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Survival in commercially insured multiple sclerosis patients and comparator subjects in the U.S.

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Abstract
Objective: Compare survival in patients with multiple sclerosis (MS) from a U.S. commercial health insurance database with a matched cohort of non-MS subjects.
Methods: 30,402 MS patients and 89,818 non-MS subjects (comparators) in the OptumInsight Research (OIR) database from 1996 to 2009 were included. An MS diagnosis required at least 3 consecutive months of database reporting, with two or more ICD-9 codes of 340 at least 30 days apart, or the combination of 1 ICD-9-340 code and at least 1 MS disease-modifying treatment (DMT) code. Comparators required the absence of ICD-9-340 and DMT codes throughout database reporting. Up to three comparators were matched to each patient for: age in the year of the first relevant code (index year – at least 3 months of reporting in that year were required); sex; region of residence in the index year. Deaths were ascertained from the National Death Index and the Social Security Administration Death Master File. Subjects not identified as deceased were assumed to be alive through the end of 2009.
Results: Annual mortality rates were 899/100,000 among MS patients and 446/100,000 among comparators. Standardized mortality ratios compared to the U.S. population were 1.70 and 0.80, respectively. Kaplan–Meier analysis yielded a median survival from birth that was 6 years lower among MS patients than among comparators.

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Conclusions: The results show, for the first time in a U.S. population, a survival disadvantage for contemporary MS patients compared to non-MS subjects from the same healthcare system. The 6-year decrement in lifespan parallels a recent report from British Columbia.

1. Introduction

Multiple sclerosis (MS) is a chronic, demyelinating disease of the central nervous system which progresses into a relentlessly degenerative phase in the majority of affected patients (Noseworthy et al., 2000). There are 250,000–350,000 patients with multiple sclerosis in the United States (Anderson et al., 1992), an overall prevalence of roughly 1/1000, with peak prevalence occurring in midlife (Confavreux, 2008). While immediate mortality due to acute or subacute MS attacks or lesions is relatively rare, data suggest that compared to the general population, patients experience a decrease in life expectancy of 5–10 years (Bronnum-Hansen et al., 2004; Compston and Coles, 2008; Grytten Torkildsen et al., 2008; Kingwell et al., 2012; Ragonese et al., 2010; Sadovnick et al., 1992). Survival in most populations has been improving over time, with the 10-year excess mortality reduced by as much as 50% since the mid-20th century (Bronnum-Hansen et al., 1994, 2004; Riise et al., 1988). Most information on survival patterns in MS has come from Europe, where populations, risk factors, medical practice, and supportive care may be different than in the U.S. Given the large number of MS patients in the U.S., the lack of data from this country represents a significant knowledge gap that should be addressed. Further, in patients who do not exhibit relapses but only experience progression, there are no approved therapies and it appears that they begin their relentless declines sooner and faster than the majority relapsing-remitting patients (Confavreux et al., 2000). Thus, the disability effects of the disease which define the condition lead ultimately towards mortality, where information is lacking.

US health plan and claims databases capture large patient cohorts and mortality is an objective endpoint that is well recorded in the US through the Social Security Administration Death Master File (SSA DMF)(Social Security Administration, 2013) and the National Death Index (NDI) (Centers for Disease Control and Prevention, 2013). We conducted a retrospective cohort study comparing survival and mortality patterns in patients with MS and a matched cohort of non-MS subjects drawn from the OptumInsight Research (OIR) database, which contains claims data from a national U.S. commercial health insurance plan. Mortality data covering 1996 through 2009 were analyzed.

2. Material and methods

2.1. Selection of subjects and determination of mortality

The OIR database contains billing claims information for over 39 million individuals insured through United HealthCare; there are approximately 15 million covered lives per year, and 7.5 million patients with laboratory data (OptumInsight, 2013). Pharmacy claims data can be tracked for medication refill patterns and changes in medications. The database is geographically diverse and representative of the U.S. commercially insured population. Compared with the general U.S. population the OIR population has a similar sex ratio, but contains fewer individuals aged 65 or older, fewer minorities, and is of higher socioeconomic status.

