Multiple Sclerosis and Related Disorders 4 (2015) 484–490

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Causes of death among persons with multiple sclerosis

Gary R. Cutter [a,*], Jeffrey Zimmerman [b], Amber R. Salter [a], Volker Knappertz [c,d], Gustavo Suarez [e], John Waterbor [b], Virginia J. Howard [b], Ruth Ann Marrie [f]

[a] University of Alabama at Birmingham, Department of Biostatistics, Birmingham, AL, United States
[b] University of Alabama at Birmingham, Department of Epidemiology, Birmingham, AL, United States
[c] Teva Pharmaceuticals, Frazer, PA United States
[d] Heinrich-Heine-Universität, Department of Neurology, Düsseldorf, Germany
[e] Bayer HealthCare Pharmaceuticals, Whippany, NJ, United States
[f] University of Manitoba, Departments of Internal Medicine & Community Health Sciences, Winnipeg, MB, Canada

ARTICLE INFO

Article history:
Received 22 April 2015
Received in revised form
30 June 2015
Accepted 17 July 2015

Keywords:
Multiple Sclerosis
MS
Mortality
PMR
Proportional Mortality Ratio
Cause-Specific Mortality

ABSTRACT

Background: Multiple Sclerosis (MS) is a leading cause of disability among young Americans. Reports suggest that life expectancy (i.e., average age at death) remains reduced as compared to the general population, but underlying causes of death (UCOD) are less well-characterized.
Objective: To describe the cause-specific mortality among participants enrolled in the North American Research Committee on Multiple Sclerosis (NARCOMS) registry and to compare the profile of these causes by age, sex, race and disability status at entry into NARCOMS, with U.S. mortality data.
Methods: The underlying cause of death (UCOD), any mention cause of death and proportionate mortality were compared among U.S. NARCOMS participants by age, sex, race and disability status.
Results: Of the 32,445 participants to be considered for this study, 2,927 had died. Compared to survivors, decedents were older at enrollment and MS diagnosis, more likely to be male, and had less education. UCOD differed markedly by age group. In both sexes, MS as the UCOD was proportionately lower by 20% or more in those aged 25-39 compared to those aged 75 or older. Cancer and cardiovascular causes were more frequent as causes of death with increasing age, but were less than expected at older ages. The effect of disability on mortality was roughly equivalent to the effect of aging on mortality.
Conclusions: Among NARCOMS participants older age at enrollment, male sex and greater disability were associated with increased mortality risk. This cohort of MS subjects had a lower proportionate mortality from cardiovascular disease and cancer compared to the U.S. population.

1. Introduction

Multiple Sclerosis (MS) is a chronic, demyelinating disease of the central nervous system (CNS) with an estimated prevalence ranging from 16.6 to 357.6 per 100,000 population in North America. Evans et al., (2013) MS is the leading non-traumatic cause of disability among young Americans. Peterson and Trapp (2005) Studies in Europe and Canada suggest that individuals with MS have a reduced life expectancy of about 6 years compared to demographically similar groups in the general population. (Kingwell et al., 2012; Grytten Torkildsen et al., 2008; Hirst et al., 2008; Koch-Henriksen et al., 1998; Lalmohamed et al., 2012; Leray et al., 2007; Pittock et al., 2004; Ragonese et al., 2010; Sadovnick et al., 1992; Smestad et al., 2009; Sumelahti et al., 2010) However, prospective studies assessing survival among MS patients in the United States (U.S.) have been limited to veterans of World War II and to a cohort from Olmstead County, Minnesota. (Pittock et al., 2004; Wallin et al., 2000)

Prior work consistently suggests that individuals with MS experience an increased mortality rate from respiratory tract infections, pneumonia, and other infections as well as from MS. (Hirst et al., 2008; Koch-Henriksen et al., 1998; Lalmohamed et al., 2012; Ragonese et al., 2010; Smestad et al., 2009; Sumelahti et al., 2010; Redelings et al., 2006; Kaufman et al., 2014) However, findings regarding mortality risk from cardiovascular disease, cancer, and suicide are inconsistent. (Grytten Torkildsen et al., 2008; Koch-

