

# **The disease-modifying drugs for multiple sclerosis and association with survival**

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**Abstract short title:** Survival and the MS disease-modifying drugs

## Abstract

**Background:** It is unknown whether the rapidly increasing use of the disease-modifying drugs (DMDs) to treat multiple sclerosis (MS) has improved survival. We examined the association between the DMDs for MS and survival in a multi-region population-based study.

**Methods:** We accessed multiple administrative health databases from four Canadian provinces (British Columbia, Saskatchewan, Manitoba and Nova Scotia). Persons with MS (aged  $\geq 18$  years) were identified and followed from the most recent of the first MS or demyelinating event or 1-January-1996 (index date), until death, emigration, or 31-December-2017. The association between DMD exposure and all-cause mortality was examined using stratified Cox proportional hazard models, and reported as adjusted hazard ratios (aHRs). Timing of the first generation DMDs – beta-interferon and glatiramer acetate initiation was explored, with findings reported at 2, 5, or 10 years post-index date, representing very early, early, or late initiation.

**Results:** We identified 35,894 persons with MS; 72% were female. The mean age at index date was 44.5 years (standard deviation=13.6). The total person-years of follow-up whilst DMD-exposed was 89,180 and total person-years whilst unexposed was 342,217. Compared to no exposure, exposure to any DMD or to any first generation DMD, was associated with a 26% lower hazard of mortality (both aHRs:0.74;95%CI:0.56-0.98), while any second generation DMD exposure was associated with a 33% lower hazard (aHR:0.67; 95%CI:0.46-0.98). Earlier initiation of beta-interferon or glatiramer acetate (versus no exposure) was associated with a significantly reduced mortality ( $p < 0.05$ ), while later initiation was not. However, the survival advantage with earlier initiation diminished over time, no longer reaching statistical significance at 15 years post-index date.

**Conclusion:** Our study provides evidence of a beneficial relationship between the DMDs for MS and survival in the real-world setting. The findings provide additional evidence to inform decision-making by clinicians and people living with MS about use of the DMDs.

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