MS patients were initially selected for inclusion in the present study if they met the following criteria:

- Inclusion in the database for ≥ 3 consecutive months during 1996–2009.
- At least two ICD-9 diagnosis codes of 340 (multiple sclerosis) ≥ 30 days apart *or* the combination of one ICD-9-340 code and at least one billing code for a MS disease modifying treatment (DMT), defined as any of the following drugs: interferon β-1a, interferon β-1b, glatiramer acetate, natalizumab.
- Age ≥ 18 years at the time of the first code.

The date of the first relevant code was used as the index date.

The presence of a diagnostic code together with a DMT prescription was considered to be sufficient evidence that the subject actually had MS, with no further validation required. To determine the accuracy of diagnoses when no DMT codes were present (36% of all MS patients), a chart review was conducted for 85 patients randomly selected from that group. The diagnosis was inconclusive for six patients, and 17 were judged not to have MS; 62 patients (73%) were judged to have definite MS – 32 on the basis of their physicians' notes, three because the use of DMTs or azathioprine was documented despite the absence of a claim for this in the database, 26 on both factors, and one who was judged by the neurologist reviewer to have MS based on other factors. Consequently, the *maximum* expected false-positive diagnostic rate is only 10% (0.36*0.27) in these circumstances. We concluded, therefore, that the "two-code" definition was sufficiently accurate for purposes of the present study.

Up to three non-MS subjects (*comparators*) were selected and matched to the MS patients according to the following criteria:

- Inclusion in the database for ≥ 3 months during the year of the matched patient's index date.
- No ICD-9-340 codes *and* no DMT codes at any time during enrollment in the database.
- The same age at index year, sex, and residence region (U.S. Census categories Northeast, Midwest, South, West) at index year as the matched patient.

Deaths among the selected subjects were identified by linkage with the NDI(Centers for Disease Control and Prevention, 2013) and the SSA DMF (Social Security

Administration, 2013). Standard algorithms, which included social security number, were used to determine matches for the NDI (National Center for Health Statistics, 2009); social security number was considered sufficient for a match with the SSA DMF. A death was considered valid if identified through either source. All remaining subjects were considered to be alive as of the end of 2009 regardless of whether they were still in the OIR database.

De-identified data for 30,436 MS patients and 90,123 comparators who met the initial screening criteria for selection were provided by OIR. To ensure a similar opportunity for mortality among MS patients and their matched comparators (i.e., to avoid a difference in "immortal time"(Suissa, 2008) between groups), we defined a starting point for follow-up that was the same for each matched set, termed "first opportunity to die" (FOTD). This was the *latest* date that the selection criteria required a set member to be alive in order to be included; for example, an MS patient had to be alive until s/he received a second code (diagnosis or DMT) and a comparator had to be alive for the first three months of the index year to fulfill the selection criteria. Subjects were only eligible for final inclusion if they were alive at the set FOTD date; thus, any patients or comparators who died before this date were excluded. To ensure that all matched sets included a patient and at least one comparator, any comparators whose matched patient was excluded and any patients for whom *all* matched comparators were excluded were also eliminated. These procedures resulted in the exclusion of 34 MS patients and 305 comparators, leaving 30,402 patients and 89,818 comparators available for inclusion in the analyses. A total of 29,411 patients (97%) had three matched comparators; 594 had two, and 397 had one.

OIR obtained approval from New England IRB for the NDI search and for the chart review validation study. IRB review was not required for transmission of the de-identified data to the study investigators because OIR policies did not permit identification of individual subjects.

2.2. Analytical methods

Person-years of follow-up were calculated for MS patients and comparators from the FOTD date through the date of death (to the nearest month) for those who died, and through 2009 for the remaining subjects. Mortality rates with 95% confidence intervals were then calculated, both overall and within various subgroups. Standardized mortality ratios (SMRs – the ratio of observed to expected deaths compared to the general U.S. population) and their 95% confidence intervals were estimated by comparison of the relevant subject group with mortality rates from U.S. Census data for 1996–2007(Centers for Disease Control and Prevention, 2011a, b) according to age, sex, and region of residence, and extrapolating the 2003–2007 data to

Table 1 Distribution of MS patients and comparators according to various factors.

