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Mortality and comorbidities in patients with multiple sclerosis compared with a population without multiple sclerosis: An observational study using the US Department of Defense administrative claims database

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ABSTRACT

Background: Data are limited for mortality and comorbidities in patients with multiple sclerosis (MS).
Objectives: Compare mortality rates and event rates for comorbidities in MS ($n=15,684$) and non-MS ($n=78,420$) cohorts from the US Department of Defense (DoD) database.
Methods: Comorbidities and all-cause mortality were assessed using the database. Causes of death (CoDs) were assessed through linkage with the National Death Index. Cohorts were compared using mortality (MRR) and event (ERR) rate ratios.
Results: All-cause mortality was 2.9-fold higher in the MS versus non-MS cohort (MRR, 95% confidence interval [CI]: 2.9, 2.7–3.2). Frequent CoDs in the MS versus non-MS cohort were infectious diseases (6.2, 4.2–9.4), diseases of the nervous (5.8, 3.7–9.0), respiratory (5.0, 3.9–6.4) and circulatory (2.1, 1.7–2.7) systems and suicide (2.6, 1.3–5.2). Comorbidities including sepsis (ERR, 95% CI: 5.7, 5.1–6.3), ischemic stroke (3.8, 3.5–4.2), attempted suicide (2.4, 1.3–4.5) and ulcerative colitis (2.0, 1.7–2.3), were higher in the MS versus non-MS cohort. The rate of cancers was also higher in the MS versus the non-MS cohort, including lymphoproliferative disorders (2.2, 1.9–2.6) and melanoma (1.7, 1.4–2.0).
Conclusions: Rates of mortality and several comorbidities are higher in the MS versus non-MS cohort. Early recognition and management of comorbidities may reduce premature mortality and improve quality of life in patients with MS.

1. Introduction

Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory disease affecting approximately 400,000 people in the USA and 2.3 million people worldwide (Multiple Sclerosis International Federation, 2013). Relative to the general population, patients with MS have an increased risk of premature mortality (Kaufman et al., 2014; Kingwell et al., 2012b; Lalmohamed et al., 2012; Sumelahti

Abbreviations: CI, confidence interval; CLD, cause most directly leading to death; CM, clinical modification; CNS, central nervous system; CoDs, causes of death; CVD, cardiovascular disease; DMTs, disease-modifying therapies; DoD, Department of Defense; EMR, electronic medical record; ER, event rate; ERR, event rate ratio; ICD, International Classification of Disease; ICD-9, International Classification of Diseases 9th revision; ICD-10, International Classification of Diseases 10th revision; MR, mortality rates; MRR, mortality rate ratio; MS, multiple sclerosis; NA, not applicable; NDI, National Death Index; SD, standard deviation; UTI, urinary tract infection.

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et al., 2010) and comorbidities such as infection-related hospital admissions (Montgomery et al., 2013), cardiovascular disease (CVD) (Christiansen et al., 2010; Jadidi et al., 2013) and other autoimmune conditions (Berkovich et al., 2011; Christiansen, 2012; Marrosu et al., 2002), while studies assessing the risk of cancer in patients with MS have been inconclusive (Bloomgren et al., 2012; Handel and Ramagopalan, 2010; Kingwell et al., 2012a). The autoimmune pathogenesis of MS may contribute to the predisposition to certain comorbidities, including type 1 diabetes and inflammatory bowel diseases (Berkovich et al., 2011). However, socioeconomic status, reduced levels of physical activity and immunomodulatory treatment may also affect the risk of premature mortality and comorbidities (Eyre et al., 2004).

Differences in mortality rates (MRs), causes of death (CoDs) and comorbidity event rates (ERs) in individuals with MS and those without MS have not been fully investigated. Such data may have important implications for the management of patients with MS, particularly if the risk of comorbidities can be reduced by focused surveillance, which may permit early detection or diagnosis, and targeted intervention. Furthermore, establishing baseline expectations of mortality and comorbidity rates in patients with MS can provide a reference against which the relative safety profiles of disease-modifying therapies (DMTs) can be assessed. Therefore, this study is an administrative claims database analysis comparing MRs, CoDs and ERs for comorbidities in a cohort of patients with MS versus a matched cohort of individuals without MS, using the US Department of Defense (DoD) Military Health System database.

2. Materials and methods

The DoD database contains information on over 10 million active US military personnel, their dependents, and retirees, and includes information on patient demographics, enrollment, healthcare providers, diagnoses, procedures and prescriptions (Dorrance et al., 2013). The DoD database also contains mortality data, and through linkage with the US National Death Index (NDI), CoDs can be identified. Demographics of the DoD database population relative to the US general population are summarized in Supplementary Fig. 1 and Supplementary Table 1. Characteristics of the DoD database are further described by Dorrance et al. (2013).

Individuals aged 18–64 years were selected from the DoD database between 1 July 2006 and 30 June 2011. An algorithm (Chastek et al., 2010), appropriate for use in administrative claims databases (Song et al., 2013), was applied to the DoD database to identify patients with MS, for whom diagnosis codes for MS (International Classification of Diseases [ICD] 9 Clinical Modification [CM] 340.xx) appeared on two or more occasions at least 30 days apart (Chastek et al., 2010). Patients were excluded from the MS cohort if they did not meet the inclusion criteria (Fig. 1). The index date for patients in the MS cohort was the date of the second entry of the MS diagnosis code in their healthcare records (Suissa, 2008). To enable assessment of medical history, only individuals with at least 1 year of pre-index enrollment were included. The MS cohort comprised treated and untreated patients with incident (newly diagnosed after entry into the DoD healthcare system) and prevalent (diagnosed before entry into the DoD healthcare system) MS. From the same time period, five individuals with no MS claims in their healthcare records and at least 1 year of pre-index enrollment, were matched to each patient with MS by age (within 5 years), gender and index date to create the non-MS cohort. Individuals aged ≥ 65 years on the index date, who may also have concurrent access to Medicare coverage, were excluded from the study due to the risk of incomplete follow-up information if treatments were reimbursed via Medicare (Social Security Administration, 2014).

