Risk factors for leaving employment due to multiple sclerosis and changes in risk over the past decades: using competing risk survival analysis

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Abstract

Background: No studies have assessed changes in employment survival in MS populations over recent decades, including the introduction of disease modifying therapies (DMTs).

Objectives: To evaluate factors associated with leaving employment due to MS; To assess whether the risk of leaving employment has changed over recent decades in Australia, stratified by MS phenotype.

Methods: We included 1,240 participants who were working before MS diagnosis. Information on employment status, reasons for leaving employment, and year of leaving were collected. Data were analysed using competing risk survival analysis.

Results: Males, progressive MS, lower education level and older age at diagnosis were associated with a higher sub-distribution hazard of leaving employment. Compared to the period before 2010, the sub-distribution hazard during 2010 -2016 for RRMS was reduced by 43% (sHR 0.67, 95% CI 0.50 to 0.90), while no significant reduction was seen for PPMS (sHR 1.25,95% CI: 0.72 to 2.16) or SPMS (sHR 1.37,95% CI: 0.84 to 2.25).

Conclusions: Males, people with progressive MS, and those of lower education level were at higher risk of leaving employment. The differential changed risk of leaving employment between people with different MS phenotype after 2010 coincides with the increased usage of high-efficacy DMTs for RRMS.

Key words: multiple sclerosis; employment; disease modifying therapies; survival analysis; competing risks; sex

Introduction

Multiple sclerosis (MS) is usually diagnosed between 20-40 years of age, a crucial period in life for career establishment and advancement. People with MS often leave the workforce prematurely, which not only impacts quality of life and psychological well-being but also contributes to a high socioeconomic burden[1-3].

Over the last few decades, improvements in health practice and the development of MS disease-modifying therapies (DMTs)[4] may have contributed to positive changes in health outcomes as well as employment outcomes in the MS population. Our previous work has shown that DMTs have beneficial effects on employment outcomes for people with MS, particularly for those using high efficacy DMTs[5]. With these drugs now widely available and widely used in Australia, it is reasonable to hypothesise that Australians with MS may have experienced improvements in retaining employment, leading to a reduced risk of leaving employment due to MS in more recent years as compared to periods when DMTs were not available. In Australia, government funded DMTs have only been available for people with relapsing forms of MS. Therefore, if increased use of high efficacy DMTs has contributed to employment retention in Australians with MS, the effects of DMTs on employment retention should be most notable in those with relapsing forms of MS. However, to date, no study to our knowledge has evaluated whether there are changes in the risk of leaving employment due to MS in the population over recent times. Demonstrating improvements in employment retention that are temporally linked with the availability of DMTs may provide further insights into the benefits and potential cost offsets of these drugs.

Using a nationally representative sample, the aims of the current study were 1) to evaluate the risk factors of leaving employment due to MS by using competing risk survival analysis; and 2) to assess whether the risk of leaving employment has reduced over recent decades in Australia, stratified by MS phenotype.

Methods

Study population and data collection

The Australian MS Longitudinal Study (AMSLS) is a voluntary national longitudinal study with ongoing recruitment supported by MS Research Australia and all Australian State and Territory MS Societies. There are now around 3,000 active participants in the AMSLS, who are broadly representative of Australians with MS[6]. Around 96% of the participants were diagnosed with definite MS by a neurologist according to the McDonald criteria[7, 8]. The data used for the current study were

from the 2016 Economic Impact Survey, that was conducted from March-May 2016 and assessed the impacts of MS on income and employment (3,163 survey invitations sent, 1,577 (49.9%) responded).

Of the 1,577 respondents of the survey, we identified those who were working before their MS diagnosis (n=1,294). We excluded 19 participants with a missing year of MS diagnosis and 34 with a missing year of leaving employment, which left 1,240 participants for analysis.

Measurements

The primary outcome was time from MS diagnosis to leaving employment due to MS (including early retirement). Participants reported their current employment status. Of the included participants who were working before MS diagnosis, those who were not currently working and were not seeking employment were classified as having left employment. Those who were working and those who were not currently employed but were seeking employment were classified as not having left employment. We also asked whether MS was the reason they left their employment (Yes/No/Not applicable), and participants specified the year they retired or left paid employment.

Information regarding age, sex, education level, year of MS diagnosis, and MS type in 2016 was also reported. Information on DMT use was collected in 2005, 2009, 2010 and 2011-2016 in the AMSLS, with the information in year 2011, 2012, 2103 and 2014 being collected retrospectively in 2015. Current DMT usage was obtained from the 2015 (conducted October 2015-January 2016) and 2016 Disease Course Survey (conducted November 2016-March 2017), in which participants reported the DMT they were currently using and the DMTs they had stopped in the past 12 months.