	MS (n=30,402)	**Comparator** (n=89,818)	*%*[a]
Sex			
Female	23,364	69,102	***77***
Male	7038	20,716	***23***
Median age at index	44 yr	44 yr	-
Region			
Northeast	3546	10,395	***12***
Midwest	9822	28,816	***32***
South	13,333	39,627	***44***
West	3701	10,980	***12***
Birth year			
1921–1929[b]	335	964	***1.1***
1930–1939	979	2836	***3.2***
1940–1949	4578	13,381	***15***
1950–1959	9436	27,848	***31***
1960–1969	8998	26,727	***30***
1970–1979	5000	14,855	***17***
1980–1989	1060	3159	***3.5***
1990–1999	16	48	***0.05***
Median insurance			
Total[c]	1097 d	1554 d	-
Coverage interval			
Post-index[c]	724 d	363 d	-
% time covered	*92*	*86*	-
Disease modifying treatment (DMT)	19,359	-	***64***

[a] Due to the matching, MS patients and comparators had the same distribution according to demographic factors.
[b] The birth year for 60 MS patients and 170 comparators born before 1921 was set to 1921 to protect privacy.
[c] Includes gaps in coverage.

2008–2009 (detailed Census mortality rates were not available for the latter years). Survival from birth was estimated using Kaplan–Meier methods.

3. Results

3.1. Description of the study populations

Because of the matching, the distribution of the MS patients and comparators was identical according to key demographic factors. Most of the subjects (77%) were female, and the median age at index date was 44 years (Table 1). The majority of subjects resided in the Midwest (32%) and South (44%). The earliest birth years were in the 1920s (a few patients and comparators born before 1921 had their birth years reset to 1921 for privacy reasons), with the peak decades being the 1950s (31%) and 1960s (30%). MS patients had a shorter overall coverage period in the database than comparators, but there was more coverage after the index date (median of approximately 2 vs. 1 year). Sixty-four percent of the MS patients had received DMTs at some point during their coverage period.

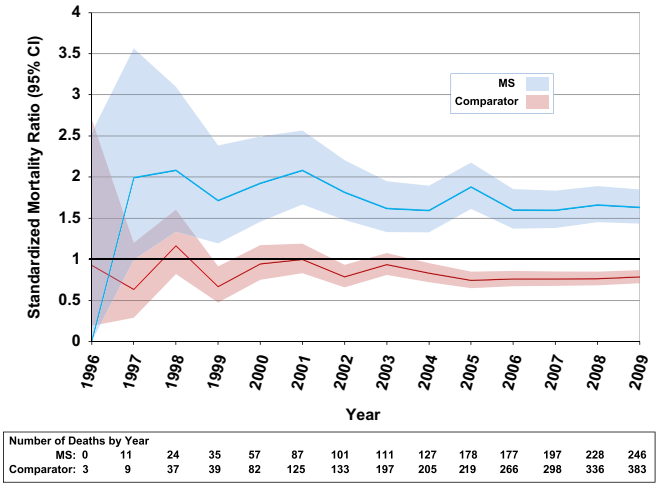

Fig. 1 Standardized mortality ratios (SMR) in MS patients and comparators by year.

Table 2 Mortality rates in MS patients and comparators.

	MS			Comparator		
	No. of deaths	Person-years	**Mortality rate** (95% CI)	No. of deaths	Person-years	**Mortality rate** (95% CI)
Total	1579	175,620	**899** (855-945)	2332	523,285	**446** (428-464)
Sex						
Female	1050	135,167	**777** (731-825)	1580	402,293	**393** (374-413)
Male	529	40,453	**1308** (1199-1424)	752	120,991	**622** (578-668)
Region						
Northeast	179	20,246	**884** (759-1024)	214	59,473	**360** (313-411)
Midwest	656	63,444	**1034** (956-1116)	1000	187,792	**533** (500-567)
South	648	73,695	**879** (813-950)	974	221,880	**439** (412-467)
West	96	18,235	**526** (426-643)	144	54,140	**266** (224-313)

Table 3 Standardized mortality ratios (SMR) in MS patients and comparators.