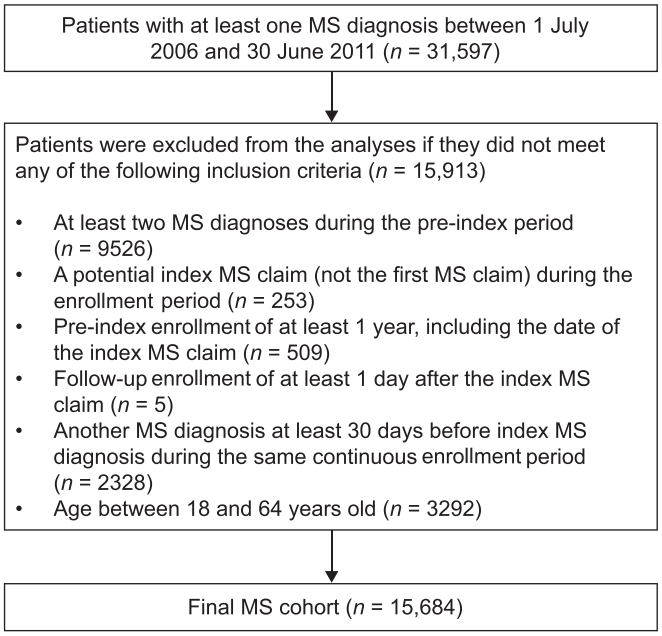


Fig. 1. Attrition of the MS cohort. MS, multiple sclerosis.

To include all medical encounters during the study period, individuals in both cohorts were followed from their index date until the date that they ceased receiving DoD healthcare benefits, their death or the end of the study period; patients were not censored if they turned 65 years of age during the follow-up period.

Individuals with the occurrence of a clinical event in the follow-up period were subsequently censored for reoccurrences of that event but continued to be assessed for the occurrence of other comorbidities. Death of an individual was identified through the registration date of their death in the NDI. To determine CoD, ICD-10-CM codes on the death certificate were ordered, listing the immediate CoD (final disease or condition resulting in death), any secondary CoDs and the primary underlying CoD (the disease or injury that initiated the events leading to death) (Goodin et al., 2014). The cause most directly leading to death (CLD) was considered as the main CoD analysis in this study because it may be more meaningful in patients with MS than immediate and primary underlying CoDs, and allows for designation of suicide (Goodwin et al., 2014). We used a definition similar to that of Goodwin et al. (2014) assess CLD, which was the ICD-10-CM code closest to the time of death, with the following exceptions: suicide was the CLD if it appeared anywhere on the death certificate; MS was the CLD only if no cause other than cardiac or respiratory arrest was given or MS was the only code mentioned; cardiac or respiratory arrest were designated as the CLD only if those causes and no others were provided on the death certificate. Over 200 comorbidities were assessed using ICD-9-CM codes. Comorbidities among a subgroup of patients in the MS cohort who had one or more claims for DMTs (fingolimod, natalizumab, glatiramer acetate, interferon beta-1a, interferon beta-1b or mitoxantrone), at any time during the study (treated MS cohort) were also compared with those in a matched non-MS cohort. In this study, the prevalence of comorbidities in the post-index period was assessed and ERs referred to both acute and chronic conditions. The distributions of mortality and event rate ratios (MRRs and ERRs) were also assessed according to gender and age.

Differences between the MS and non-MS cohorts in terms of pre-index characteristics were assessed using a *t*-test for continuous variables and a Wilcoxon rank-sum test, a χ^2 test or a Fisher's exact test for categorical variables. MRs and ERs for

comorbidities were calculated for each cohort and used to derive MRRs and ERRs with 95% confidence intervals (CIs; Table 1). Rate ratios were reported because they are more likely to be independent of population- and database-specific biases compared with MRs and ERs and are therefore more generalizable.

3. Results

3.1. Study attrition and cohort characteristics

Initially, 31,597 patients with an MS diagnosis were identified in the database. After applying the study selection criteria, the final MS (Fig. 1) and non-MS cohorts included 15,684 and 78,420 individuals, respectively.

Demographic and clinical characteristics for each cohort are summarized in Table 2. Owing to matching, the mean age of individuals (46.0 ± 11.7 years) and the proportion of women (76.5%) were similar in both cohorts. The mean duration of follow-up was significantly longer in the MS cohort (1518 ± 638 days) than in the non-MS cohort (1414 ± 716 days; $p < 0.0001$).

3.2. Mortality and CoD

For all-cause mortality, the MRR was 2.9 (95% CI, 2.7–3.2; Fig. 2) and was highest among individuals aged 18–29 years (MRR, 95% CI: 8.8, 3.7–21.0).

For the CLD, the MRR was highest for infectious diseases (6.2, 4.2–9.4; Fig. 2) and ratios were higher among those aged 50–59 years (9.4, 5.3–16.7) than in any other age group. Following infectious diseases as the CLD, MRRs were high for diseases of the nervous system (5.8, 3.7–9.0; excluding MS), respiratory system (5.0, 3.9–6.4; excluding respiratory arrest) and circulatory system (2.1, 1.7–2.7; excluding cardiac arrest). For diseases of the nervous system as the CLD, MRRs were higher in men than in women (11.9, 4.2–33.3 versus 4.7, 2.8–7.9). The MRR for suicide was 2.6 (1.3–5.2) and was higher in women than in men (3.4, 1.4–8.5 versus 1.7, 0.5–5.2) and highest among those aged 18–29 years (10.1, 1.1–97.4). A full list of CLDs is presented in Supplementary Table 2. MS was the leading contributor to immediate and primary underlying CoDs in the MS cohort versus the non-MS cohort (Table 3). Following MS, MRRs were highest for infectious diseases and diseases of the respiratory system (excluding respiratory arrest) for the immediate CoD and diseases of the nervous system (excluding MS) and infectious diseases for the primary underlying CoD.

3.3. Prevalent comorbidities

The ERs and ERRs for comorbidities are presented in Fig. 3 and Supplementary Table 3 and data for those comorbidities

Table 1
Statistical analyses used to assess mortality rates and event rates for comorbidities.