* Correspondence to: Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, 1665 University Blvd, Ryals 410B, Birmingham, AL 35294.
E-mail addresses: cutterg@uab.edu (G.R. Cutter), zimmerjaug@gmail.com (J. Zimmerman), asalter@uab.edu (A.R. Salter), knappertz@yahoo.com (V. Knappertz), gustavo.suarez@bayer.com (G. Suarez), h2obor@uab.edu (J. Waterbor), vjhoward@uab.edu (V.J. Howard), rmarrie@hsc.mb.ca (R. Ann Marrie).

http://dx.doi.org/10.1016/j.msard.2015.07.008
2211-0348/

Henriksen et al., 1998; Lalmohamed et al., 2012; Pittock et al., 2004; Ragonese et al., 2010; Redelings et al., 2006; Phadke 1987; Nielsen et al., 2006; Sadovnick et al., 1991) Cause-specific mortality of persons with MS in the U.S. has been investigated in two commercially insured populations and in one study that identified MS cases from death certificates. (Redelings et al., 2006; Kaufman et al., 2014) However, at least 35% of all persons with MS may not have MS listed as a cause of death on their death certificate, suggesting that the population of persons in the U.S. with MS was not fully captured in the latter study. (Grytten Torkildsen et al., 2008; Hirst et al., 2008; Pittock et al., 2004; Bronnum-Hansen et al., 2004) Thus, cause-specific mortality in persons with MS is incompletely understood. Further, a recent study suggested that the introduction of disease-modifying agents may improve survival. Goodin et al., (2012) If survival is prolonged the profile of causes of death may shift toward the causes commonly experienced at older ages, but this has not been evaluated.

Given the large registration, broad age and disease range of participants enrolled and a period of over 15 years of follow-up in the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry, NARCOMS provides a reasonable opportunity to estimate mortality and causes of death in persons with MS in the U.S. with particular consideration of causes of death that may occur at older ages. We aimed to evaluate differences in mortality profile by demographic characteristics, and to evaluate the proportional cause-specific mortality among MS cases enrolled in the NARCOMS Registry as it changes with age and disability status.

2. Methods

2.1. Participants

NARCOMS is a volunteer registry for persons with MS for which most participants reside in the U.S. It was established in 1993 by the Consortium of Multiple Sclerosis Centers and has registered over 38,000 persons with MS. A validation study estimated that 98% of all registered individuals have been diagnosed with MS. Marrie et al., (2007) The methods used to register participants and collect data are described elsewhere. (Consortium of Multiple Sclerosis Centers) Demographic characteristics captured at enrollment include sex, race (Caucasian, African American, other), date of birth, and education (high school or less, more than high school). Disability status is captured at enrollment and semi-annually using the Patient Determined Disease Steps (PDDS), a validated measure that correlates well with a physician-scored Expanded Disability Status Scale (EDSS). (Marrie and Goldman 2007; Learmonth et al., 2013) It is scored ordinally from 0 to 8 (Normal to Bedridden). A score of 0 approximates an EDSS score of 0, a score of 3 represents early gait disability without need for an assistive device and approximates an EDSS score of 4.0 to 4.5; and scores of 4, 5, and 6 (Bilateral Support) represent EDSS scores of 6 to 6.5.

2.2. Mortality

This study included U.S. NARCOMS participants enrolled before 2010. Of these participants, anyone responding to a survey after 2010 was considered as alive during the period of evaluation through December 31, 2009. For those whose last contact was before 2010, their information was sent to the National Death Index (NDI) to determine whether that person matched a decedent in the database of U.S. deaths. National Center of Health Statistics Division of Vital Statistics (1999) Variables sent to NDI for assessment of match status included first name, middle initial (if available), last name, maiden name, date of birth, sex, race, and U.S. birth state. Commonly, social security number is the key matching variable for use with the NDI, but this variable is not collected in NARCOMS for privacy reasons. The NDI provides two variables used to aid in confirming a match: whether the record matches exactly on the submitted criteria; and a status code to indicate certainty in the match (true match=1 or false match=0). For this study we included deaths that were exact matches regardless of the status code. For the NDI matched deaths, NDI provided the date of death (from which we determined age at death), underlying cause of death (UCOD), and any mention of MS as the cause of death (AMCOD) which included all causes (including underlying) mentioned in Part 1 and Part 2 of the standard U.S. Death Certificate.