	MS			Comparator		
	Observed deaths	Expected deaths	**SMR**[a] (95% CI)	Observed deaths	Expected deaths	**SMR*** (95% CI)
Total	1579	931	**1.70** (1.61-1.78)	2332	2908	**0.80** (0.77-0.84)
Sex						
Female	1050	617	**1.70** (1.60-1.81)	1580	1915	**0.83** (0.79-0.87)
Male	529	314	**1.69** (1.54-1.84)	752	993	**0.76** (0.70-0.81)

[a]Standardized to the U.S. adult population according to age, sex, and region.

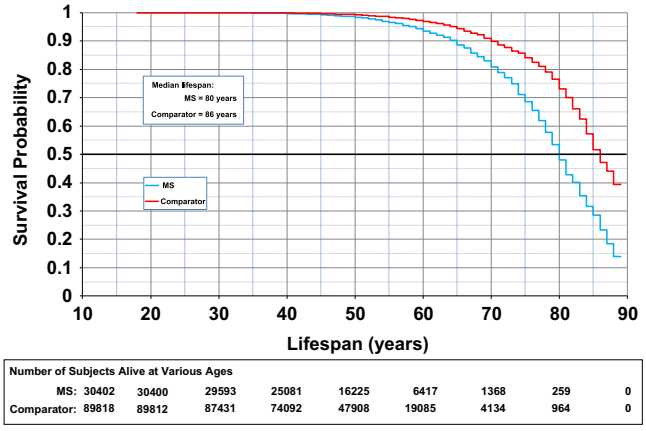

Fig. 2 Survival among MS patients and comparators.

3.2. Mortality rates and standardized mortality ratios

There were 1579 deaths among the MS patients and 2332 among the comparators. As shown in Table 2, the overall mortality rate (per 100,000 person-years) among the patients was approximately double that among their matched comparators (899 vs. 446). This difference between MS and comparators was apparent among both females and males, but the actual rates were considerably higher among MS males (1308) compared to females (777). The MS/comparator difference was also consistent across the four geographic regions; mortality was highest in the Midwest and lowest in the West (1034 vs. 526 in MS patients). With the large numbers, all noted differences were statistically significant with non-overlapping confidence intervals.

As shown in Table 3, compared with the U.S. adult population, the SMR for MS patients was 1.70 overall, and closely similar for females (1.70) and males (1.69). The SMR for comparators was 0.80, indicating lower mortality in this commercially insured population compared with the general U.S. population. The SMR for female comparators was higher (0.83) than for males (0.76). All differences between patients and comparators were highly statistically significant. The SMRs did not display time-trends when calculated by year (Fig. 1): between 2000 (the first year with at least 50 deaths in each group) and 2009, the range of MS SMRs was 1.60 (in 2006) to 2.08 (in 2001), and the comparator SMRs, 0.74 (in 2005) to 1.00 (in 2001).

3.3. Survival

Fig. 2 shows the Kaplan–Meier survival curves from birth for MS patients and comparators. The curves begin to diverge between the ages of 50 and 55, and after that point, MS patients had consistently lower survival. The estimated median lifespan was 80 years (95% confidence interval, 80–81) for MS and 86 years (85–87) for comparators. Among females, the corresponding median lifespans were 81 years for MS and 86 for comparators, and among males, 78 and 85, respectively (stratified survival curves not shown).