	Methodology	Analysis
Mortality rate (for all-cause and specific causes of death)	Calculated by dividing the number of patients who died during follow-up, or died from a specific cause, by the sum of the person-time during follow-up for each cohort; person-time is defined as the number of days from the index date to the date of death or the end of the follow-up	Presented as number of patients with that outcome per 1000 patient-years with 95% CIs
Mortality rate ratio (for all-cause and specific causes of death)	Dividing the mortality rate in the MS cohort by that in the non-MS cohort	Presented with 95% CIs calculated using a binomial distribution; a number greater than one indicates an increased rate of all-cause mortality or death from a specific cause in the MS cohort versus the non-MS cohort
Event rate for each comorbidity of interest	Calculated by dividing the number of patients with the outcome during follow-up by the person-time at risk for that outcome in each cohort (censored by first event occurrence)	Presented as number of patients with that outcome per 1000 patient-years with 95% CIs
Event rate ratio for each comorbidity of interest	Dividing the event rate in the MS cohort by that in the non-MS cohort	Presented with 95% CIs calculated using a binomial distribution; a number greater than one indicates an increased rate of a comorbidity in the MS cohort versus the non-MS cohort

CI, confidence interval; MS, multiple sclerosis

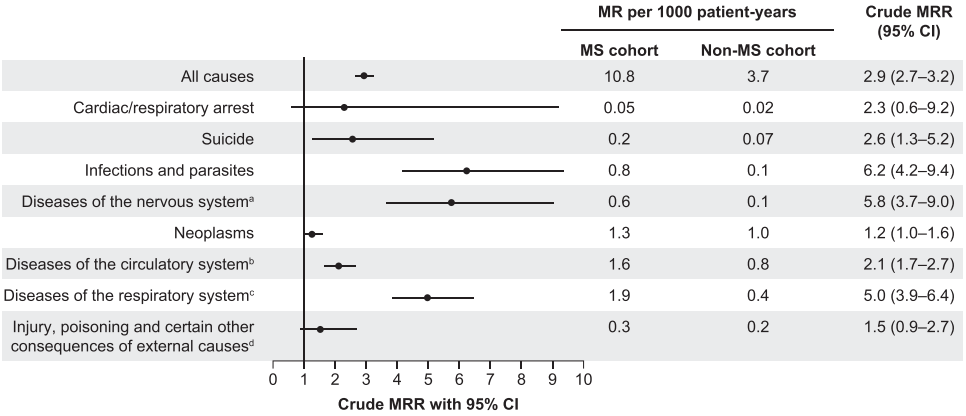


Fig. 2. Forest plots of crude MRRs for all-cause mortality and selected causes leading to death in the MS cohort versus the non-MS cohort. Error bars indicate 95% CIs. CI, confidence interval; MR, mortality rate; MRR, mortality rate ratio; MS, multiple sclerosis. [a]excluding MS; [b]excluding cardiac arrest; [c]excluding respiratory arrest; [d]excluding suicide.

Table 2
Demographic and disease characteristics of individuals in the MS and non-MS cohorts during the 1-year pre-index[a] period.

Characteristic	MS cohort ($n=15,684$)	Non-MS cohort ($n=78,420$)	p value[b]
Age at index date, years			
Mean ± SD	46.0 ± 11.7	46.0 ± 11.7	0.81
Median (range)	47 (18–64)	47 (18–64)	
Female, *n* (%)	11,992 (76.5)	59,960 (76.5)	
Use of ambulatory aids,[c] *n* (%)			
No claims for ambulatory aids	13,503 (86.1)	76,622 (97.7)	< 0.0001
Walks with assistance	789 (5.0)	1356 (1.7)	
Cannot walk with assistance	1233 (7.9)	423 (0.5)	
Restricted to bed	159 (1.0)	19 (0.02)	
Duration of follow-up, days			
Mean ± SD	1517.7 ± 637.5	1413.4 ± 716.4	< 0.0001
Median (range)	1733 (2–2191)	1616 (1–2191)	
Pre-index drugs that can be used in the treatment of MS,[d] *n* (%)			
Systemic corticosteroids[e]	5114 (32.6)	9992 (12.7)	< 0.0001
Interferon beta-1a	3591 (22.9)	2 (0.002)	
Glatiramer acetate	2242 (14.3)	0 (0.0)	
Interferon beta-1b	1148 (7.3)	0 (0.0)	
Methotrexate[e]	184 (1.2)	311 (0.4)	< 0.0001
Azathioprine[e]	77 (0.5)	81 (0.1)	< 0.0001
Natalizumab	70 (0.4)	0 (0.0)	< 0.0001
Cyclophosphamide[e]	30 (0.2)	71 (0.09)	0.0004
Fingolimod	8 (0.05)	0 (0.0)	< 0.0001
Mitoxantrone	4 (0.03)	0 (0.0)	0.0008

MS, multiple sclerosis; SD, standard deviation.

[a] The index date is defined as the date of the second MS diagnosis following at least 1 year of continuous enrollment.
[b] *P*-values from *t*-test for continuous variables, chi-square or Fisher's exact test for nominal categorical variables, and Wilcoxon rank sum for ordinal categorical variables.
[c] Disease severity defined during the 1-year pre-index period and up to 1 year post index.
[d] Drug utilization identified any time during the pre-index period. The total numbers may not be the same as the number of patients receiving treatment because some may have received multiple drugs.
[e] These drugs are not specifically indicated for MS and can be used to treat other conditions.

Table 3
Causes of death in the MS and non-MS cohort.[a]