Statistical analysis

Competing risk survival analysis was conducted to assess factors associated with leaving employment due to MS. Competing risks are other events that could happen and preclude the chance of experiencing the event of interest. In our case, there would be no chance of leaving employment due to MS if participants had permanently left employment due to other reasons, such as other health problems or family issues, which are competing events (competing risks) for leaving employment due to MS. The assumption of conventional survival analysis is that censoring is not associated with an altered chance of failure event occurring[9], which is violated and could lead to biased estimates of probability of the event of interest when competing events exists. Survival data with competing risks are commonly analysed by cause-specific hazard models (estimate the effect of covariates on the rate of event of interest among those who are event free) and subdistribution hazard models (also called as Fine-Grey models, which estimate the effect of covariates on the absolute risk of the event of interest over time)[10, 11]. Fine-Grey models directly link the cumulative incidence function to explanatory variables[12]. The estimates of a Fine-Grey model are sub-

distribution hazard ratios (sHR), which can be interpreted as a comparison of the cumulative incidence functions [13]. A higher sHR represents a higher risk (incidence) of the event associated with the exposure of interest. We conducted both cause-specific hazard models and subdistribution hazard models to estimate cause-specific hazard ratios (csHR) and sHR.

The primary event of interest was "leaving employment due to MS prior to age 65, as the upper limit of working age is often defined as 65 years in Australia. While the mean age of retirement may have gradually increased over time, as the eligible age for accessing age pension has increased from 60 years to 65 years for women and remained 65 years for men during the study period[14], we used the same criteria of working-age for men and women across different periods. Leaving employment prior to age 65 due to non-MS reasons was considered a competing event. Follow-up time started at the year of MS diagnosis and stopped at the following events, whichever occurred first: 1) year of leaving employment, 2) year of reaching age 65, or 3) year of the survey. Regression models were conducted to evaluate the effects of sex, education level (categorised as primary/ secondary school, occupational certificate or diploma, and university degree), MS phenotype, and age of diagnosis(categorised as diagnosed before 35 years old, 35-49 years, after 49 years) on the risk of leaving employment due to MS and due to other reasons. To understand the changes in the risk of leaving employment due to MS over past decades, we assessed the effects of different time periods on employment survival by including 'time period' as a covariate in separate models for people with RRMS, PPMS and SPMS. To ensure sufficient participant numbers for meaningful and reliable estimates, we treated 'time period' as a binary variable (years before a cut-point vs. years after a cut-point) and then gradually shifted the cut-point. The chosen cut-points follow the milestones of DMTs availability in Australia, including 1996 (first DMT was approved in Australia), 2006 (natalizumab was approved), 2010 (fingolimod was approved), 2013 (alemtuzumab was approved)[15].

From the DMT information collected in the AMSLS, we calculated the percentage of people with RRMS using a specific DMT in each year to show the changes in DMT treatment in Australians with RRMS in the past years. As the DMT information were not evaluated prospectively at different time points for all the participants included in the regression analysis, DMT treatment was not included in regression models to examine the impact of DMT on the risk of leaving employment directly. All analyses were performed using STATA (version 15; StataCorp LP).

Results

The median length of cohort follow-up was 10 years. The included participants were diagnosed between 1949 and 2015 (IQR: 1997-2007), with the mean age at diagnosis being 39.8 (SD 10.2) years and 77.8% being female (Table 1). Of those who had left employment (n=525), 78.7% left due to MS,

and the mean age at which they left employment was 48.6 (SD 9.2) years. Overall, 67.1% reported their MS course in 2016 as RRMS and 7.6% PPMS. Of 1171 who also reported whether they were using a DMT in 2015/2016 survey, 68.1% (n=798) were using a DMT. The most commonly used DMTs were fingolimod (21.4%), β-interferons (16.4), glatiramer acetate (9.7%) and natalizumab (8.1%) in 2015/2016.

We compared the respondents vs. non-respondents of the 2016 Economic Impact survey. Of all the 3,163 invited participants, the 1,577 respondents were similar to the non-respondents (1,568) by sex (78.9% females vs. 78.5%, p=0.76). Respondents were slightly older (55.4 years vs. 53.7 years, p<0.001), had a slightly older age of MS diagnosis (41.0 years vs. 40.0, p=0.006),had a higher education level (38.3% university degree vs. 31.5%, p<0.001), and had a slightly longer MS duration since diagnosis (15.2 years vs. 14.6 years, p=0.022).

The univariable subdistribution hazard models and cause-specific hazard models (Table 2) showed that the risk of leaving employment due to MS was higher in male, people with progressive MS type, those of lower education level, and those diagnosed at an older age. The higher risks remained statistically significant in the multivariable models (Table 3) including all these covariates. For example, the adjusted sub-hazard ratio of leaving employment due to MS for those with an education level of secondary school or less was 2.58 (95% CI: 2.19 to 4.09) as compared to those with a university degree. The adjusted sub-hazard of leaving employment due to MS was 1.54 times higher for males than females (95% CI: 1.24 to 1.90). The adjusted sub-hazard of leaving employment due to MS was 1.90 times higher for people with PPMS than those with RRMS (95% CI: 1.41 to 2.56). The cause-specific hazard models showed similar results. In contrast, the multivariable models showed that MS types and education level were not associated with leaving employment due to other reasons while the adjusted sub-hazard of leaving employment due to other reasons was 49% lower in male compared to female. Older age at diagnosis was also associated with a higher sub-hazard and cause-specific hazard of leaving employment due to other reasons.