4. Discussion

The present results have shown, for the first time in a contemporary U.S. population, the survival disadvantage among MS patients that has been reported from other countries (Bronnum-Hansen et al., 2004; Compston and Coles, 2008; Grytten Torkildsen et al., 2008; Kingwell et al., 2012; Ragonese et al., 2010). Based on commercial health insurance claims for patient identification and death records from national registries, we estimated that the median lifespan is 6 years shorter for MS patients compared to plan members who did not have MS and were matched to the patients for year of birth, sex, and geographic region. The shorter lifespan for MS patients was apparent in both female and male subjects, with a slightly larger difference in males.

Other findings include mortality rates that were approximately twice as high in MS patients as in comparators, both overall (899 vs. 446 per 100,000 person-years) and in subgroups defined according to sex and geography. The calculated SMRs also showed that mortality was greater among MS patients and lower among comparators than in the general U.S. population. The latter result suggests that, as anticipated, the commercially insured are in better health than the population as a whole.

While a number of previous studies have evaluated survival in MS patients, there are only a few that provided general population comparisons (Bronnum-Hansen et al., 2004; Ekestern and Lebhart, 2004; Grytten Torkildsen et al., 2008; Kingwell et al., 2012; Ragonese et al., 2010; Sadovnick et al., 1992). The most recent, a study of a population-based cohort identified from clinics in British Columbia, also reported on median survival from birth (Kingwell et al., 2012). There was an approximate 6-year deficit in lifespan compared to the general provincial population among both female (78.5 vs. 84.5 years) and male (74 vs. 80 years) patients identified between 1980 and 2004 and followed through 2007, a finding that closely parallels the present U.S. results. An earlier, considerably smaller clinic-based study from British Columbia and Ontario reported a similar 6–7 year deficit based on survival from onset of MS (Sadovnick et al., 1992). Other reports were from Europe (Bronnum-Hansen et al., 2004; Ekestern and Lebhart, 2004; Grytten Torkildsen et al., 2008; Ragonese et al., 2010), and also focused on survival from

onset rather than lifespan. These include an approximate 10-year deficit among patients in the Danish Multiple Sclerosis Registry who developed the disease between 1949 and 1996 and were followed through 1999, compared with age-matched general population survival (38 vs. 45 years among females, 28 vs. 38 years among males) (Bronnum-Hansen et al., 2004); an 8-year deficit in patients from a single county in Norway with disease onset from 1953 to 2003 followed through 2004 and compared with general population mortality statistics (43 vs. 51 years among females, 36 vs. 46 years among males) (Grytten Torkildsen et al., 2008); and an approximate 10-year deficit in patients identified in Sicily and followed through mid-2007 (onset dates were not provided) compared with a series of controls matched for birthdate, sex, and municipality (Ragonese et al., 2010). An outlier to the other European studies was a report from Austria based on deaths attributed to MS from 1970 to 2001 compared with other causes in the population, which showed deficits of 15 years in the median age at death among females (60 vs. 75 years) and 11 years among males (57 vs. 68 years) (Ekestern and Lebhart, 2004). Although the European survival deficits are somewhat larger than what we have reported, those cohorts were generally older, and the disease onset for many patients was before the era of DMT treatment, which began in 1993 and may be associated with a beneficial effect on survival (Goodin et al., 2012).

A final comparison is provided by the North American Committee on Multiple Sclerosis (NARCOMS) database, a voluntary national registry of MS patients in the U.S. that was initiated in 1993, with more than 36,000 participants (Lo et al., 2005). In a recent analysis, the median survival in NARCOMS was 81.5 years (Reshef et al., 2012), similar to what we observed among MS patients in the present study. The overall survival curve was also generally similar.

SMRs have also been reported from numerous population-based case series, with an approximate range of 2–3 (Bronnum-Hansen et al., 1994, 2004; Grytten Torkildsen et al., 2008; Hirst et al., 2008; Kingwell et al., 2012; Koch-Henriksen et al., 1998; Reshef et al., 2012; Smestad et al., 2009). While this study's SMR for MS patients was lower (1.70), a more appropriate comparison is with the *ratio* of SMRs from the MS patients to the comparators (whose SMR was 0.80), because the latter subjects were drawn from the same population as the patients in the present study. That ratio is 2.13, which is within the range of other reported estimates.