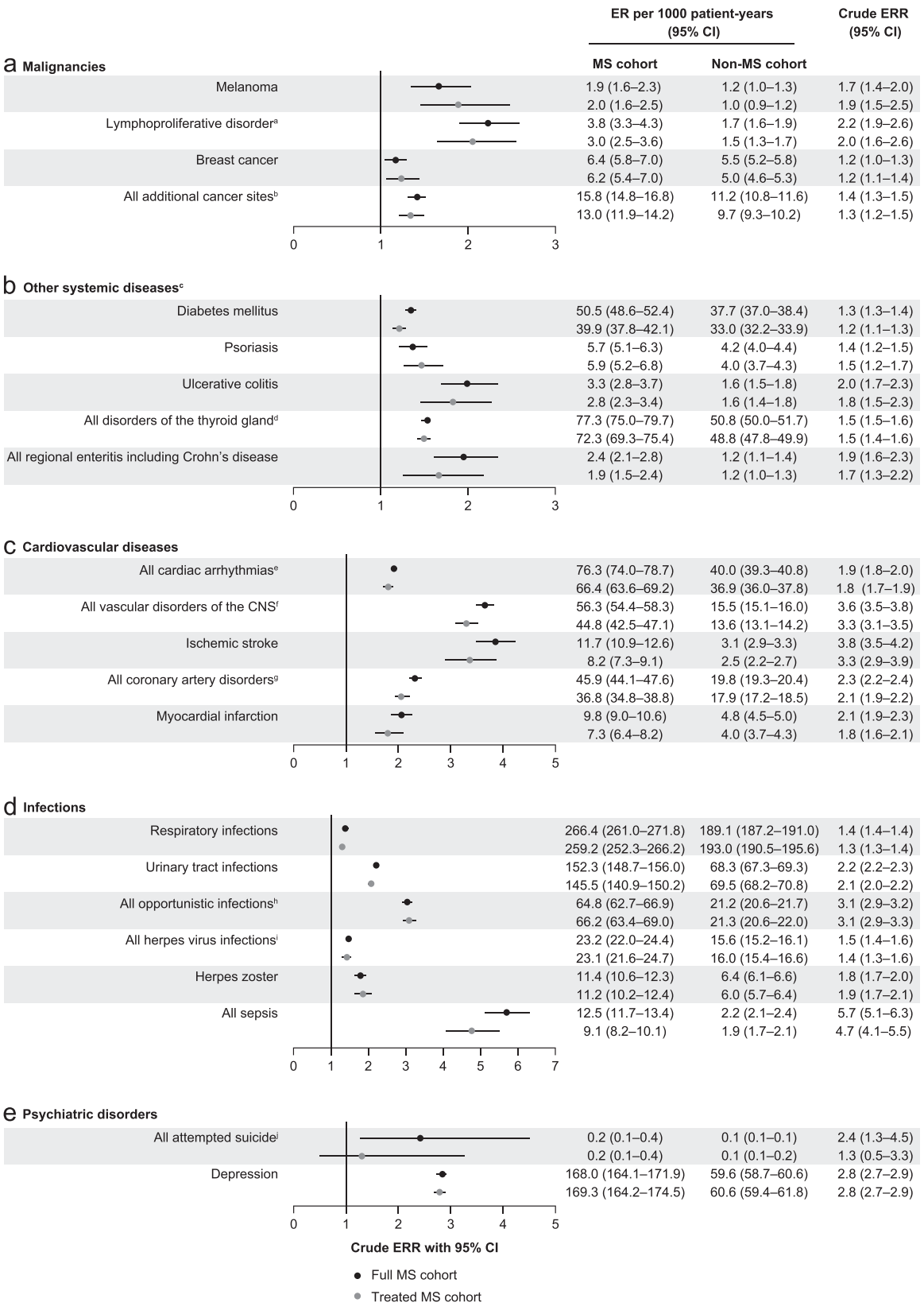
	Cause leading to death		Primary underlying cause of death		Immediate cause of death	
	Mortality rate ratio	95% CI	Mortality rate ratio	95% CI	Mortality rate ratio	95% CI
Causes of death[b]						
Cardiac/respiratory arrest	2.30	0.58–9.20	1.85	0.58–5.89	3.62	2.76–4.77
Suicide	2.56	1.26–5.16	2.56	1.26–5.16	NA	NA
Other causes of death (by ICD-10 category)[c]						
Certain infectious and parasitic diseases	6.24	4.17–9.36	3.50	1.99–6.16	5.77	3.65–9.13
Neoplasms	1.24	0.97–1.57	1.20	0.96–1.49	1.27	0.99–1.64
Diseases of the nervous system (excluding MS)	5.75	3.66–9.04	6.45	3.68–11.31	2.92	1.67–5.11
Diseases of the circulatory system (excluding cardiac arrest)	2.12	1.68–2.66	1.74	1.36–2.24	1.91	1.48–2.47
Diseases of the respiratory system (excluding respiratory arrest)	4.99	3.86–6.44	2.20	1.47–3.29	4.80	3.64–6.32
Injury, poisoning and certain other consequences of external causes (excluding suicide)	1.52	0.87–2.68	NA	NA	1.92	1.23–2.97

CI, confidence interval; CoD, cause of death; ICD-10, International Classification of Diseases 10th revision; MRR, mortality rate ratios; MS, multiple sclerosis; NA, not applicable.

[a] Of those who died, cause of death data was available for 89.6% of individuals in the MS cohort and 86.6% of individuals in the non-MS cohort. Cause of death data was not available for all patients due to the 2-year delay in NDI reporting.
[b] For MS as a CoD the MRR outcome for each CoD category was NA.
[c] A full list of the conditions in each CoD category is provided in the World Health Organization International Statistical Classification of Diseases and Related Health Problems 10th Revision (World Health Organization, 2010).

demonstrating an age- or gender-related difference are presented in Supplementary Fig. 2.

The rate of all evaluated malignancies was higher in the MS cohort versus the non-MS cohort and varied by cancer type, being highest for lymphoproliferative disorders (ERR, 95% CI: 2.2, 1.9–2.6) and melanoma (1.7, 1.4–2.0; Fig. 3a). For melanoma, ERRs were higher in


