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Multiple sclerosis: effect of beta interferon treatment on survival

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Worldwide, the beta interferons remain the most commonly prescribed disease-modifying drugs for multiple sclerosis. However, it is unclear if they alter survival. We investigated the association between beta interferon and mortality in the 'real-world' setting. This was a multi-centre population-based observational study of patients with relapsing-onset multiple sclerosis who were initially registered at a clinic in British Columbia, Canada (1980–2004) or Rennes, France (1976–2013). Data on this cohort were accessed from the clinical multiple sclerosis databases and from individually linked health administrative data; all data were collected prospectively. Participants were followed from the latter of their first multiple sclerosis clinic visit, 18th birthday or 1 January 1996; until death, emigration or 31 December 2013. Only those who were naïve to disease-modifying therapy and immunosuppressant treatment of multiple sclerosis at the start of their follow-up were included in the analysis. A nested case-control approach was used. Up to 20 controls, matched to cases (deaths) by country, sex, age ± 5 years, year and disability level at study entry, were randomly selected from the cohort by incidence density sampling. The associations between all-cause mortality and at least 6 months beta interferon exposure, and also cumulative exposure ('low', 6 months to 3 years; and 'high', >3 years), were estimated by conditional logistic regression adjusting for treatment with other disease-modifying therapies and age in years. Further analyses included separate analyses by sex and country, additional adjustment for comorbidity burden in the Canadian cohort, and estimation of the association between beta interferon and multiple sclerosis-related death in both countries. Among 5989 participants (75% female) with a mean age of 42 (standard deviation, SD 11) years at study entry, there were 742 deaths (70% female) and the mean age at death was 61 (SD 13) years. Of these cases, 649 were matched to between one and 20 controls. Results of the conditional logistic regression analyses are expressed as adjusted odds ratios with 95% confidence intervals. The odds of beta interferon exposure were 32% lower among cases than controls (0.68; 0.53–0.89). Increased survival was associated with >3 years beta interferon exposure (0.44; 0.30–0.66), but not between 6 months and 3 years exposure (1.00; 0.73–1.38). Findings were similar within sex and country, and for multiple sclerosis-related death. Beta interferon treatment was associated with a lower mortality risk among people with relapsing-onset multiple sclerosis. Findings were consistent between two geographically distinct regions in North America and Europe.

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Abbreviation: EDSS = Expanded Disability Status Scale

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Introduction

Multiple sclerosis is a devastating chronic disease of the CNS that typically first affects young adults. Multiple sclerosis confers a survival disadvantage in comparison to the general population, with 6–14 fewer years lived (Bronnum-Hansen *et al.*, 2004; Kingwell *et al.*, 2012; Scalfari *et al.*, 2013; Rodriguez-Antiguedad Zarranz *et al.*, 2014; Leray *et al.*, 2015; Marrie *et al.*, 2015). Among people with multiple sclerosis, the proportion of deaths directly attributed to this condition has ranged from 50% to more than 75% (Sadovnick *et al.*, 1991; Midgard *et al.*, 1995; Koch-Henriksen *et al.*, 1998; Leray *et al.*, 2007; Rodriguez-Antiguedad Zarranz *et al.*, 2014; Leray *et al.*, 2015).

The first disease-modifying drugs, the beta interferons, were approved to treat relapsing-onset multiple sclerosis in the 1990s. Although newer therapies are now available, including orally active and infused medications, the beta interferons remain among the most commonly prescribed for multiple sclerosis worldwide (Atlas of MS, 2013; Westad *et al.*, 2017). However, while they have shown modest efficacy in short-term clinical trials including reductions in relapse rates, relapse severity, and MRI abnormalities [IFNB Multiple Sclerosis Study Group, 1993; Johnson *et al.*, 1995; Jacobs *et al.*, 1996; PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group, 1998] their effects on disability progression, or over the long-term and in clinical practice are less certain (Tramacere *et al.*, 2015; Signori *et al.*, 2016).

Preliminary observations from a small group of 366 individuals who were enrolled in one of the original beta interferon-1b clinical trials suggested that this drug might increase survival and reduce the risk of multiple sclerosis-related death (Goodin *et al.*, 2012*a*, *b*). However, concerns were raised over the study design, including *post hoc* analyses in a small group of clinical trial participants; it remains possible that the observed survival advantage was due to chance alone (Goodin and Reder, 2012; Gronseth and Ashman, 2012). Long-term randomized clinical trials that are specifically designed to assess the survival impact of disease-modifying therapies are neither feasible nor ethical. We used the nested case-control approach with a large population-based combined cohort of relapsing-onset multiple sclerosis patients from British Columbia, Canada and Rennes, France to examine the association of the beta interferons with all-cause, and multiple sclerosis-related, mortality in the real-world clinical setting.

