivity, may have been expected to suffer most from this bias as it is the most subjective of the three outcomes. We observed the strongest magnitude of effects for work attendance and the least strong effects for work productivity, arguing somewhat against the presence of this bias.

**Table 5** Patient-reported effects of DMTs on work productivity

| | No. (%) reporting no change† | No. (%) reporting increase | No. (%) reporting decrease | Reporting increase versus reporting no change | | Reporting decrease versus reporting no change | |
|---|---|---|---|---|---|---|---|
| | | | | RR | 95% CI | RR | 95% CI |
| Comparing effects between different DMTs categories | | | | | | | |
| Univariable model | | | | | | | |
| Category 1 DMTs | 570 (87.0) | 58 (8.9) | 27 (4.1) | 1 (reference) | | 1 (reference) | |
| Category 2 DMTs | 146 (85.9) | 17 (10.0) | 7 (4.1) | 1.13 | 0.68 to 1.86 | 1.00 | 0.30 to 1.90 |
| Category 3 DMTs | 342 (76.0) | 90 (20.0) | 18 (4.0) | **2.26** | **1.64 to 3.10**** | 0.97 | 0.45 to 1.48 |
| Test for trend | | | | | **p<0.001** | | p=0.917 |
| Multivariable model, adjustment for duration of DMT use and age | | | | | | | |
| Category 1 DMTs | | | | 1 (reference) | | 1 (reference) | |
| Category 2 DMTs | | | | 1.38 | 0.81 to 2.37 | 0.76 | 0.44 to 1.58 |
| Category 3 DMTs | | | | **2.50** | **1.81 to 3.44**** | 0.82 | 0.28 to 1.63 |
| Test for trend | | | | | **p<0.001** | | p=0.511 |
| Comparing effects between individual DMTs | | | | | | | |
| Univariable model | | | | | | | |
| β -interferons | 354 (84.9) | 38 (9.3) | 23 (5.6) | 1 (reference) | | 1 (reference) | |
| Glatiramer acetate | 216 (91.1) | 18 (8.2) | 3 (1.4) | 0.88 | 0.50 to 1.56 | **0.24** | **0.07 to 0.80*** |
| Dimethyl fumarate | 122 (87.8) | 11 (8.6) | 5 (3.9) | 0.92 | 0.50 to 1.72 | 0.69 | 0.27 to 1.80 |
| Fingolimod | 230 (79.6) | 46 (17.3) | 11 (4.1) | **1.85** | **1.27 to 2.70*** | 0.73 | 0.39 to 1.39 |
| Natalizumab | 128 (73.1) | 39 (24.1) | 7 (4.3) | **2.59** | **1.71 to 3.92**** | 0.77 | 0.34 to 1.71 |
| Multivariable model, adjustment for duration of DMT use and age | | | | | | | |
| β -interferons | | | | 1 (reference) | | 1 (reference) | |
| Glatiramer acetate | | | | 0.93 | 0.52 to 1.66 | **0.21** | **0.06 to 0.68*** |
| Dimethyl fumarate | | | | 1.10 | 0.58 to 2.09 | 0.41 | 0.15 to 1.10 |
| Fingolimod | | | | **2.02** | **1.36 to 2.98**** | 0.57 | 0.27 to 1.21 |
| Natalizumab | | | | **2.88** | **1.90 to 4.36**** | 0.51 | 0.20 to 1.30 |
| Head-to-head comparison between fingolimod and natalizumab | | | | | | | |
| Univariable model | | | | | | | |
| Fingolimod | | | | 1 (reference) | | 1 (reference) | |
| Natalizumab | | | | 1.40 | 0.97 to 2.01 | 1.05 | 0.44 to 2.52 |
| Multivariable model, adjustment for duration of DMT use and age | | | | | | | |
| Fingolimod | | | | 1 (reference) | | 1 (reference) | |
| Natalizumab | | | | **1.46** | **1.02 to 2.10*** | 0.85 | 0.28 to 2.54 |

Data in bold indicate statistical significance.
*P<0.05; **P<0.001.
†Base outcome to calculate risk ratio.
DMT, disease-modifying therapy; RR, risk ratio.