ER per 1000 patient-years (95% CI)
Crude ERR (95% CI)
MS cohort
Non-MS cohort
a Malignancies
Melanoma
1.9 (1.6–2.3) 1.2 (1.0–1.3) 1.7 (1.4–2.0)
2.0 (1.6–2.5) 1.0 (0.9–1.2) 1.9 (1.5–2.5)
Lymphoproliferative disorder[a]
3.8 (3.3–4.3) 1.7 (1.6–1.9) 2.2 (1.9–2.6)
3.0 (2.5–3.6) 1.5 (1.3–1.7) 2.0 (1.6–2.6)
Breast cancer
6.4 (5.8–7.0) 5.5 (5.2–5.8) 1.2 (1.0–1.3)
6.2 (5.4–7.0) 5.0 (4.6–5.3) 1.2 (1.1–1.4)
All additional cancer sites[b]
15.8 (14.8–16.8) 11.2 (10.8–11.6) 1.4 (1.3–1.5)
13.0 (11.9–14.2) 9.7 (9.3–10.2) 1.3 (1.2–1.5)
0 1 2 3
b Other systemic diseases[c]
Diabetes mellitus
50.5 (48.6–52.4) 37.7 (37.0–38.4) 1.3 (1.3–1.4)
39.9 (37.8–42.1) 33.0 (32.2–33.9) 1.2 (1.1–1.3)
Psoriasis
5.7 (5.1–6.3) 4.2 (4.0–4.4) 1.4 (1.2–1.5)
5.9 (5.2–6.8) 4.0 (3.7–4.3) 1.5 (1.2–1.7)
Ulcerative colitis
3.3 (2.8–3.7) 1.6 (1.5–1.8) 2.0 (1.7–2.3)
2.8 (2.3–3.4) 1.6 (1.4–1.8) 1.8 (1.5–2.3)
All disorders of the thyroid gland[d]
77.3 (75.0–79.7) 50.8 (50.0–51.7) 1.5 (1.5–1.6)
72.3 (69.3–75.4) 48.8 (47.8–49.9) 1.5 (1.4–1.6)
All regional enteritis including Crohn's disease
2.4 (2.1–2.8) 1.2 (1.1–1.4) 1.9 (1.6–2.3)
1.9 (1.5–2.4) 1.2 (1.0–1.3) 1.7 (1.3–2.2)
0 1 2 3
c Cardiovascular diseases
All cardiac arrhythmias[e]
76.3 (74.0–78.7) 40.0 (39.3–40.8) 1.9 (1.8–2.0)
66.4 (63.6–69.2) 36.9 (36.0–37.8) 1.8 (1.7–1.9)
All vascular disorders of the CNS[f]
56.3 (54.4–58.3) 15.5 (15.1–16.0) 3.6 (3.5–3.8)
44.8 (42.5–47.1) 13.6 (13.1–14.2) 3.3 (3.1–3.5)
Ischemic stroke
11.7 (10.9–12.6) 3.1 (2.9–3.3) 3.8 (3.5–4.2)
8.2 (7.3–9.1) 2.5 (2.2–2.7) 3.3 (2.9–3.9)
All coronary artery disorders[g]
45.9 (44.1–47.6) 19.8 (19.3–20.4) 2.3 (2.2–2.4)
36.8 (34.8–38.8) 17.9 (17.2–18.5) 2.1 (1.9–2.2)
Myocardial infarction
9.8 (9.0–10.6) 4.8 (4.5–5.0) 2.1 (1.9–2.3)
7.3 (6.4–8.2) 4.0 (3.7–4.3) 1.8 (1.6–2.1)
0 1 2 3 4 5
d Infections
Respiratory infections
266.4 (261.0–271.8) 189.1 (187.2–191.0) 1.4 (1.4–1.4)
259.2 (252.3–266.2) 193.0 (190.5–195.6) 1.3 (1.3–1.4)
Urinary tract infections
152.3 (148.7–156.0) 68.3 (67.3–69.3) 2.2 (2.2–2.3)
145.5 (140.9–150.2) 69.5 (68.2–70.8) 2.1 (2.0–2.2)
All opportunistic infections[h]
64.8 (62.7–66.9) 21.2 (20.6–21.7) 3.1 (2.9–3.2)
66.2 (63.4–69.0) 21.3 (20.6–22.0) 3.1 (2.9–3.3)
All herpes virus infections[i]
23.2 (22.0–24.4) 15.6 (15.2–16.1) 1.5 (1.4–1.6)
23.1 (21.6–24.7) 16.0 (15.4–16.6) 1.4 (1.3–1.6)
Herpes zoster
11.4 (10.6–12.3) 6.4 (6.1–6.6) 1.8 (1.7–2.0)
11.2 (10.2–12.4) 6.0 (5.7–6.4) 1.9 (1.7–2.1)
All sepsis
12.5 (11.7–13.4) 2.2 (2.1–2.4) 5.7 (5.1–6.3)
9.1 (8.2–10.1) 1.9 (1.7–2.1) 4.7 (4.1–5.5)
0 1 2 3 4 5 6 7
e Psychiatric disorders
All attempted suicide[j]
0.2 (0.1–0.4) 0.1 (0.1–0.1) 2.4 (1.3–4.5)
0.2 (0.1–0.4) 0.1 (0.1–0.2) 1.3 (0.5–3.3)
Depression
168.0 (164.1–171.9) 59.6 (58.7–60.6) 2.8 (2.7–2.9)
169.3 (164.2–174.5) 60.6 (59.4–61.8) 2.8 (2.7–2.9)
0 1 2 3 4 5
Crude ERR with 95% CI
Full MS cohort
Treated MS cohort

women than in men (1.8, 1.5–2.3 versus 1.2, 0.8–1.9) and were highest in those aged 18–29 years (4.0, 1.3–11.9; Supplementary Fig. 2a). For breast cancer in women, the highest ERRs were reported for those aged 30–39 years (2.1, 1.3–3.3; Supplementary Fig. 2b).

Other systemic diseases (including autoimmune disorders) such as ulcerative colitis (2.0, 1.7–2.3), regional enteritis (1.9, 1.6–2.3) and thyroid gland disorders (1.5, 1.5–1.6) were more common in the MS cohort than in the non-MS cohort (Fig. 3b). For diabetes mellitus, ERRs decreased with increasing age (Supplementary Fig. 2c).

For cardiovascular comorbidities, vascular disorders of the central nervous system (CNS) were more common in the MS cohort than in the non-MS cohort (3.6, 3.5–3.8), with the highest ERR being for ischemic stroke (3.8, 3.5–4.2; Fig. 3c). For myocardial infarction, the ERR was 2.1 (1.9–2.3; Fig. 3c) and the ratio was higher in women than in men (2.3, 2.0–2.6 versus 1.6, 1.4–1.9; Supplementary Fig. 2e). ERRs for cardiovascular comorbidities generally decreased with increasing age (Supplementary Fig. 2d–g).

For infections, the highest ERRs were for sepsis (5.7, 5.1–6.3), opportunistic infections (3.1, 2.9–3.2) and urinary tract infections (UTIs; 2.2, 2.2–2.3; Fig. 3d). ERRs for infections decreased with increasing age, with the exception of UTIs which increased with age. ERRs were higher in men than in women for UTIs (3.0, 2.8–3.3 versus 2.2, 2.1–2.3; Supplementary Fig. 2h) and for sepsis (7.5, 6.1–9.2 versus 5.1, 4.6–5.8; Supplementary Fig. 2i).

The ERR for attempted suicide was 2.4 (1.3–4.5), which is very similar to the MRR for suicide as a CLD (2.6, 1.3–5.2). For all depression, the ERR was 2.8 (2.7–2.9; Fig. 3e) and was higher in men than in women (4.1, 3.9–4.4 versus 2.7, 2.6–2.8; Supplementary Fig. 2j).

The results thus far given are for the entire MS cohort, of which 60.4% of patients had received DMTs in the past. In general, ERRs for the DMT treated MS subcohort (Fig. 3, gray data points) were similar to those for the full MS cohort (Fig. 3, black data points), with the exception of slightly lower ERRs for diabetes mellitus, coronary artery disorders, respiratory infections and UTIs in the treated MS subcohort versus the full MS cohort.