Materials and methods

Data and cohort selection

We used prospectively collected linked data from population-based multiple sclerosis clinical and health administrative databases. The cohort comprised adults with relapsing-onset multiple sclerosis, initially registered at one of the four multiple sclerosis clinics in British Columbia between 1980 and 2004, or the Rennes multiple sclerosis clinic between 1976 and 2013. These individuals were linked to their health administrative data via unique personal health number (Canada), or name, sex, birthdate and birthplace (France). This enabled access to provincial (Canada) and national (France) death dates, and all causes listed on the death certificate. Additional linkage, for Canada only, provided outpatient and community dispensations of disease-modifying therapy; hospital and physician derived diagnoses recorded via the International Classification of Diseases system to calculate the Charlson Comorbidity Index (Deyo *et al.*, 1992); registration dates in the compulsory provincial healthcare plan (to confirm residency in British Columbia); and quintiles of estimated socioeconomic status based on neighbourhood income. See Supplementary material and Supplementary Table 1 for details.

Only persons with relapsing-onset multiple sclerosis (i.e. relapsing remitting or secondary progressive multiple sclerosis at study entry) who were naïve to any disease-modifying therapy or immunosuppressant at study entry were included. For the main analyses, an Expanded Disability Status Scale (EDSS) score within 3 years of study entry was required for inclusion. The study entry was the most recent of 1 January 1996, the first clinic visit, or the 18th birthday. The first full calendar year of beta interferon availability in both jurisdictions was 1996 (prior use was limited to clinical trials). Follow-up continued until the earlier of death, 31 December 2013 or, for the Canadian cohort only, emigration from the province of British Columbia. Such censoring at emigration from British Columbia was necessary because death outcomes and treatment exposure were only captured for residents of the province. Treatment status after the last clinic visit was unknown for a subset of the French cohort; follow-up for these individuals was censored at their last clinic visit. However, all deaths registered anywhere in France were captured, and while emigration from France was not captured this was considered negligible.

Outcome and exposure measures

The primary outcome was death due to any cause; all persons who died during follow-up were considered cases. The secondary outcome was multiple sclerosis-related death, identified using the underlying or contributing causes on the death certificate by a study-specific algorithm formulated *a priori* (Fig. 1). The algorithm was developed by reference to the existing literature on increased mortality risk due to specific causes among people with multiple sclerosis (Sadovnick *et al.*, 1991; Koch-Henriksen *et al.*, 1998; Bronnum-Hansen *et al.*, 2004; Grytten Torkildsen *et al.*, 2008; Smestad *et al.*, 2009; Sumelahti *et al.*, 2010; Goodin *et al.*, 2014), and by consensus of the study team which included two experienced multiple sclerosis specialist neurologists (G.E. and J.O.). For this analysis, multiple sclerosis-related deaths were cases and all other deaths in the cohort during follow-up were censored on the date of death.

All beta interferons were considered as one group; 'exposed' was defined as $\geqslant 6$ months of cumulative exposure between study entry and death, or between study entry and the analogous date for controls. Lower (6 months to 3 years), or higher (>3 years) cumulative exposure to beta interferon was