We then compared the risk of leaving employment due to MS between the more recent periods of calendar years to the prior periods for people with RRMS, SPMS and PPMS (Table 4). We divided calendar years into different periods using shifting cut-points. For RRMS, using the year 1996 as a cut-point, there was no difference in sub-hazard when comparing the period of 1996-2016 to the period prior to year 1996 (sHR 1.07 (0.61-1.89) after adjusting for age of diagnosis, sex and education level, but the sub-hazard and cause-specific hazard of leaving employment due to MS was reduced when using more recent cut-points and this became stronger and significant when using 2010, 2012 and 2013 as cut-points. For example, the adjusted sub-hazard of leaving employment

due to MS for RRMS was reduced by 33% during the period between year 2010 and 2016 as compared to the period before year 2010, reduced by 43% during the period between year 2012 and 2016 as compared to the period before year 2012, and reduced by 51% during the period between 2013 and 2016 as compared to the prior period. In contrast, the sub-hazard ratios for people with PPMS and SPMS were consistently above or close to 1.00 for all cut-points. The cumulative incidence of leaving employment due to MS estimated from Fine and Gary models is shown in figure 1 (comparison between RRMS and PPMS) and supplementary figure A (comparison between RRMS and SPMS). The panel D of figure 1 shows, for example, that for people with RRMS, the estimated cumulative incidence of leaving employment due to MS at 10 years after MS diagnosis during period before year 2010 was around 18% and reduced to 11% in the period between year 2010 to 2016.

Figure 2 shows the use of DMTs in people with RRMS in Australia over time. We found that the use of lower efficacy DMTs (the classical injectable DMTs represented by β-interferons and glatiramer acetate) substantially decreased between 2005 and 2015, with the downward rate accelerating after 2010. For example, 60.5% used β-interferons or glatiramer acetate in 2010 and this reduced to 29.3% in 2015. The uptake of higher efficacy DMTs increased after 2010, from 8.4% (represented by natalizumab only) in 2010 to 48.0% (22.7% fingolimod + 14.7% teriflunomide/dimethyl fumarate + 8.5% natalizumab + 1.7% alemtuzumab) in 2015.

Discussion

By using a large MS sample, we found that the risk of leaving employment due to MS since diagnosis was reduced in more recent years in RRMS while this pattern was not seen for PPMS or SPMS. The statistically significant reduction for RRMS started to occur when comparing the period 2010-2016 to period before 2010, and became stronger thereafter, which coincided with the increasing usage of higher efficacy DMTs in Australia during that period. The multivariable model showed that males, people with progressive MS, those with a lower education level and those older at diagnosis were at a higher risk of leaving their employment due to MS, suggesting that they may need additional assistance in order to stay longer in the labour force.

We found that, for RRMS, the sub-hazard of leaving employment due to MS was 33% lower in 2010-2016 as compared to before 2010 and this increased to 43% and 51% when using 2012 and 2013 as time cut-points. In contrast, the sHR for PPMS and SPMS were above or close to 1.00 for all cut-points. The differential pattern coincides with the increased usage of higher efficacy DMTs in participants with RRMS, increasing from 0.0% in 2005 to 8.4% in 2010 to 48.0% in 2015. Moreover, earlier diagnosis[16] and treatment due to changes in diagnostic criteria[7] may also have contributed to better health and employment outcomes in RRMS. The widespread development of multidisciplinary

MS clinics and expansion of the roles of MS nurse specialists could also have improved overall care of people with MS in Australia. This may have impacted most on those with RRMS who tend to be seen more frequently due to the requirements of monitoring for DMT usage.

Although, to our knowledge, no other studies have evaluated changes in employment survival over the past decades in MS, a recent study from Sweden, which included participants diagnosed between 1996-2005 using national MS registry data, reported similar changes in disability progression in MS[17]. They found that being diagnosed more recently was associated with a longer time to reach disability milestones for relapsing-onset MS while no change was seen for progressive-onset MS[17]. Given the differential access to DMTs between people with different forms of MS, the authors also suggested that DMTs might be a driver for the differential changes. Another cohort study from MSBase showed that initial treatment with high efficacy DMTs (natalizumab, fingolimod or alemtuzumab) was associated with a lower risk of conversion to SPMS than initial treatment with glatiramer acetate or interferon beta[18], also suggesting the potential superior long-term effects of high efficacy DMTs in improving health outcomes.

While people with SPMS could have experienced beneficial effects from DMTs during the relapsing-remitting phase, we did not observe a significantly reduced risk in more recent periods in SPMS. However, almost 50% of our SPMS participants were diagnosed before 1996, and we did not know when they converted to SPMS. Unless the conversion to SPMS happened in more recent years (i.e. after higher efficacy DMTs became available), it is very unlikely that they received high efficacy DMTs whilst they had RRMS. It is therefore not surprising that our results for people with SPMS line up with those with PPMS. Also, while some people with SPMS and PPMS may still have used DMTs, the efficacy of DMTs in these populations is significantly lower than in RRMS group. Therefore, if there were SPMS/PPMS participants using DMTs and were misclassified as RRMS, this would have reduced the effect size.