While there is no other readily available type of data in the U.S. for a large-scale evaluation of survival patterns in MS with matched comparators, insurance claims have not previously been used for this purpose, and potential validity issues must be considered. The diagnosis of MS was based on having either an ICD-9 code signifying MS and at least one prescription for a DMT, which we considered sufficiently specific to be an accurate indication that the patient truly had MS, or a minimum of two ICD-9 codes at least 30 days apart. A validation study on a sample of patients meeting the latter criteria confirmed the diagnosis for 73%. Since 64% of the patients had been treated with DMTs, this suggests that the *maximum* proportion of false positives in the complete study population would have been 10% of the total, which is not enough to have materially affected the results, and if anything would have led to underestimation of the mortality difference between MS patients and comparators.

Another potential limitation with the claims data is that patients were not identified at the time of diagnosis, but rather when they met the inclusion criteria during their enrollment in the insurance plan. The median age at the first code was 44 years, which is almost 15 years after mean disease onset (Bronnum-Hansen et al., 2004). While our approach excluded patients who died before they could be enrolled in the insurance plan, most MS deaths occur later in life (Bronnum-Hansen et al., 2004), and indeed the median survival in our data was 80 years. Thus, any bias introduced by this "immortal time" (Suissa, 2008) that excluded early deaths would have been slight. Importantly, because they were matched to patients on the age at the first code, the comparators were subject to the same immortal time as the patients. While this alleviates concerns about biased *comparisons*, the immortal time in both groups inevitably led to some overestimation of the respective lifespans, and the focus should thus remain on the difference between MS and comparators.

Nevertheless, the lack of information about the date of diagnosis or onset in the claims data means that survival could not be measured from either of these time-points. Instead, we compared survival from birth (lifespan) in patients and matched comparators. A similar measure was reported in the recent British Columbia study (Kingwell et al., 2012), and it can be argued that, given the insidious onset of MS, lifespan is actually a more consistent and accurate parameter for comparative analysis.

It is common in the U.S. setting to change health insurance with changes in employment. Although coverage periods in the insurance plans were relatively short for both MS patients and comparators, this should have had a minimal effect on the survival analyses because plan membership was used only to *identify* subjects. Vital status was determined separately via the NDI and SSA DMF; these data sources are quite complete, with only a few deaths occurring outside the U.S. likely to have been missed. It is not clear that these would have been distributed differently in the comparison groups, and in any event, the numbers would have been too small to explain the large differences observed.

A limitation of our analyses is that information on type and severity of MS was not available in the claims data, and information on comorbidities was confined to claims from the relatively brief period of enrollment in the health care plan. An examination of survival according to type, severity, and general health state could provide valuable insight into the relationship of death to the underlying MS. Indeed, it might be anticipated that the claims data would underestimate the mortality from MS because severely disabled patients might lose commercial insurance (unless insured under a family member) or rely on government programs (e.g., Medicare or Medicaid). However, as MS is a progressive illness, these patients may still be initially captured in the insurance data base, which suffices for mortality ascertainment through the subsequent NDI and SSA DMF searches. While the key question of the impact of DMTs on survival still remains, we did not investigate this within the dataset we created. Such an exploration would have been difficult for at least two reasons: (1) the relatively incomplete treatment histories due to inclusion in the insurance plans for short durations; (2) the problem of confounding by indication, in which the type of treatment may vary according to

severity of disease and survival prospects in ways that cannot be measured. While the more complete picture afforded by including severity and type of MS, comorbidities, and DMT treatment in the analyses would be desirable, the overall investigation of survival patterns that we conducted is valuable because it is the first time this has been explored with U.S. data. Differences in the characteristics of national populations and medical care systems could lead to different survival outcomes, and it is thus important to determine whether previously observed relationships also apply in this country.