4. Discussion

This study, utilizing the US DoD database, provides a comprehensive analysis of mortality and more than 200 comorbidities in patients with MS. This analysis showed that rates of mortality and comorbidities were generally higher in the MS cohort than in the matched non-MS cohort. The higher rate of all-cause mortality (MRR, 95% CI: 2.9, 2.7–3.2) in the MS cohort versus the non-MS cohort is within the range previously reported (1.7–3.5-fold) (Jick et al., 2014; Kaufman et al., 2014; Kingwell et al., 2012b; Lalmohamed et al., 2012; Rodriguez-Antiguedad Zarranz et al., 2014). In CLD analyses, patients with MS had significantly higher rates of death caused by infections (6.2, 4.2–9.4) than the matched non-MS cohort. In addition, rates of death caused by diseases of the nervous system (5.8, 3.7–9.0; excluding MS), respiratory system (5.0, 3.9–6.4; excluding respiratory arrest) and circulatory system (2.1, 1.7–2.7; excluding cardiac arrest) were also higher for the MS cohort versus the non-MS cohort; for circulatory system diseases, rates were unexpectedly high and it may be because of the inclusion of multiple comorbidities within this category (World Health Organization, 2010). These MRRs are higher than those of Goodin et al. (2014) but are in agreement with their finding that infections (3.4-fold higher), CVD (1.5-fold higher) and pulmonary disorders (2.5-fold higher) were the most frequent CLDs in individuals with MS compared with those without MS (Goodwin et al., 2014). Therefore, the present study validates the findings of Goodin et al. (2014), which was performed in a different population.

Consistent with other reports on comorbidities in patients with MS, this study found that infections, CVDs, other systemic diseases (including autoimmune disorders) and psychiatric disorders were more common in the MS cohort than in the non-MS cohort (Berkovich et al., 2011; Christiansen, 2012; Marrie et al., 2014; Marrosu et al., 2002; Montgomery et al., 2013; Patten et al., 2003). For some conditions, there were age- and gender-related differences in the ERRs. In particular, the influence of MS on the risk of CVDs was especially important in younger patients. Gender-related differences in comorbidities were generally maintained across most age groups (data not shown). In contrast to results reported from registry studies, which described a reduced risk of cancer (Bahmanyar et al., 2009; Kingwell et al., 2012a; Lebrun et al., 2008; Nielsen et al., 2006), we observed higher rates of all evaluated malignancies in the MS cohort versus the non-MS cohort. Differences in observations between this study and registry studies may reflect differences in cohort selection criteria, patient populations, levels of data availability from claims databases versus registries, sample sizes and follow-up time, as well as variations in data recording and collection methods. Differences in study design complicate the comparisons that can be made between this study and others, as well as the conclusions that can be drawn (Marrie et al., 2015b). Further studies are therefore warranted to fully explore the complex relationship between MS and cancer. This study focused on individuals aged 18–64 years, which is the age range generally included in clinical trials. By excluding patients aged $\geq$65 years, who are likely to have an increased rate of certain comorbidities, regardless of whether they have MS, this study is likely to be more informative to clinicians as ERRs and MRRs would not be diminished by the effect of increased age.

This study emphasizes that the medical issues faced by individuals with MS are not limited to MS, but include an increased frequency of certain comorbidities, which may contribute to a higher risk of premature mortality. Therefore, by reporting the increased risk of comorbidities and premature mortality in the MS population, this study encourages the enhanced medical surveillance of patients with MS to identify those at risk so that MS-treating clinicians can recommend protective lifestyles and collaborate closely with general medical professionals to achieve earlier diagnoses and therapy. This could prevent and/or reduce the

Fig. 3. Forest plots of crude ERRs for (a) malignancies, (b) autoimmune disorders, (c) cardiovascular diseases, (d) infections and (e) psychiatric disorders in the full MS (black data points) and treated MS (gray data points) cohorts versus the non-MS cohort. Error bars indicate 95% CI. CI, confidence interval; CNS, central nervous system; ER, event rate; ERR, event rate ratio; MS, multiple sclerosis. [a]Lymphoproliferative disorders comprised lymphomas, leukemia and multiple myeloma except myelodysplastic syndromes. [b]All additional cancer sites comprised brain and other nervous system organs, colon and rectum, lung and bronchus, cervix uteri, corpus uteri, ovary, stomach, liver, pancreas, kidney, urinary/bladder, esophagus, thyroid and all solid organ malignant neoplasms. [c]The 'Other systemic diseases' category includes autoimmune disorders. [d]All disorders of the thyroid gland included simple and unspecified goiter, non-toxic nodular goiter, thyrotoxicosis with or without goiter, acquired hypothyroidism, thyroiditis, other disorders of the thyroid, benign neoplasm of the thyroid glands, thyroid dysfunction complicating pregnancy, childbirth or the puerperium, tuberculosis of the thyroid gland, endocrine exophthalmos, open wound of the thyroid gland with or without mention of complication, echinococcus granulosus infection of the thyroid, non-specific abnormal results of function of the thyroid. Congenital hypothyroidism and parathyroid disorders were excluded. [e]All cardiac arrhythmias included cardiac conduction disorder, ventricular fibrillation/flutter, ventricular tachycardia and cardiac arrest. [f]All central nervous system vascular disorders included ischemic stroke, hemorrhagic stroke, other stroke and transient cerebrovascular disease/accident. [g]All coronary artery disorders included angina pectoris, acute myocardial infarction, myocardial infarction, coronary artery embolism/thrombosis, ischemic coronary artery disorder and ischemic heart disease. [h]All opportunistic infections comprised parasite, fungal, mycobacterial and viral infections. [i]All herpes virus infections comprised chicken pox, herpes zoster, herpes simplex and other human herpes viruses. [j]All attempted suicide comprised poisoning by solid or liquid substances, poisoning by gases in domestic use, poisoning by other gases and vapors, hanging, strangulation and suffocation, submersion, injury by firearms, air guns and explosives, injury by cutting and piercing instruments, injury by jumping from high places, injury by other and unspecified means and late effects of self-inflicted injury.

impact of comorbidities, which in turn may enhance quality of life and prolong the survival of patients with MS. While some comorbidities could be linked to the pathogenesis of MS (Christiansen, 2012; Jadidi et al., 2013; Kingwell et al., 2012a), other significant contributors may include lower socioeconomic status (Marrie et al., 2014), smoking, obesity, alcohol consumption and the consequences of reduced physical activity as a result of MS-induced physical impairment. However, the contributions of these other factors are beyond the scope of the present study.

Post-approval observational studies have provided valuable information on the safety profiles of MS treatments (Holmen et al., 2011; Ontaneda et al., 2012), but have not considered the possibility that adverse events may be linked to the underlying increased risk of certain comorbidities in patients with MS rather than solely due to DMTs. In the present study, ERRs for the subcohort of patients with MS who had received DMTs at any time during the study were similar to ERRs for the full MS cohort versus the matched non-MS cohort. ERRs were not calculated for the untreated MS subcohort versus the treated MS subcohort because of the potential considerable measurable and non-measurable differences between these populations, including differences in disease severity, time since diagnosis and age, which make subcohort matching difficult. Generally, our data provide insights into comorbidities associated with patients with MS in current clinical practice, which could be used to compare the safety profiles of new DMTs. We suggest that further studies are carried out to investigate the influence of DMTs on the comorbid profile of patients with MS, by carrying out analyses combining claims data and registry data.