We showed that males, those with progressive MS, those of a lower education level, and those diagnosed at an older age were independently associated with a higher risk of leaving employment due to MS after diagnosis. Some of these factors (progressive MS, male sex, and older age at diagnosis) have also been associated with a worse prognosis[19-22], thus they may have experienced higher symptom loads and greater disability burden, resulting in more difficulties to remain in employment. Males or those with a lower education level are more likely to take labour intensive jobs[23], such as blue-collar jobs, which may be harder to maintain with MS-related disability. Moreover, as health promotion and support programs have sometimes been viewed as an unessential cost burden, support networks for managing disability at work are less readily available

in blue-collar than white-collar workplaces[23]. Studies have also suggested that males tend to have reduced help-seeking behaviour for health-related matters compared to females[24, 25], which could also lead to leaving employment earlier. Future studies are needed to better understand the potential difference in difficulties and needs in employment maintenance between males and females, people with different education levels, and across age groups, in order to provide effective and tailored employment interventions/assistance. For example, while the use of internet-based resources for information on managing MS is increasing, it is older people, males or those with lower education levels who are less likely to make use of online resources when seeking help for managing the symptoms and demands of MS[26, 27]. Providing tailored health information and guidance are likely to improve the efficacy of health interventions[28-30].

Employment outcomes are indicators reflecting the burden of MS on individuals and society, and are closely associated with many MS symptoms, disability, disease progression[31 32, 33]and MRI markers[34]. We recommend that regular monitoring of work-related outcomes together with treatment and disease outcomes should be incorporated in future prospective MS studies and registries. As the current study did not provide direct evidence of the effects of DMTs on reducing risk of leaving employment in MS, future prospective studies assessing DMTs treatment, disease characteristics and employment outcomes would extend the understanding of the effects of DMTs on employment retention in MS.

Major strengths of our study include that our study sample was large and that the AMSLS participants have been shown to be representative[6]. In addition, participants had a wide range in year of diagnosis, including years when DMTs were not available, which allowed us to evaluate the changes in the risk over several decades. Also, we used a disease-specific outcome, i.e. leaving employment due to MS, and used a statistical approach that accounts for the presence of leaving employment due to other reasons. Several limitations should be acknowledged as well. Firstly, although the AMSLS participants have been shown to representative of Australians with MS,[6] we identified small differences in age, age at diagnosis and education level between those who participated in the survey and those who did not. Moreover, it is possible that those with more severe disability and rapidly worsening disease progression, who were more likely to experience employment loss, were not adequately captured. As these people were more likely to be at an older age, they were likely to be diagnosed in earlier years. If this was the case, the sHR for more recent periods might be underestimated. Secondly, our data were collected retrospectively, which may have caused error in the recall of the year of leaving employment. Thirdly, while we found that the sHR for PPMS as well as for SPMS were consistently greater or close to 1 (opposite direction of effects as compared to RRMS) for all comparisons using different cut-points, we acknowledge that

these analyses were conducted on relatively low numbers. In addition, occupation type, disability, DMTs, MS symptoms and comorbidities were not evaluated at different time points, so we were unable to assess the effects of these time-varying variables. Despite being time-varying, MS phenotype and education level were only measured in 2016.

In summary, we found that the risk of leaving employment due to MS was reduced in more recent years in people with RRMS while this pattern was not seen for people with PPMS and SPMS. The differential changes seem to coincide with the increased usage of high efficacy DMTs in Australia during that period. The higher risk of leaving employment due to MS among males, those with progressive MS and those with a lower education level suggests that additional assistance should be provided in their employment maintenance after MS onset and over the disease course.

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Table 1. Participants characteristics

Characteristics	N=1,240
Age at MS diagnosis (years), mean (SD)	39.8 (10.2)
Year of MS diagnosis, median (IQR)	2003 (1997-2007)
Length of cohort follow-up (years), median (IQR)	10 (5-15)
Employment status at the end of follow-up	
Had left employment due to MS before age 65, n (%)	413 (33.3)
Had left employment due to other reasons before age 65, n (%)	82 (6.6)
In the labour force or left employment at age 65 years or after, n (%)	745 (60.1)
Age when left employment	
Those who left due to MS (years), mean (SD)	48.6 (9.2)
Those who left due to other reasons (years), mean (SD)	55.7 (8.1)
Female sex, n (%)	965 (77.8)
MS type at 2016, n (%)	
Relapsing-remitting MS	777 (67.1)
Secondary-progressive MS	145 (12.5)
Primary-progressive MS	88 (7.6)
Progressive-relapsing MS	25 (2.2)
Unsure	123 (10.6)
Education level, n (%)	
Primary school or secondary school	380 (30.7)
Occupational certificate or diploma	356 (28.7)
University degree	504 (40.7)
DMT treatment, n(%)*	
Not using a DMT	373 (31.9)
β-interferons	192 (16.4)
Glatiramer acetate	113 (9.7)
Dimethyl fumarate	89 (7.6)
Teriflunomide	37 (3.2)
Fingolimod	250 (21.4)
Natalizumab	95 (8.1)
Alemtuzumab	22 (1.9)

IQR : interquartile range ; SD : standard deviation.
* Data on 1171 of the 1240 participants with the DMT type reported in 2015 or 2016 survey.