Because MS patients from the claims data are all commercially insured, they are not representative of the full U.S. adult population – approximately 68% of U.S. adults under age 65 have private health insurance (Adams et al., 2009). The restriction of patients to this population has relevance not only for extrapolation of our results, but also for the choice of comparison group for survival patterns. The comparators were subjects without MS, but from the same database (i.e., the same health plans), who were matched to the MS patients on relevant characteristics. There would have been a similar exclusion of early deaths as in the patients; furthermore, the follow-up period for discerning mortality was set to be the same in patients and their matched comparators, thereby avoiding immortal time bias in the comparisons. The comparators also provide an anchor point for considering how the commercially insured population may differ from the general population in terms of mortality. As expected, the SMR for comparators was below 1.0, indicating that this population is somewhat healthier. These patterns, along with the similarity of the lifespan difference between patients and comparators in the claims data and the British Columbia study (Kingwell et al., 2012), provide some face validity for the present results, and more generally for the use of claims data in mortality studies.

5. Conclusion

Our results suggest that commercially insured MS patients in the U.S. have a lifespan approximately 6 years less than the general commercially insured non-MS population. This finding demonstrates, for the first time with U.S. data, the survival disadvantage reported in European populations, and is similar to the gap identified in British Columbia, the other North American population that has recently provided such a comparison. It remains to be determined whether modern treatment practices will over time lead to a reduction in excess mortality in MS patients. That will require longer follow-up periods from the DMT era than are presently available and a strategy for addressing confounding by indication. Such a determination will, in the future, provide extremely important information about how the introduction of DMTs in the 1990s (Compston and Coles, 2008) has impacted survival in MS.

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David Kaufman has received personal compensation for activities with Bayer HealthCare Pharmaceuticals, McNeil Consumer Healthcare, and UCB as a consultant. Dr. Kaufman has received research support from McNeil Consumer HealthCare, CSL Behring, Onyx Pharmaceuticals, Incyte Corporation, and Sanofi-Aventis.

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Michael Corwin has received personal compensation for activities with Bayer HealthCare Pharmaceuticals, Ameritox, and Genova Diagnostics as a consultant. Dr. Corwin has received personal compensation for participation as a Medical Monitor and on Data and Safety Monitoring Committees for Edimer Pharmaceuticals, SynapDx, BioDelivery Sciences International, Stratatech, KV Pharmaceuticals, and Meridian Medical Technologies.

Douglas Goodin has participated (or is currently participating) in several industry-sponsored clinical trials in multiple sclerosis; the sponsoring pharmaceutical companies for these trials have included (or do include) Ares-Serono, Merck Serono, Novartis, Berlex Laboratories, Bayer Schering HealthCare, Biogen Idec, Schering AG and Teva Neuroscience. He has also lectured at both medical conferences and in public on various aspects of the epidemiology, diagnosis, and management of multiple sclerosis, and in many cases these talks have been sponsored directly or indirectly by one or another of the above listed companies. He has served as a temporary ad hoc consultant to several of these organizations on several occasions.

Volker Knappertz was a salaried employee of Bayer HealthCare Pharmaceuticals.

Dirk Pleimes is a salaried employee of Bayer HealthCare Pharmaceuticals.

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References

Adams PF, Heyman KM, Vickerie JL. Summary health statistics for the U.S. population: National Health Interview Survey, 2008. National Center for Health Statistics, Vital Health Stat. 2009;10.

Anderson DW, Ellenberg JH, Leventhal CM, Reingold SC, Rodriguez M, Silberberg DH. Revised estimate of the prevalence of multiple sclerosis in the United States. Ann Neurol 1992;31:333–6.

Bronnum-Hansen H, Koch-Henriksen N, Hyllested K. Survival of patients with multiple sclerosis in Denmark: a nationwide, long-term epidemiologic survey. Neurology 1994;44:1901–7.

Bronnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain 2004;127:844–50.

Centers for Disease Control and Prevention. National Death Index; 2013 [accessed January 2013, at ⟨http://www.cdc.gov/nchs/ndi.htm⟩].