2.3. Cause of Death

All causes of death were coded using the International Classification of Diseases version 10 codes (ICD-10) from the National Center for Health Statistics. (Center of Disease Control and Prevention) As in other studies, we present proportions of death due to cardiovascular disease, cancer, suicide, accidents, pneumonia, and septicemia, by age, race and sex. The ICD-10 codes corresponding to each disease class of interest are presented in Supplemental Table 1. Heron (2012)

For comparison, data about the U.S. general population were extracted from the table, “CDC Health Data Interactive Mortality by underlying and multiple cause, ages 18+: US, 1999-2010” created by the National Center for Health Statistics, Centers for Disease Control (CDC) and Prevention. (Center of Disease Control and Prevention)

2.4. Statistical Analyses

Age was rounded down to the closest integer. For age at enrollment and death we used the age groupings 25-34, 35-44, 45-54, 55-64, 65-74, 75+ years because the CDC groups their cause-specific mortality data in this manner, allowing comparisons between the U.S. population and NARCOMS deaths. (Center of Disease Control and Prevention)

Descriptive statistics and mortality rates per 100,000 persons were used to characterize mortality within the NARCOMS cohort. Because those not matched to the NDI were assumed alive as of December 31, 2009, using proportions that died is equivalent to survival and cumulative death probabilities for the enrolled cohort. Cox proportional hazard models were used to examine the effects of age, sex and disability on survival. For the survival models, the date of death or December 31, 2009 was used as the date of censoring, whichever came first.

The proportionate mortality rate (PMR) was calculated by dividing the proportion of cause-specific deaths (UCOD) in our cohort by the expected proportion of deaths from that cause, stratified by sex, race and age group. The PMR is useful for comparisons within the NARCOMS population. We used the normative U.S. population to generate an expected number of deaths based on the person-years of follow-up for each UCOD stratified by age group, race and sex in order to compare the mortality from within the NARCOMS population to the general U.S.; effectively a direct standardized rate comparison. We computed these expected deaths for the causes of death shown in Supplemental Table 1. We did not adjust the U.S. general population for MS deaths because their contribution to the deaths overall is quite small and makes these comparisons slightly conservative. All statistical analyses were conducted using SAS Version 9.3 (SAS Institute Inc., Cary, NC).

Table 1.
Baseline Data at Enrollment for Survivors and Decedents in NARCOMS Database.

Characteristic	Survivors (n=29518)	Decedents (n=2927)*
Female, n (%)	23344 (75.6)	1521 (49.7)
Education, n (%)		
High school or less	10919 (41.6)	1525 (53.8)
> High school	15321 (58.4)	1311 (46.2)
Employed	13376 (45.9)	329 (11.5)
Race, n (%)		
African American	1299 (4.2)	141 (4.6)
Caucasian	27345 (88.5)	2729 (89.5)
Other	2240 (7.3)	181 (5.9)
Age at Enrollment, mean (SD)	46.3 (10.1)	55.8 (11.6)
Age at Diagnosis, mean (SD)	37.6 (28.4)	39.1 (11.2)
Age at Death or Dec 2009, mean (SD)	54.0 (10.7)	61.4 (11.9)
Years Followed, mean (SD)	8.6 (3.1)	6.1 (3.0)
PDDS* at enrollment, n (%)		
Normal (0)	4772 (16.8)	59 (2.1)
Mild Disability (1)	3423 (12.0)	73 (2.6)
Moderate Disability (2)	2535 (8.9)	90 (3.2)
Gait Disability (3)	4879 (17.1)	189 (6.6)
Early Cane (4)	4321 (15.2)	289 (10.1)
Late Cane (5)	3425 (12.0)	396 (13.9)
Bilateral Support (6)	2208 (7.8)	433 (15.2)
Wheelchair/Scooter and Bedridden (7&8)	2930 (10.2)	1320 (46.3)
PDDS at Enrollment, median (IQR)	3 (1, 5)	6 (5, 7)
Final PDDS assessed (years), median (IQR)	4 (1, 6)	7 (5, 7)

NARCOMS=North American Research Committee on Multiple Sclerosis; PDDS=Patient Determined Disease Steps; SD=Standard Deviation; IQR=Interquartile Range

* denominators may differ due to missing values.