Table 2. Univariable analysis evaluating factors associated with leaving employment due to MS and other reasons from cause-specific and subdistribution hazard models.

			Subdistribution Hazard Model		**Cause-specific Hazard Model**	
Variables	Experienced event of interest (leaving employment due to MS), N (%)	Did not experience event of interest at the end of follow-up[§], N (%)	Leaving employment **due to MS** sHR (95% CI)	Leaving employment **due to other reasons** sHR (95% CI)	Leaving employment **due to MS** csHR (95% CI)	Leaving employment **due to other reasons** csHR (95% CI)
Sex						
Female	113 (16.3)	582 (83.7)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Male	51 (30.0)	119 (70.0)	**1.88 (1.26 to 2.82)****	0.67 (0.38 to 1.21)	**1.73 (1.41 to 2.13)****	0.79 (0.44 to 1.40)
Education level						
University degree	57 (15.8)	303 (84.2)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Occupational certificate or diploma	80 (31.4)	175 (68.6)	**2.02 (1.45 to 2.82)****	1.27 (0.71 to 2.27)	**1.53 (1.18 to 1.98)***	1.38 (0.77 to 2.47)
Primary or secondary	114 (45.6)	136 (54.4)	**2.99 (2.19 to 4.09)**	**1.81 (1.08 to 3.03)***	**2.43 (1.92 to 3.07)****	**2.19 (1.30 to 3.67)***
Test for trend			**P<0.001**	**P=0.024**	**P<0.001**	**P=0.003**
MS type at 2016						
Relapsing-remitting MS	196 (25.2)	581 (74.8)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Primary progressive MS	55 (62.5)	33 (37.5)	**2.62 (1.97 to 3.50)****	1.31 (0.58 to 2.95)	**2.70 (2.00 to 3.65)****	1.74 (0.78 to 3.91)
Secondary progressive MS	81 (55.9)	64 (44.1)	**1.95 (1.51 to 2.51)****	1.03 (0.51 to 2.11)	**1.94 (1.50 to 2.52)****	1.11 (0.55 to 2.25)
Progressive relapsing MS	8 (32.0)	17 (68.0)	1.02 (0.51 to 2.06)	2.68 (0.92 to 7.79)	1.09 (0.54 to 2.21)	2.57 (0.91 to 7.22)
Unsure	50 (40.7)	73 (59.3)	**1.51 (1.13 to 2.02)***	**2.70 (1.51 5o 4.82)***	**1.62 (1.19 to 2.21)***	**2.80 (1.59 to 4.93)****
Age at MS diagnosis						
<35 years	57 (19.8)	231 (80.2)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
35-49 years	122 (28.7)	303 (71.3)	**1.84 (1.36 to 2.49)****	**1.95 (1.09 to 3.51)***	**1.84 (1.45 to 2.35)****	**4.76 (2.29 to 9.90)****
49+ years	72 (47.4)	80 (52.6)	**4.48 (3.19 to 6.31)****	**6.57 (3.69 to 11.71)****	**4.38 (3.27 to 5.85)****	**38.62 (16.90 to 88.26)****
Test for trend			**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**

sHR: Sub-distribution hazard ratio from subdistribution hazard models (Fine-Gray models); csHR: cause-specific hazard ratio from Cause-specific Hazard Model;
CI: confidence interval; * p<0.05; **p<0.001

Table 3. Multivariable analysis evaluating factors associated with leaving employment due to MS and other reasons from cause-specific and subdistribution hazard models.

	Subdistribution Hazard Model		**Cause-Specific Hazard Model**	
Variables	Leaving employment **due to MS**	Leaving employment **due to other reasons**	Leaving employment **due to MS**	Leaving employment **due to other reasons**
	sHR (95% CI)	sHR (95% CI)	csHR (95% CI)	csHR (95% CI)
Sex				
Female	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Male	**1.54 (1.24 to 1.90)***	**0.51 (0.28 to 0.95)***	**1.47 (1.18 to 1.83)***	0.61 (0.33 to 1.13)
Education level				
University degree	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Occupational certificate or diploma	**1.49 (1.15 to 1.94)***	1.14 (0.63 to 2.08)	**1.51 (1.16 to 1.97)***	1.25 (0.82 to 2.49)
Primary or secondary school	**2.58 (1.94 to 3.44)****	1.29 (0.74 to 2.26)	**2.14 (1.67 to 2.75)**	1.42 (0.82 to 2.49)
Test for trend	**P<0.001**	P=0.368	**P<0.001**	P=0.211
MS type at 2016				
Relapsing-remitting MS	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Primary progressive MS	**1.90 (1.41 to 2.56)****	1.13 (0.48 to 2.66)	**1.91 (1.40 to 2.60)****	1.39 (0.61 to 3.17)
Secondary progressive MS	**1.85 (1.44 to 2.38)****	1.14 (0.55 to 2.34)	**1.84 (1.41 to 2.39)****	1.12 (1.55 to 2.28)
Progressive relapsing MS	0.98 (0.48 to 2.03)	2.91 (0.98 to 8.62)	1.13 (0.55 to 2.29)	2.64 (0.93 to 7.49)
Unsure	1.18 (0.86 to 1.62)	**2.64 (1.49 to 4.69)***	1.28 (0.93 to 1.76)	**2.22 (1.25 to 3.94)***
Age at MS diagnosis				
<35 years	1 (reference)	1 (reference)	1 (reference)	1 (reference)
35-49 years	**1.55 (1.23 to 1.96)****	**2.25 (1.20 to 4.20)***	**1.74 (1.35 to 2.24)****	**5.13 (2.34 to 11.21)****
49+ years	**2.58 (1.94 to 3.44)****	**7.13 (3.79 to 13.42)****	**3.59 (2.63 to 4.89)****	**36.44 (15.12 to 87.79)****
Test for trend	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**