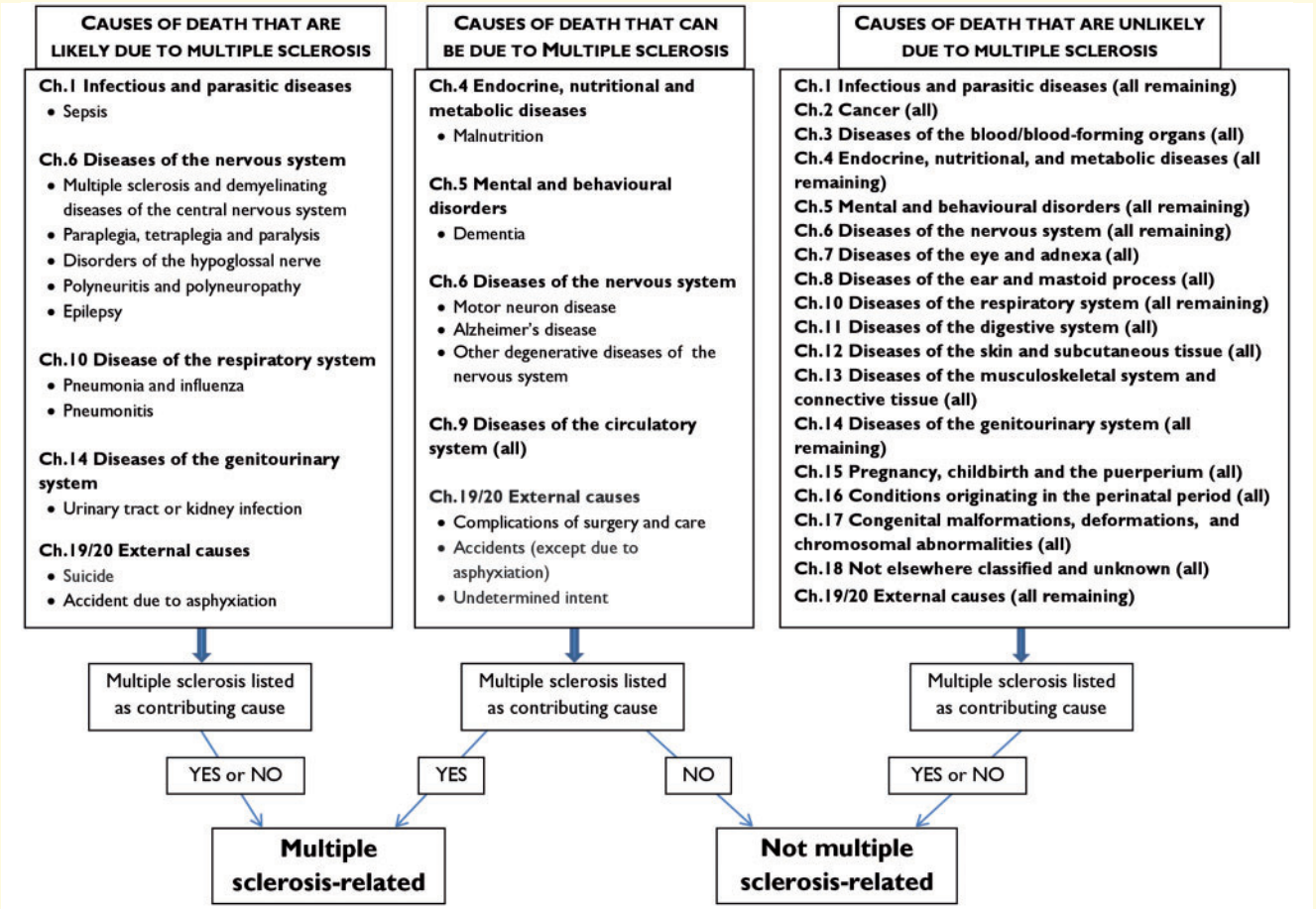

Figure 1 Algorithm to classify multiple sclerosis-related death based on the underlying cause and multiple sclerosis as a contributing cause from the death certificate among patients with multiple sclerosis. All deaths with multiple sclerosis listed as the underlying cause were considered to be multiple sclerosis-related, as were deaths attributed (as the underlying cause) to suicide, certain diseases of the nervous system, sepsis, respiratory infection/inflammation or genitourinary system infection. Deaths due to certain other underlying causes; diseases of the circulatory system, malnutrition, dementia, other specific nervous system diseases, accidents and complications of medical care, were considered multiple sclerosis-related only if multiple sclerosis was mentioned as contributing to the death. Lastly, the remaining underlying causes, including cancer, were considered as not multiple sclerosis-related whether multiple sclerosis was mentioned as contributing or not. The cause of death data from the death certificate were accessed through the British Columbia Vital Statistics Agency in Canada and the 'Répertoire National d'Identification des Personnes,' and 'Institut National de la Santé et de la Recherche Médicale' in France. The underlying and contributing causes were coded by International Classification of Diseases version 9 and 10 codes. The International Classification of Diseases-10 chapters were used to guide formulation and visualization of the algorithm.

considered in secondary analysis to explore potential dose-response relationships; exposure duration categories were determined *a priori* based on the distribution of beta interferon exposure in the cases and controls combined. The effects of 'early' or 'late' beta interferon initiation were also examined by (i) time since multiple sclerosis symptom onset (<5 and $\geqslant 5$ years); and (ii) age (<40 years and $\geqslant 40$ years or older). Exposure to the second most commonly used disease-modifying therapy during this study period, glatiramer acetate (for at least 6 months) was considered as a covariate. The 6-month minimum exposure for beta interferon and glatiramer acetate was decided upon with reference to the minimum length of time that these agents might be expected to yield a clinical response (Karussis *et al.*, 2006). All other disease-modifying therapies that were available or approved during the study period (immunosuppressants such as azathioprine or mitoxantrone, as well as natalizumab and fingolimod) were combined into one variable and categorized as 'any' (at least 1 day) or 'no' exposure. The 1-day minimum exposure for the 'other disease-modifying therapy' variable reflects both its heterogeneous nature and the assumption that exposure to any duration of these therapies could serve as a marker for more severe disease.