Another potential limitation is indication bias,[30] where factors associated with treatment choices are determined by multiple factors other than randomisation. We were unable to assess all of these factors when participants started a new DMT. In clinical practice, those who had failed to realise a sustained benefit from first-line DMTs or experienced rapid worsening of disability would have been more likely to initiate a higher efficacy DMT.[18 29 31–33] Since these patients are on a worse disease trajectory, subsequent disease outcomes may be worse as well. This effect may have underestimated the effects of category 2 or 3 DMTs in improving employment outcomes. It could also explain the finding that those using category 3 DMTs were slightly more likely to report a decreased work attendance. The different route and frequency of administration of DMTs could also impact employment outcomes. For example, natalizumab requires administration by intravenous infusion every 28 days, which means natalizumab requires more hospital visits (and thus time off work) than people taking oral tablets like fingolimod. This may be another explanation for why those using natalizumab were more likely to report a decreased work attendance than those using fingolimod.

In addition to disease characteristics, work-related factors and other factors associated with allocation of patients could also have confounded the estimates, such as preference of individual and treating doctors, but it is hard to fully account for all these factors in observational studies. Future perspective observational studies collecting more information on patient characteristics and work factors, and using appropriate analytical methods, like propensity weighting are needed to address this issue. They would also be able to assess whether the effects of DMTs in improving employment outcomes are mediated through a reduction in relapses, disability progression and/or symptom improvement.

In summary, we found that the probability of experiencing improvements in employment outcomes was higher for those using higher efficacy DMTs. Natalizumab and fingolimod demonstrated superior effectiveness on the patient-reported employment outcomes than β-interferons, glatiramer acetate and dimethyl fumarate, with natalizumab having the largest magnitude of effect. These findings indicate that natalizumab and fingolimod are potentially more effective in controlling disease activity or symptoms than the other DMTs, thus using a higher

efficacy DMT may give people with RRMS significant beneficial effects on their working life. However, these treatments do have higher risks associated with their use and all treatment decisions need to be made in the full knowledge of the risk/benefit analysis for each individual with MS. Future prospective studies using employment or symptoms as outcomes are needed to confirm our results. Further cost-effectiveness studies should include benefits of DMTs on employment outcomes.

**Acknowledgements** The authors thank all the participants in the Australian Multiple Sclerosis Longitudinal Study for their support and willingness to complete surveys.

**Contributors** IM designed the study. JC performed the data analysis and drafted the manuscript. BT and LB provided advice on data analysis. IM, BT and JC were involved in the data interpretation; All authors critically revised the manuscript.

**Funding** This study was supported by the Multiple Sclerosis Research Australia.

**Competing interests** The authors have no conflicts of interest to declare.

**Patient consent** Patient consent obtained.

**Ethical approval** Ethical approval was obtained from the Australian Capital Territory Health Human Research Ethics Committee until 2014 when the AMSLS was relocated to Tasmania and then ethical approval was obtained from the Tasmanian Health and Medical Human Research Ethics Committee.