sHR: Sub-distribution hazard ratio from subdistribution hazard models (Fine-Gray models); csHR: cause-specific hazard ratio from Cause-specific hazard models; CI: confidence interval; * p<0.05; **p<0.001

Table 4. The risk of *leaving employment due to MS* in different time periods between people with relapsing-remitting MS, primary progressive MS and secondary progressive MS by splitting periods with shifting cut-off points.

Periods of calendar year	Relapsing remitting MS		Primary progressive MS		Secondary progressive MS	
	sHR (95% CI)‡	csHR (95% CI)‡	sHR (95% CI)‡	csHR (95% CI)‡	sHR (95% CI)‡	csHR (95% CI)‡
Before 1996	1	1	1	1	1	1
1996-2016	1.07 (0.61 to 1.89)	1.06 (0.60 to 1.87)	1.70 (0.82 to 3.55)	1.73 (0.82 to 3.64)	1.84 (0.94 to 3.61)	1.76 (0.90 to 3.47)
Before 2000	1	1	1	1	1	1
2000 -2016	0.87 (0.59 to 1.28)	0.87 (0.59 to 1.30)	**2.41 (1.20 to 4.84)***	**2.36 (1.17 to 4.77)***	1.56 (0.96 to 2.53)	1.54 (0.95 to 2.51)
Before 2006	1	1	1	1	1	1
2006 -2016	0.91 (0.69 to 1.22)	0.92 (0.69 to 1.24)	1.68 (0.97 to 2.91)	1.65 (0.93 to 2.92)	1.25 (0.82 to 1.93)	1.36 (0.87 to 2.12)
Before 2010	1	1	1	1	1	1
2010 -2016	**0.67 (0.50 to 0.90)***	**0.67 (0.59 to 0.90)***	1.25 (0.72 to 2.16)	1.28 (0.74 to 2.24)	1.37 (0.84 to 2.25)	1.39 (0.85 to 2.29)
Before 2012	1	1	1	1	1	1
2012 -2016	**0.57 (0.41 to 0.80)***	**0.59 (0.41 to 0.82)***	1.31 (0.74 to 2.33)	1.45 (0.81 to 2.61)	1.33 (0.77 to 2.29)	1.38 (0.80 to 2.34)
Before 2013	1	1	1	1	1	1
2013 -2016	**0.49 (0.33 to 0.72)****	**0.49 (0.33 to 0.73)****	0.90 (0.41 to 1.95)	1.06 (0.48 to 2.31)	0.85 (0.41 to 1.13)	0.91 (0.44 to 1.87)

sHR: Sub-distribution hazard ratio from subdistribution hazard models (Fine-Gray models); csHR: cause-specific hazard ratio from cause-specific hazard models; CI: confidence interval; * $p<0.05$; ** $p<0.001$. ǂ: Adjusted for age of diagnosis, sex and education level.