The required sample size to address the primary and secondary questions of the association between beta interferon and all-cause mortality, and multiple sclerosis-related mortality, was estimated *a priori*, assuming a two-tailed test with a 5% probability of type I error and at least 80% power. We anticipated sufficient power to assess the effects of beta interferon exposure on all-cause death, and multiple sclerosis-related death. Given low exposure rates for the non-beta interferon therapies (glatiramer acetate and 'other' disease modifying

therapies) in this cohort, we did not have sufficient power to query their effects on survival; these exposures were measured and included in the analyses to adjust for confounding.

Study design

A nested case-control approach was used with incidence density sampling. Up to 20 controls were randomly selected for each case, matched at study entry by sex, country, age (±5 years), calendar year, and EDSS score (within 3 years of study entry and categorized as scores of ⩽3.0; 3.5–5.0; 5.5–6.5; >6.5). Hence, controls were alive at the time of the case's death, cases and controls were matched for follow-up duration, and eligible controls could be selected for more than one case or could become cases later during follow-up. If only 20 or fewer controls were available all available matched controls were used; all cases with at least one control were included in the analysis. The odds ratio (OR) estimated with this approach will be similar to the hazard ratio that would be obtained using Cox regression modeling (when the parametric assumptions of the Cox model are met) of the whole cohort with time dependent disease-modifying therapy exposures (Essebag *et al.*, 2005). However, the nested case-control approach provides tighter control of the important confounding variables through matching. The cases are directly compared only to persons in the cohort who are still alive at the time of the death in the case and who are similar to them in terms of age; sex; disability level; and time period and duration of follow-up. As with the time-dependent Cox model, the nested case-control approach accounts for the time dependence of exposure, and varying levels of exposure over time.

Statistical analyses

The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated using conditional logistic regression models adjusted for a more precise measure of age (in years and months) at study entry, exposure to glatiramer acetate, and exposure to other disease-modifying therapies. Disease duration (years between multiple sclerosis onset and study entry), and in Canada only, the quintile of socioeconomic status at study entry and the Charlson Comorbidity Index measured over the year before study entry, were included in multivariable models only if associated with case-control status in the univariate model ($P \leqslant 0.1$). Odd ratios were estimated for the combined cohort, and separately by country and sex.

Complementary analyses facilitated inclusion of additional data and tested assumptions by: allowing earlier study entry (1 January 1986); imputing EDSS scores for those without a score at study entry; imputing beta interferon status after the last clinic visit if subsequent treatment was unknown (France only); and changing criteria for exposure to beta interferon or glatiramer acetate to at least one day ('intention to treat'). More details are provided in the Supplementary material.

The analyses were performed using R (version 3.4.2). The study was approved by the relevant ethics boards and data stewards (see 'Acknowledgements' section).

Data availability

The individual clinical data and linked administrative health and vital statistics data that support these findings are protected by strict privacy and data sharing agreements and cannot be distributed openly.

Results

The combined Canadian and French cohort included 5989 persons with relapsing-onset multiple sclerosis who were naïve to disease-modifying therapies at study entry; 75% were female and the mean age was 42 (SD 11) years. During an average of 11, and up to 18 years of follow-up, 32% of persons in the cohort were exposed to beta interferon for at least 6 months, 12% to glatiramer acetate for at least 6 months, and 13% to another disease-modifying therapy for at least 1 day.

There were 742 deaths due to any cause [mean age at death was 61 years (SD 13)]. Of these, 649 were successfully matched with up to 20 controls; the number of controls per case is shown in Supplementary Table 2. At study entry, cases were slightly older than controls, although by less than half a year (50.7 versus 50.3; $P = 0.002$), and comparable by sex, EDSS score and country (Table 1). Comorbidity was associated with case-control status ($P = 0.02$) in the Canadian cohort whereas multiple sclerosis disease duration and socioeconomic status were not ($P \geqslant 0.20$).

After adjustment for age and other disease-modifying therapy exposure, persons with relapsing-onset multiple sclerosis who died had lower odds of beta interferon exposure compared to persons with relapsing-onset multiple sclerosis who survived (OR: 0.68; 95% CI: 0.53–0.89); this can be interpreted as a 32% lower mortality risk for exposed compared to unexposed individuals. Increased survival was associated with a higher cumulative beta interferon exposure (>3 years; OR: 0.44; 95% CI: 0.30–0.66) but not with a lower exposure (between 6 months and 3 years; OR: 1.00; 95% CI: 0.73–1.38) (Table 2).