Although the DoD database is smaller than some other US claims databases, a strength of this study is that it comprises information from a large, single-payer, lifetime healthcare system and contains high-quality data for individuals with and without MS, including their comorbidities and all their medications covered by the healthcare system. Thus, the clinical course of MS can be investigated and compared against a non-MS cohort selected from the same dataset. Approximately 60% of encounters recorded in the database occur in civilian facilities, which are recorded as administrative claims data. The remaining 40% occur in military facilities and include information from electronic medical records (EMRs) in addition to claims information. To maximize the sample size and generalizability, claims-level information from both settings was used for the analyses presented here. In future analyses, EMR-level data could provide greater insight into the cohorts being investigated. Furthermore, in contrast to other administrative claims databases, the DoD database collects mortality data for the entire database population, facilitating the study of all-cause mortality and CoDs, through linkage with the NDI. Owing to the 2-year delay in NDI reporting, it was not possible to determine the CLD for 10% and 13% of individuals in the MS and non-MS cohorts, respectively.

A limitation of this study is that there may be significant demographic differences between the DoD database population and the general US population, such as the racial/ethnic composition, socioeconomic and educational status (Stewart, 2005), although there is evidence to suggest that these populations are comparable in terms of overall disease profiles (Dorrance et al., 2013). A similar analysis of comorbidities in the US MarketScan Research administrative claims database, which contains data on a population regarded as being broadly representative of the commercially insured US population (Truven Health Analytics, 2012) provided similar ERR results (Capkun et al., 2014). A general limitation of claims databases, including the DoD database, is the short follow-up duration, although the length of follow-up in this study was longer than that of many other claims databases and clinical trials. While shorter follow-up data may limit assessment of mortality, comorbidity results may be more meaningful in the short-term as longer time frames are associated with increased patient drop-out. The follow-up time in the MS cohort was 7% longer than that in the non-MS cohort; this small but significant difference may have led to some bias in the ERRs. However, overall, any bias arising from the follow-up duration is unlikely to diminish the impact of the results.

There is also a possibility of over-reporting comorbidity events identified through claims because diagnosis codes also serve as billing codes to justify medical services. Surveillance bias arising from more attentive and cautious medical management of patients with MS may lead to greater opportunities for recording billing codes and otherwise non-reported comorbidities and may partially account for the increased frequency observed for some comorbidities (e.g. infections) in the MS cohort versus the non-MS cohort (Montgomery et al., 2013). However, major events (e.g. myocardial infarction) are unlikely to be missed in either cohort and would therefore not be subject to surveillance bias. To limit bias when assessing comorbidities, relative ERs were assessed (ERRs) rather than comparing absolute ERs.

In this study, comorbidities were identified from a single claim, and did not use a second claim to provide confirmation of events, which may bias results (Marrie et al., 2015a). However, using lymphoma as an example, we have demonstrated that increasing the number of claims (from one claim to two) did not substantially alter the significance of the findings (data on file). However, the impact of the number of claims used to identify comorbidities from administrative claims databases may vary across diseases. For individuals in the MS cohort, two ICD-9-CM claims for MS were required; claims for DMTs were not included as an additional criterion for inclusion in the MS cohort, owing to the fact that not all patients with MS receive DMTs. While this may have led to some misclassification of individuals without MS into the MS cohort, this is unlikely to have had a significant impact on the results. Owing to the absence of specific codes for the onset of certain comorbidities, and the limited medical history information (requirement of at least 1-year pre-index enrollment), it was not possible to accurately estimate the onset of MS or the incidence rates of comorbidities (new onset events first occurring during follow-up) in this study. In addition, although data on congenital disorders and pregnancy conditions were available, these analyses would require a different study design from that used to assess the other comorbidities and were therefore not included here. Finally, other than adjusting for age and gender, these analyses did not control for other cohort differences, such as lifestyle changes and disease severity, because data were not available.

4.1. Conclusions

Using high-quality data from the DoD database, this study provides insights into the long-term health profile of patients with MS in clinical practice and demonstrates that the MS population are at greater risk of premature death and certain comorbidities compared with the non-MS population. The results of this study extend our understanding of concurrent and/or complicating diseases in MS, providing a context from which clinicians can gain insight into the impact of MS on patients. This study may alert clinicians to the importance of increased surveillance of the MS population to permit targeted earlier interventions that can reduce the impact of comorbidities on the functional status of patients in addition to reducing the risk of premature mortality. Finally, this research may aid in the evaluation and interpretation of adverse events encountered in the post-approval stage of MS therapies.

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To access the underlying research materials related to this paper please contact the Department of Defense.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2015.08.005.

References

Bahmanyar, S., Montgomery, S.M., Hillert, J., Ekbom, A., Olsson, T., 2009. Cancer risk among patients with multiple sclerosis and their parents. Neurology 72, 1170–1177.

Berkovich, R., Subhani, D., Steinman, L., 2011. Autoimmune comorbid conditions in multiple sclerosis. US Neurol. 7, 132–138.

Bloomgren, G., Sperling, B., Cushing, K., Wenten, M., 2012. Assessment of malignancy risk in patients with multiple sclerosis treated with intramuscular interferon beta-1a: retrospective evaluation using a health insurance claims database and postmarketing surveillance data. Ther. Clin. Risk Manag. 8, 313–321.

Capkun G., Lahoz R., Chen W., Moore A., Bischof D., Geissbuehler Y., et al., 2014. Comorbidities in patients with multiple sclerosis compared with the general population: retrospective analysis of the US MarketScan Database. Poster presented at the joint European Committee for Treatment and Research in Multiple Sclerosis-Americas Committee for Treatment and Research in Multiple Sclerosis meeting, Boston, USA, 10–13 September 2014, Poster number 179.

Chastek, B.J., Oleen-Burkey, M., Lopez-Bresnahan, M.V., 2010. Medical chart validation of an algorithm for identifying multiple sclerosis relapse in healthcare claims. J. Med. Econ. 13, 618–625.

Christiansen, C.F., 2012. Risk of vascular disease in patients with multiple sclerosis: a review. Neurol. Res. 34, 746–753.