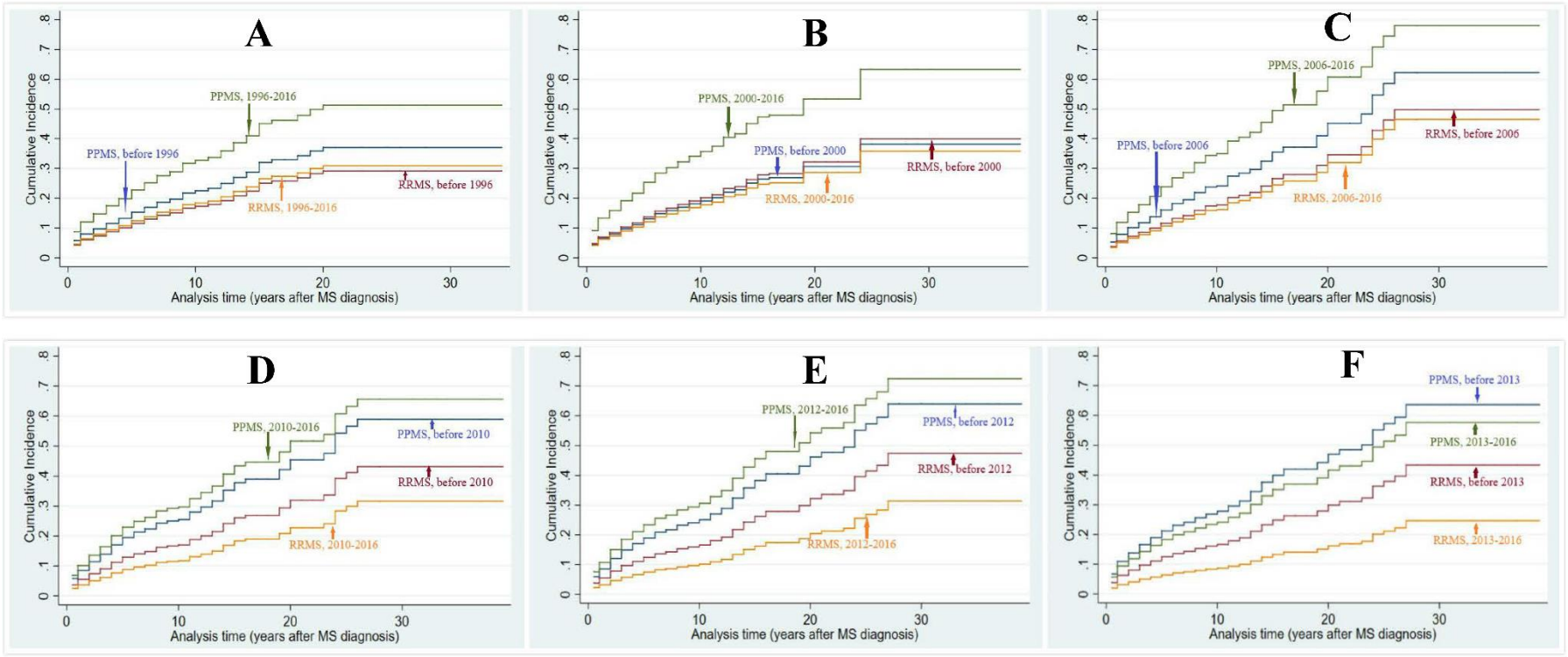


Figure 1. Curves illustrating the cumulative incidence of leaving employment due to MS over time after diagnosis for people with RRMS and PPMS in different periods.

RRMS: relapsing-remitting MS; PPMS: primary progressive MS.

A. Cumulative incidence in period before year 1996 vs. 1996-2016. B. Cumulative incidence in period before year 2000 vs. 2000-2016.

C. Cumulative incidence in period before year 2006 vs. 2006-2016. D. Cumulative incidence in period before year 2010 vs. 2010-2016.

E. Cumulative incidence in period before year 2012 vs. 2012-2016. F. Cumulative incidence in period before year 2013 vs. 2013-2016.