Stratified analyses by country (Table 2) and sex (Table 3), resulted in qualitatively similar findings, although confidence intervals were wider in these subgroups. The adjusted odds ratios for Canada and France were essentially identical but for the smaller French cohort, with 80 matched cases, the confidence interval included one (Table 2). While findings did not differ significantly between the sexes (the confidence intervals overlapped), statistical significance was not reached for females except with higher cumulative beta interferon exposure. Further, the effect size was greater among males than among females (Table 3).

Since the analysis included people who died before the end of follow-up (cases) and their matched controls of comparable age, sex and disability level, both the average age (50 years) and the average disease duration (17 years) at study entry were greater than the average age and disease duration of the source cohort (i.e. those who were older or had a longer disease duration at study entry were less likely to survive to study end). The older age and more advanced disease duration at study start means that few had the

Table 1 Characteristics of the all-cause death cases and their matched controls from the combined Canadian and French multiple sclerosis cohorts

	Cases[a] (*n* = 649)	Controls[b] (*n* = 8412)	*P*-value[c]
Age[d], years, mean (SD)	50.7 (11.4)	50.3 (10.6)	0.002
Sex, *n* (%)			n/a
Males	195 (30.0)	195 (30.0)	
females	454 (70.0)	454 (70.0)	
Country, *n* (%)			n/a
Canada (British Columbia)	569 (87.7)	569 (87.7)	
France (Rennes)	80 (12.3)	80 (12.3)	
EDSS, *n* (%)			n/a
⩽3.0	160 (24.7)	160 (24.7)	
3.5–5.0	131 (20.2)	131 (20.2)	
5.5–6.5	164 (25.3)	164 (25.3)	
7–9.5	194 (29.9)	194 (29.9)	
Socioeconomic status[e], *n* (%)			0.20
Lowest	108 (19.0)	99.2 (17.4)	
Mid–low	93 (16.3)	94.1 (16.5)	
Middle	105 (18.5)	114.7 (20.2)	
Mid–high	132 (23.2)	126.9 (22.3)	
Highest	107 (18.8)	117.7 (20.7)	
Disease duration[d], years, mean (SD)	17.1 (11.4)	17.5 (7.9)	0.42
Comorbidity Index[f], mean (SD)	0.24 (0.65)	0.18 (0.25)	0.02
Follow-up time[g], years, mean (SD)	9.3 (4.6)	9.3 (4.6)	n/a
Disease modifying therapies[h], *n* (%)			
Beta interferon	85 (13.1)	113.3 (17.4)	0.004
Glatiramer acetate	24 (3.7)	24.1 (3.7)	0.77
Other disease-modifying therapies	45 (6.9)	42.0 (6.5)	0.36
Cumulative exposure beta interferon; *n* (%)			<0.001
Lower (6 months–3 years)	53 (8.2)	49.4 (7.6)	
Higher (>3 years)	32 (4.9)	63.8 (9.8)	
Early/late start beta interferon; *n* (%)			
Time since onset			0.003
Early (<5 years)	31 (4.8)	29.9 (4.6)	
Late (⩾5 years)	54 (8.3)	83.4 (12.8)	
Age			0.01
Early (under 40 years)	24 (3.7)	28.0 (4.3)	
Late (40 years or over)	61 (9.4)	85.3 (13.1)	

[a]Cases: 649 of 742 deaths were successfully matched to at least one control. After matching 100% of the deaths by sex, six cases did not have a match for age or EDSS. For the remaining 87 unmatched cases, there was no available control with a matching calendar year.
[b]To account for variation in the number of controls per case (1–20) between risk sets, all means, SDs, *n* and % presented here were weighted by the inverse of the number of controls in each set.
[c]Univariate conditional logistic regression.
[d]Measured at study entry.
[e]Socioeconomic status [neighbourhood income quintile measured at study entry (for the 569 Canadian cases and their controls only)]; 4% of the cases and 3% of their controls had an unknown socioeconomic status (missing) at study entry.
[f]Charlson Comorbidity Index measured during the 12 months before study entry (for the 569 Canadian cases and their controls only); potential scores range from zero to 9.0 and a higher score indicates greater comorbidity burden.
[g]Follow-up time from study entry date to death in the cases and equivalent time point for the controls.
[h]Disease-modifying therapy exposure during follow-up; beta interferon and glatiramer acetate exposure defined as at least 6 months; Other disease-modifying therapy exposure defined as any exposure.

opportunity to start treatment 'early' (at <5 years disease duration or under age 40); consequently, the proportion of cases and controls who initiated beta interferon early was <5% (Table 1). Our assessment of the effects of delayed initiation, whether measured by time since disease onset or age, resulted in findings consistent with the main analyses, with no evidence that late initiation was disadvantageous (the confidence intervals for early and late initiation overlapped, and for early initiation they included one; Tables 2 and 3).