3. Results

3.1. Participants

At the end of 2009, NARCOMS had 34,364 participants ever enrolled. Approximately 4.4% ($n=1504$) did not provide age information or the data were unreliable (ages that were based on dates of birth that lead to unreasonable old or negative ages) and were excluded. Additionally, to compare with the CDC data, only participants aged 25 years and older were included in the analyses (Supplemental Fig. 1). Of the 3071 matched deaths, 2927 were considered in this analysis. Of those 2927 deaths, 2180 (74.5%) had a status code of 1 (true match). The decedents had an average (SD) number of 2.8 (1.6) cause of deaths listed on their death certificates with a median of 3 and a maximum of 12.

On average, the NARCOMS population had follow-up information from enrollment for a period of 8.4 years (range: 0.5-17 years). Table 1 shows the basic demographics of the NARCOMS survivors and decedents. Given the large study population, all comparisons between decedents and survivors were statistically significantly different although some differences were not clinically relevant. Compared to decedents, survivors were younger at enrollment, younger at diagnosis, more likely to be female, and had higher levels of education. Survivors also had lower disability at entry into NARCOMS, with about 30% of survivors and 75% of decedents receiving PDDS scores of 6–8 that indicate severe disability.

3.2. Mortality Rates

The distributions of deaths by age at enrollment and sex for the three racial categories of NARCOMS participants are presented in Table 2. The mortality risks increased with age as expected. Males had higher mortality rates than females but as expected the ratio of male to female mortality declined with increasing age. The mean (SD) age at death among males was 63.3 (11.8) years as compared to 59.4 (11.9) for females ($p<0.0001$), which reflects the older age at enrollment of males in the deceased NARCOMS participants (57.6 (11.5) in males versus 53.9 (11.5) in females). African Americans had slightly higher mortality rates than Caucasians or other races, particularly at younger ages.

Fig. 1 (a and b) shows the proportion dying over the follow-up period by sex, age and disability (PDDS) at enrollment to assess the risk from a common starting point, enrollment. The risk of death associated with higher levels of disability can be seen within all age and sex groups. To account for varying follow-up time from enrollment, we assessed mortality via proportional hazards regression analysis based on years of follow-up from enrollment by age and PDDS (hazard ratio, HR [95% confidence interval]). Older age groups at enrollment compared to younger (55-64 years to 25-34 years, 2.7 [2.17, 3.47]; 65-74 years, 4.4 [3.47, 5.65]; 75+ years, 8.4 [6.46, 11.11]), male sex (1.7 [1.59, 1.85]), and PDDS levels compared to Normal (Late Cane, 4.8 [3.67, 6.43]; Bilateral Support, 6.7 [5.14, 9.01]; Wheelchair/Scooter and Bedridden, 12.9 [9.96, 17.08]), all had an increased risk of death (all $p<0.0001$). Race, however, was not associated with the risk of death ($p=0.139$) after adjustment for age, sex and PDDS.

Table 3 shows the mortality rates by age group, sex and disability measured by the PDDS. For a given age group, as the level of disability increases the mortality rate increases. There was a similar or greater increase in mortality rates for a given disability level as age increased. For example amongst those with no disability (PDDS=0), females aged 25-39 years had a mortality rate of 3.16 per 100,000 while females aged 65-74 had a mortality rate of 93.02 per 100,000 (relative risk ($RR=29$). By comparison, for the females aged 25-39 years, the mortality rate rose from 3.16 per 100,000 for those with no disability to 127.70 per 100,000 for those with a PDDS of 7 or higher ($RR=40$). A similar pattern was seen for males. Overall, the ratio of male death rates to female was 2.7, but this was higher at younger ages and lower disability levels.