Christiansen, C.F., Christensen, S., Farkas, D.K., Miret, M., Sorensen, H.T., Pedersen, L., 2010. Risk of arterial cardiovascular diseases in patients with multiple sclerosis: a population-based cohort study. Neuroepidemiology 35, 267–274.

Dorrance, K.A., Ramchandani, S., Neil, N., Fisher, H., 2013. Leveraging the military health system as a laboratory for health care reform. Mil. Med. 178, 142–145.

Eyre, H., Kahn, R., Robertson, R.M., Clark, N.G., Doyle, C., Hong, Y., et al., 2004. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. Circulation 109, 3244–3255.

Goodwin, D.S., Corwin, M., Kaufman, D., Golub, H., Reshef, S., Rametta, M.J., et al., 2014. Causes of death among commercially insured multiple sclerosis patients in the United States. PLoS One 9, e105207.

Handel, A.E., Ramagopalan, S.V., 2010. Multiple sclerosis and risk of cancer: a meta-analysis. J. Neurol. Neurosurg. Psychiatry 81, 1413–1414.

Holmen, C., Piehl, F., Hillert, J., Fogdell-Hahn, A., Lundkvist, M., Karlberg, E., et al., 2011. A Swedish national post-marketing surveillance study of natalizumab treatment in multiple sclerosis. Mult. Scler. 17, 708–719.

Jadidi, E., Mohammadi, M., Moradi, T., 2013. High risk of cardiovascular diseases after diagnosis of multiple sclerosis. Mult. Scler. 19, 1336–1340.

Jick, S.S., Li, L., Falcone, G.J., Vassilev, Z.P., Wallander, M.A., 2014. Mortality of patients with multiple sclerosis: a cohort study in UK primary care. J. Neurol. 261, 1508–1517.

Kaufman, D.W., Reshef, S., Golub, H.L., Peucker, M., Corwin, M.J., Goodin, D.S., et al., 2014. Survival in commercially insured multiple sclerosis patients and comparator subjects in the US. Mult. Scler. Relat. Disord. 3, 364–371.

Kingwell, E., Bajdik, C., Phillips, N., Zhu, F., Oger, J., Hashimoto, S., et al., 2012a. Cancer risk in multiple sclerosis: findings from British Columbia, Canada. Brain 135, 2973–2979.

Kingwell, E., van der Kop, M., Zhao, Y., Shirani, A., Zhu, F., Oger, J., et al., 2012b. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J. Neurol. Neurosurg. Psychiatry 83, 61–66.

Lalmohamed, A., Bazelier, M.T., Van Staa, T.P., Uitdehaag, B.M., Leufkens, H.G., De Boer, A., et al., 2012. Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study. Eur. J. Neurol. 19, 1007–1014.

Lebrun, C., Debouverie, M., Vermersch, P., Clavelou, P., Rumbach, L., de Seze, J., et al., 2008. Cancer risk and impact of disease-modifying treatments in patients with multiple sclerosis. Mult. Scler. 14, 399–405.

Marrie, R.A., Cohen, J., Stuve, O., Trojano, M., Sorensen, P.S., Reingold, S., et al., 2015a. A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: overview. Mult. Scler. 21, 263–281.

Marrie, R.A., Elliott, L., Marriott, J., Cossoy, M., Blanchard, J., Tennakoon, A., et al., 2014. Dramatically changing rates and reasons for hospitalization in multiple sclerosis. Neurology 83, 929–937.

Marrie, R.A., Reider, N., Cohen, J., Stuve, O., Trojano, M., Sorensen, P.S., et al., 2015b. A systematic review of the incidence and prevalence of cancer in multiple sclerosis. Mult. Scler. 21, 294–304.

Marrosu, M.G., Cocco, E., Lai, M., Spinicci, G., Pischedda, M.P., Contu, P., 2002. Patients with multiple sclerosis and risk of type 1 diabetes mellitus in Sardinia, Italy: a cohort study. Lancet. 359, 1461–1465.

Montgomery, S., Hillert, J., Bahmanyar, S., 2013. Hospital admission due to infections in multiple sclerosis patients. Eur J Neurol. 20, 1153–1160.

Multiple Sclerosis International Federation, 2013. Atlas of MS 2013: Mapping multiple sclerosis around the world.

Nielsen, N.M., Rostgaard, K., Rasmussen, S., Koch-Henriksen, N., Storm, H.H., Melbye, M., et al., 2006. Cancer risk among patients with multiple sclerosis: a population-based register study. Int. J. Cancer 118, 979–984.

Ontaneda, D., Hara-Cleaver, C., Rudick, R.A., Cohen, J.A., Bermel, R.A., 2012. Early tolerability and safety of fingolimod in clinical practice. J. Neurol. Sci. 15, 167–172.

Patten, S.B., Beck, C.A., Williams, J.V., Barbui, C., Metz, L.M., 2003. Major depression in multiple sclerosis: a population-based perspective. Neurology 61, 1524–1527.

Rodriguez-Antiguedad Zarranz, A., Mendibe Bilbao, M., Llarena Gonzalez, C., Audicana, C., 2014. Mortality and cause of death in multiple sclerosis: findings from a prospective population-based cohort in Bizkaia, Basque Country, Spain. Neuroepidemiology 42, 219–225.

Social Security Administration, 2014. Social Security: Medicare. ⟨http://www.ssa.gov/pubs/EN-05-10043.pdf⟩ (accessed 14.10.14).

Song, X., Capkun-Niggli, G., Johnson, B.H., Kahler, K., Krapfenbauer, D., 2013. Medical and pharmacy claims-based algorithms for identifying patients with multiple sclerosis. Value Health 16, A111.

Stewart D.B. 2005. Military Personnel: reporting additional service member demographics could enhance congressional oversight: United States Government Accountability Office.

Suissa, S., 2008. Immortal time bias in pharmaco-epidemiology. Am. J. Epidemiol. 167, 492–499.

Sumelahti, M.L., Hakama, M., Elovaara, I., Pukkala, E., 2010. Causes of death among patients with multiple sclerosis. Mult. Scler. 16, 1437–1442.

Truven Health Analytics. 2012. Data for Healthcare Research. ⟨http://truvenhealth.com/portals/0/assets/ACRS_11223_0912_MarketScanResearch_SS_Web.pdf⟩ (accessed on 26.06.14).

World Health Organization, 2010. International Statistical Classification of Diseases and Related Health Problems 10th Revision. ⟨http://apps.who.int/classifications/icd10/browse/2010/en⟩ (accessed 26.06.14).