Among the 742 deaths, 489 (66%) were multiple sclerosis-related with a mean age at death of 59 years (SD 13);

Table 2 Estimates of association between beta interferon exposure and all-cause death for the Canadian and French multiple sclerosis cohorts separately and combined

OR (95% CI)[a]	Canada Cases[f]: 569	France Cases[f]: 80	Combined Cases[f]: 649
Beta interferon[b]	**0.67 (0.50–0.90)**	0.67 (0.35–1.28)	**0.68 (0.53–0.89)**
Glatiramer acetate[b]	1.26 (0.73–2.16)	0.78 (0.32–1.92)	1.11 (0.70–1.78)
Other disease-modifying therapy[c]	1.26 (0.69–2.28)	1.37 (0.76–2.46)	1.27 (0.84–1.92)
Age, years[d]	**1.04 (1.01–1.07)**	1.04 (0.95–1.15)	**1.04 (1.01–1.07)**
Comorbidity burden[e]	**1.18 (1.02–1.36)**		
Cumulative exposure beta interferon[b]			
Lower (6 months–3 years)	0.95 (0.67–1.36)	1.11 (0.52–2.40)	1.00 (0.73–1.38)
Higher (>3 years)	**0.46 (0.30–0.70)**	**0.37 (0.15–0.95)**	**0.44 (0.30–0.66)**
Early/late start beta interferon[b]			
Time since onset			
Early (<5 years)	1.16 (0.73–1.85)	0.34 (0.10–1.19)	0.93 (0.61–1.43)
Late (⩾5 years)	**0.54 (0.38–0.76)**	0.84 (0.42–1.69)	**0.61 (0.45–0.83)**
Age			
Early (under 40 years)	0.89 (0.49–1.59)	0.58 (0.19–1.77)	0.83 (0.49–1.40)
Late (40 years or older)	**0.63 (0.46–0.87)**	0.72 (0.34–1.53)	**0.65 (0.48–0.87)**

[a]All odds ratios are adjusted. Model covariates: beta interferon exposure, glatiramer acetate exposure, other disease-modifying therapy exposure, age at study entry and, for Canada only, comorbidity burden calculated for the year before study entry.
[b]Reference category is <6 months exposure.
[c]Reference category is no exposure.
[d]Age in years (continuous).
[e]Charlson Comorbidity Index.
[f]There were between 1 and 20 matched controls for each case.
Bold indicates statistically significant estimates ($P < 0.05$).

Table 3 Estimates of association between beta interferon exposure and all-cause deaths for the combined Canadian and French multiple sclerosis cohorts by sex

OR (95% CI)[a]	Females Cases[e]: 454	Males Cases[e]: 195
Beta interferon[b]	0.78 (0.58–1.06)	**0.42 (0.24–0.77)**
Glatiramer acetate[b]	1.19 (0.71–2.02)	0.89 (0.31–2.53)
Other disease-modifying therapy[c]	**1.68 (1.06–2.67)**	0.54 (0.21–1.42)
Age[d]	**1.05 (1.01–1.08)**	1.03 (0.98–1.09)
Cumulative exposure beta interferon[b]		
Lower (6 months–3 years)	1.25 (0.86–1.81)	0.55 (0.28–1.08)
Higher (>3 years)	**0.49 (0.32–0.76)**	**0.29 (0.12–0.70)**
Early/late start beta interferon[b]		
Time since onset		
Early (<5 years)	1.08 (0.68–1.73)	0.47 (0.16–1.36)
Late (⩾5 years)	**0.68 (0.47–0.97)**	**0.42 (0.22–0.78)**
Age		
Early (under 40 years)	0.99 (0.55–1.80)	0.49 (0.16–1.44)
Late (40 years or older)	0.74 (0.53–1.03)	**0.41 (0.20–0.80)**

[a]Model covariates: beta interferon exposure, glatiramer acetate exposure, other disease-modifying therapy exposure, age at study entry in years.
[b]Reference category = <6 months exposure.
[c]Reference category = no exposure.
[d]Age in years (continuous).
[e]There were between 1 and 20 matched controls for each case.
Bold indicates statistically significant estimates ($P < 0.05$).

of these 433 were matched with up to 20 controls. As with all-cause deaths, the odds of beta interferon exposure were lower among multiple sclerosis-related death cases compared to their matched controls (OR: 0.71; 95% CI:0.51–0.98). When analysed by cumulative exposure or separately by sex, findings for multiple sclerosis-related death were similar to the all-cause death analysis (lower exposure: OR: 1.15; 95% CI: 0.78–1.68; higher exposure: OR: 0.38; 95% CI: 0.23–0.63; females OR: 0.84; 95% CI: 0.58–1.21; males: OR: 0.38; 95% CI:0.18–0.80).