**Provenance and peer review** Not commissioned; externally peer reviewed.



## REFERENCE

1 Moore P, Harding KE, Clarkson H, *et al*. Demographic and clinical factors associated with changes in employment in multiple sclerosis. *Mult Scler* 2013;19:1647–54.
2 Coyne KS, Boscoe AN, Currie BM, *et al*. Understanding drivers of employment changes in a multiple sclerosis population. *Int J MS Care* 2015;17:245–52.
3 Simmons RD, Tribe KL, McDonald EA. Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management. *J Neurol* 2010;257:926–36.
4 Palmer AJ, Colman S, O'Leary B, *et al*. The economic impact of multiple sclerosis in Australia in 2010. *Mult Scler* 2013;19:1640–6.
5 Kobelt G, Berg J, Atherly D, *et al*. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. *Neurology* 2006;66:1696–702.
6 Glanz BI, Dégano IR, Rintell DJ, *et al*. Work productivity in relapsing multiple sclerosis: associations with disability, depression, fatigue, anxiety, cognition, and health-related quality of life. *Value Health* 2012;15:1029–35.
7 Gupta S, Goren A, Phillips AL, *et al*. Self-reported severity among patients with multiple sclerosis in the U.S. and its association with health outcomes. *Mult Scler Relat Disord* 2014;3:78–88.
8 Polman CH, O'Connor PW, Havrdova E, *et al*. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899–910.
9 Tramacere I, Del Giovane C, Salanti G, *et al*. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev* 2015;9:CD011381.
10 Wickström A, Dahle C, Vrethem M, *et al*. Reduced sick leave in multiple sclerosis after one year of natalizumab treatment. A prospective ad hoc analysis of the TYNERGY trial. *Mult Scler* 2014;20:1095–101.
11 Wickström A, Fagerström M, Wickström L, *et al*. The impact of adjusted work conditions and disease-modifying drugs on work ability in multiple sclerosis. *Mult Scler* 2017;23:1137–47.
12 Van Dijk PA, Kirk-Brown AK, Taylor B, *et al*. Closing the gap: Longitudinal changes in employment for Australians with multiple sclerosis. *Mult Scler* 2017;23:1415-1423.
13 Broadley SA, Barnett MH, Boggild M, *et al*. Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: an Australian and New Zealand perspective: part 1 historical and established therapies. MS Neurology Group of the Australian and New Zealand Association of Neurologists. *J Clin Neurosci* 2014;21:1835–46.
14 Taylor BV, Palmer A, Simpson S, *et al*. Assessing possible selection bias in a national voluntary MS longitudinal study in Australia. *Mult Scler* 2013;19:1627–31.
15 Polman CH, Reingold SC, Banwell B, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.
16 Polman CH, Reingold SC, Edan G, *et al*. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005;58:840–6.
17 Broadley SA, Barnett MH, Boggild M, *et al*. Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: an Australian and New Zealand perspective: part 2 new and emerging therapies and their efficacy. MS Neurology Group of the Australian and New Zealand Association of Neurologists. *J Clin Neurosci* 2014;21:1847–56.
18 Broadley SA, Barnett MH, Boggild M, *et al*. MS Neurology Group of the Australian and New Zealand Association of Neurologists. Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: an Australian and New Zealand perspective: part 3 treatment practicalities and recommendations. MS Neurology Group of the Australian and New Zealand Association of Neurologists. *J Clin Neurosci* 2014;21:1857–65.
19 Marrie RA, Cutter G, Tyry T, *et al*. Does multiple sclerosis-associated disability differ between races? *Neurology* 2006;66:1235–40.
20 Marrie RA, Goldman M. Validity of performance scales for disability assessment in multiple sclerosis. *Mult Scler* 2007;13:1176–82.
21 Hohol MJ, Orav EJ, Weiner HL. Disease steps in multiple sclerosis: a longitudinal study comparing disease steps and EDSS to evaluate disease progression. *Mult Scler* 1999;5:349–54.
22 Learmonth YC, Motl RW, Sandroff BM, *et al*. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMC Neurol* 2013;13:37.
23 Krupp LB, LaRocca NG, Muir-Nash J, *et al*. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121–3.
24 Spinhoven P, Ormel J, Sloekers PP, *et al*. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of dutch subjects. *Psychol Med* 1997;27:363–70.
25 Noyes K, Bajorska A, Chappel A, *et al*. Cost-effectiveness of disease-modifying therapy for multiple sclerosis: a population-based study. *Neurology* 2011;77:355–63.
26 Yamamoto D, Campbell JD. Cost-effectiveness of multiple sclerosis disease-modifying therapies: a systematic review of the literature. *Autoimmune Dis* 2012;2012:1–13.
27 Braune S, Lang M, Bergmann A, *et al*. Efficacy of fingolimod is superior to injectable disease modifying therapies in second-line therapy of relapsing remitting multiple sclerosis. *J Neurol* 2016;263:327–33.
28 Barbin L, Rousseau C, Jousset N, *et al*. Comparative efficacy of fingolimod vs natalizumab: a French multicenter observational study. *Neurology* 2016;86:771–8.
29 Kalincik T, Horakova D, Spelman T, *et al*. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. *Ann Neurol* 2015;77:425–35.
30 Bosco JL, Silliman RA, Thwin SS, *et al*. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol* 2010;63:64–74.
31 Huisman E, Papadimitropoulou K, Jarrett J, *et al*. Systematic literature review and network meta-analysis in highly active relapsing-remitting multiple sclerosis and rapidly evolving severe multiple sclerosis. *BMJ Open* 2017;7:e013430.
32 Scolding N, Barnes D, Cader S, *et al*. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol* 2015;15:273–9.
33 Boster A, Edan G, Frohman E, *et al*. Intense immunosuppression in patients with rapidly worsening multiple sclerosis: treatment guidelines for the clinician. *Lancet Neurol* 2008;7:173–83.