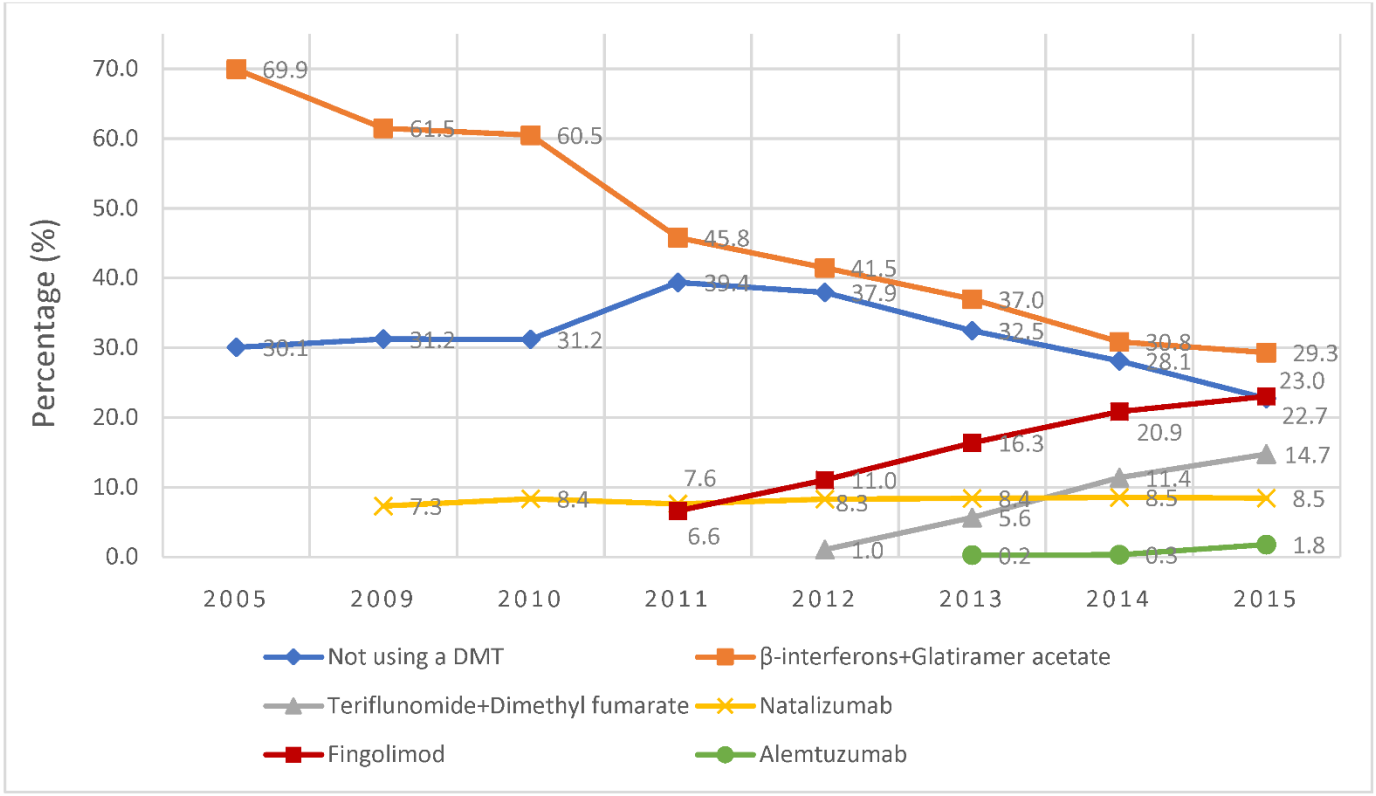
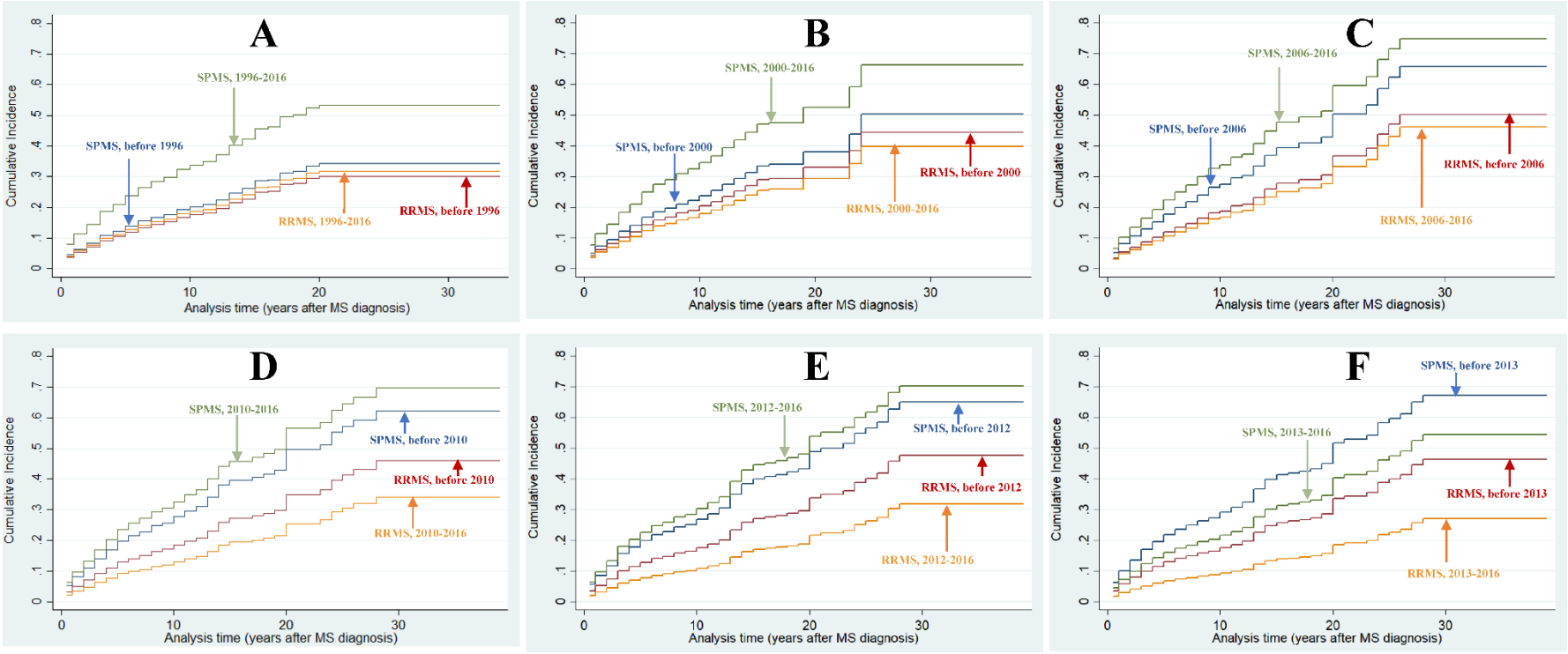


Figure 2. Different DMTs usage from 2005 to 2015 in the AMSLS participants with RRMS.



Supplementary figure A. Curves illustrating the cumulative incidence of leaving employment due to MS over time after diagnosis for people with RRMS and SPMS in different periods.

RRMS: relapsing-remitting MS; SPMS: secondary progressive MS.

A. Cumulative incidence in period before year 1996 vs. 1996-2016. B. Cumulative incidence in period before year 2000 vs. 2000-2016.

C. Cumulative incidence in period before year 2006 vs. 2006-2016. D. Cumulative incidence in period before year 2010 vs. 2010-2016.

E. Cumulative incidence in period before year 2012 vs. 2012-2016. F. Cumulative incidence in period before year 2013 vs. 2013-2016.

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