An earlier study entry date (1 January 1986), imputation of missing EDSS scores, and imputation of treatment status for those with unknown beta interferon exposure after their last clinic visit allowed inclusion of more cases (up to 956) and a longer follow-up of up to 28 years. All findings from these complementary analyses, including the 'intention to treat' approach, were consistent with the main analyses although the estimated effect was greater with imputation of beta interferon exposure (Supplementary material and Supplementary Tables 3–6).

Discussion

We observed a survival advantage associated with beta interferon exposure among persons with relapsing-onset multiple sclerosis; those who were exposed to beta interferon had a 32% lower mortality risk when compared to

those who were not exposed. These findings were consistent between two geographically distinct multiple sclerosis cohorts, for males and females, and when only multiple sclerosis-related deaths were considered. Further, we found evidence of a cumulative dose response, with an increased survival associated with a longer (>3 years) but not with shorter (between 6 months and 3 years) cumulative exposure to beta interferon.

There are few published studies with which to compare our findings. Observations from a cohort of 366 relapsing-remitting multiple sclerosis participants in a beta interferon clinical trial, of whom 81 died, suggested a survival advantage among those randomized to beta interferon compared to placebo 21 years previously (Goodin *et al.*, 2012*b*). However, there were no available data on the baseline distribution of risk factors for shorter survival, such as smoking, lipid status or comorbidity, and the analyses of the survival outcomes were *post hoc* (Goodin and Reder, 2012; Gronseth and Ashman, 2012). A Taiwanese population-based study that included 88 deaths among 1149 patients with multiple sclerosis reported an apparent survival advantage for patients who were treated with beta interferon or glatiramer acetate (Tsai and Lee, 2013) but, because of the inclusion of 'immortal time' (Suissa, 2008) in the study design, the findings would be expected to be biased in favour of treatment, rendering the findings indeterminate.

Interestingly, we found no evidence to suggest that later initiation of beta interferon (after age 40 or 5 years of disease duration) was less advantageous than early initiation. While results from some clinical trials have suggested a disadvantage with later (relative to earlier) beta interferon initiation for other outcomes, including changes on magnetic resonance imaging, disability progression and transition from clinically isolated syndrome to definite multiple sclerosis (Bates, 2011; Freedman, 2011), these observations are from highly select groups of patients, typically excluding older adults such as those over 50 or 55 years, or those with longer disease duration (IFNB Multiple Sclerosis Study Group, 1993; Jacobs *et al.*, 1996; European Study Group on Interferon B-1b in Secondary Progressive MS, 1998; The OWIMS Study Group, 1999; Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS Study Group, 2001). In addition, findings from extension studies can potentially be affected by 'informative censoring' if those who do not do well are more likely to drop out and be lost to follow-up (Sormani and Bruzzi, 2015). Our results suggest that delayed treatment with beta interferon can provide benefit, although we had limited power to assess the effects of early initiation due to a low number of 'early initiators'. This limitation is not surprising given that it is less than two and half decades since the beta interferons first became available, and multiple sclerosis is not shortly fatal; recent studies have shown patients with multiple sclerosis, on average, survive into their eighth decade of life (Kingwell *et al.*, 2012; Scalfari *et al.*, 2013; Leray *et al.*, 2015; Lunde *et al.*, 2017).

Previously, we found no significant associations between disability progression, as measured by EDSS milestones, and beta interferon exposure, although evidence of such an association has been inconsistent between studies (Tramacere *et al.*, 2015; Signori *et al.*, 2016). It is feasible that disability progression and survival are influenced by different factors and that an effect of beta interferon on survival is independent of any relationship with disability progression. Dissociation between outcomes in multiple sclerosis is not uncommon, notably for relapses and EDSS score (Confavreux *et al.*, 2000; Tremlett *et al.*, 2009). Further, death is unarguably a more definitive representation of survival, and less susceptible to measurement error than the EDSS is of disability. One plausible mechanism through which the beta interferons might influence mortality is by a reduction in the risk of viral infections (Goodbourn *et al.*, 2000; Dhib-Jalbut and Marks, 2010). This study did not have sufficient power to assess death due to specific causes, such as infections; a larger cohort or longer follow-up would be required to gather sufficient cases by specific cause of death. Previous observations though have suggested a protective effect for hospitalizations for pneumonia/respiratory infection (Evans *et al.*, 2014) and, with at least 2 years cumulative exposure to beta interferon, for bronchitis or upper respiratory infections (de Jong *et al.*, 2017).