Centers for Disease Control and Prevention NCfHS. Compressed Mortality File 1979-1998. CDC WONDER On-line Database, compiled from Compressed Mortality File CMF 1968-1988, Series 20, No. 2A, 2000 and CMF 1989-1998, Series 20, No. 2E, 2003; 2011a [accessed August 31, 2011, at ⟨http://wonder.cdc.gov/cmf-icd9.html⟩].

Centers for Disease Control and Prevention NCfHS. Compressed Mortality File 1999-2007. CDC WONDER On-line Database, compiled from Compressed Mortality File 1999-2007 Series 20 No. 2M, 2010; 2011b [accessed August 31, 2011, at ⟨http://wonder.cdc.gov/cmf-icd10.html⟩].

Compston A, Coles A. Multiple sclerosis. Lancet 2008;372:1502–17.

Confavreux C. Defining the natural history of MS: the need for complete data and rigorous definitions. Mult Scler 2008;14:289–91.

Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med 2000;343:1430–8.

Ekestern E, Lebhart G. Mortality from multiple sclerosis in Austria 1970-2001: dynamics, trends, and prospects. Eur J Neurol 2004;11:511–20.

Goodin DS, Reder AT, Ebers GC, Cutter G, Kremenchutzky M, Oger J, et al. Survival in MS: a randomized cohort study 21 years after the start of the pivotal IFNbeta-1b trial. Neurology 2012;78:1315–22.

Grytten Torkildsen N, Lie SA, Aarseth JH, Nyland H, Myhr KM. Survival and cause of death in multiple sclerosis: results from a 50-year follow-up in Western Norway. Mult Scler 2008;14:1191–8.

Hirst C, Swingler R, Compston DA, Ben-Shlomo Y, Robertson NP. Survival and cause of death in multiple sclerosis: a prospective population-based study. J Neurol Neurosurg Psychiatry 2008;79:1016–21.

Kingwell E, van der Kop M, Zhao Y, Shirani A, Zhu F, Oger J, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J Neurol Neurosurg Psychiatry 2012;83:61–6.

Koch-Henriksen N, Bronnum-Hansen H, Stenager E. Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry. J Neurol Neurosurg Psychiatry 1998;65:56–9.

Lo AC, Hadjimichael O, Vollmer TL. Treatment patterns of multiple sclerosis patients: a comparison of veterans and non-veterans using the NARCOMS registry. Mult Scler 2005;11:33–40.

National Center for Health Statistics. NDI User's Guide (Draft 10/06/09): National Center for Health Statistics; 2009.

Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med 2000;343:938–52.

OptumInsight. OptumInsight Retrospective Database; 2013 [accessed January 2013, at ⟨http://www.optuminsight.com/life-sciences/solutions/real-world-evidence/data-assets/retrospective-database/overview/⟩].

Ragonese P, Aridon P, Mazzola MA, Callari G, Palmeri B, Famoso G, et al. Multiple sclerosis survival: a population-based study in Sicily. Eur J Neurol 2010;17:391–7.

Reshef S, Cutter G, Golub HL, Kaufman DW, Brueckner A. Mortality in multiple sclerosis in the United States (MIMS-US): a retrospective, cohort study of survival and mortality trends. Annual Meeting of American Academy of Neurology, New Orleans2012.

Riise T, Gronning M, Aarli JA, Nyland H, Larsen JP, Edland A. Prognostic factors for life expectancy in multiple sclerosis analysed by Cox-models. J Clin Epidemiol 1988;41:1031–6.

Sadovnick AD, Ebers GC, Wilson RW, Paty DW. Life expectancy in patients attending multiple sclerosis clinics. Neurology 1992;42:991–4.

Smestad C, Sandvik L, Celius EG. Excess mortality and cause of death in a cohort of Norwegian multiple sclerosis patients. Mult Scler 2009;15:1263–70.

Social Security Administration. Social Security's Death Master File; 2013 [accessed January 2013, at ⟨http://ssa-custhelp.ssa.gov/app/answers/detail/a_id/149/∼/social-security's-death-master-file⟩].

Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;167:492–9.