We were able to assess the association between beta interferon and multiple sclerosis-related deaths, as defined by the causes listed on the death certificate. The majority (66%) of deaths were considered multiple sclerosis-related; this falls within the range reported from other multiple sclerosis cohorts (Koch-Henriksen *et al.*, 1998; Bronnum-Hansen *et al.*, 2004; Leray *et al.*, 2007; Goodin *et al.*, 2012*a*; Rodriguez-Antiguedad Zarranz *et al.*, 2014), although some variation is to be expected due to different criteria for defining multiple sclerosis-related death and different ages and duration of follow-up. Similar to deaths due to any cause, we found a survival advantage for beta interferon exposure, with a 29% lower risk of multiple sclerosis-related death among treated, compared to untreated, persons with relapsing-onset multiple sclerosis.

The strengths of our study include up to 28 years follow-up of an international cohort with nearly 6000 relapsing-onset multiple sclerosis patients (more than 7000 in complementary analyses) from two distinct regions in North America and Europe, all of whom were diagnosed by specialist multiple sclerosis-neurologists, and a sizable number of death outcomes (649, rising to 956 in the complementary analyses). Access to population-based prospectively collected data ensured reliable and unbiased identification and coding of deaths, disease-modifying therapy exposure and, for the Canadian cohort, comorbidity information and estimates of socioeconomic status. The nested case-control approach with incidence density sampling provided an efficient study design with strict control of age, sex, year and disability level through matching, thus ensuring that controls were similar to cases and had the

same duration of follow-up with equal opportunity for exposure to disease-modifying therapies during the same calendar time period. This approach has been shown to yield virtually identical findings to Cox regression modeling using the full cohort (Essebag *et al.*, 2005).

We were able to consider comorbidity and disability in our analyses; both were independent predictors of survival in our cohort and have previously been identified as important predictors of mortality in multiple sclerosis (Leray *et al.*, 2007; Marrie *et al.*, 2015; Salter *et al.*, 2016). While the conservative approach for our main analysis focused on a cohort of persons with relapsing-onset multiple sclerosis who were naïve to disease-modifying therapy when the beta interferons were first approved, our complementary analyses, with study entry 10 years earlier and imputation of EDSS scores to include those with missing disability assessments, enabled inclusion of more cases; both provided similar findings of a survival advantage with beta interferon treatment. Because treatment status was unknown for some patients with relapsing-onset multiple sclerosis in the French cohort, they were censored at their last clinic visit. However, imputation of exposure to beta interferon treatment and reanalysis after inclusion of their additional available follow-up time did not change the interpretation of findings. Although the confidence intervals overlapped, the effect size was larger which suggests that any bias due to this missing data would likely have been towards an underestimate of the association.

As with all observational studies, there is potential for residual confounding, despite our consideration of important predictors of mortality through matching or adjustment; information on smoking, or other health behaviours, for example were not captured. Indication bias cannot be completely ruled out; it is feasible that non-responders to treatment, or those with declining health, might have stopped treatment early and the results of the cumulative exposure analyses should therefore be interpreted cautiously. On the other hand, a survival advantage was observed even in the complementary analysis with exposure to disease-modifying therapy determined as any treatment at all (at least 1 day), akin to an 'intention to treat' approach. This ensured that responders and non-responders, and those who stopped treatment very early, were all considered treated. It has been suggested that an indication bias with beta interferon might be driven by a greater likelihood of treatment among patients with multiple sclerosis who are progressing or not doing well (Sormani and Bruzzi, 2015). If this were true it would tend to bias observed differences towards the null, implying that our estimates could be conservative. It is important to note that due to lower exposure rates to glatiramer acetate and the other multiple sclerosis therapies during the follow-up period there was insufficient power to assess their association with, or potential impact on, survival. These exposures were considered only as potential confounders of the relationship between beta interferon and survival and measures of their effect on survival cannot be interpreted from these analyses.

Our study provides evidence for a significant survival advantage among people with relapsing-onset multiple sclerosis who are exposed to beta interferons during routine clinical practice. Further, a dose-response effect was observed with an increased survival associated with longer cumulative exposure to beta interferon.

Worldwide, the beta interferons remain the most commonly used disease-modifying therapies to treat multiple sclerosis. These findings provide additional valuable information for patients and clinicians with respect to important and realistic treatment outcomes. Further work is warranted to assess whether this survival advantage extends to other disease-modifying therapies for multiple sclerosis and whether this observed survival advantage results in a measurable improvement in the quality of life lived.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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