3.3. Cause-specific Mortality

In 41.4% of the NARCOMS decedents, MS was reported as the UCOD (Table 4). Approximately one-third of decedents had no mention of MS on their death certificate whereas over two-thirds ($n=2056$) of the decedents had a mention of MS as a cause of death reported. For UCOD other than MS, the most common

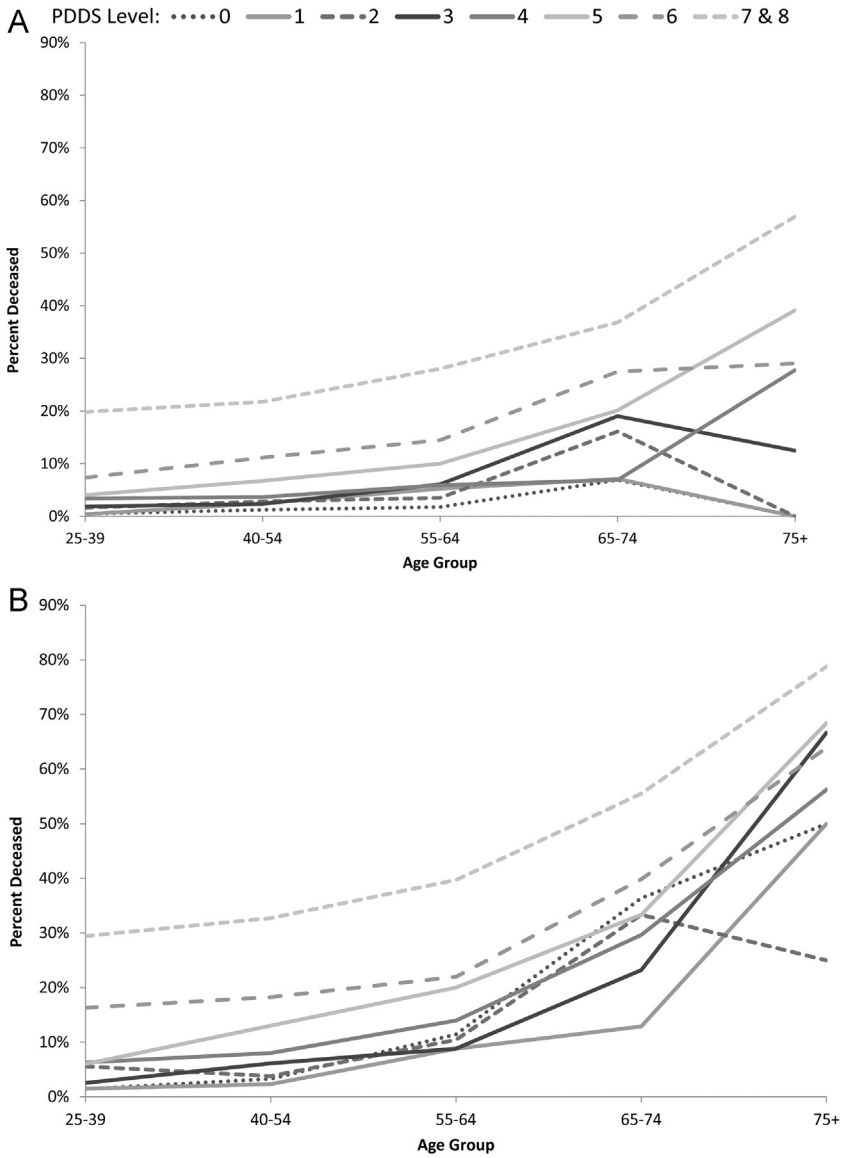

Fig 1.. Percent deceased by Patient Determined Disease Steps (PDDS) at Enrollment, Age Group and Sex. (A) Females and (B) Males.

Table 2.
Age group at enrollment, sex and racial distribution of NARCOMS[a] participants.

	Age Group	Female N (%died)	Male N (%died)	Rate Ratio Male:Female
African American	25-44	503 (4.6)	114 (14.0)	3.1
	45-54	300 (7.7)	124 (17.7)	7.1
	55-64	109 (15.6)	45 (24.4)	1.6
	65-74	17 (29.4)	18 (38.9)	1.3
	≥ 75	2 (50.0)	1 (0.03)	0
White	25-44	8374 (2.9)	2101 (7.4)	2.5
	45-54	6826 (6.3)	2660 (13.8)	2.2
	55-64	2889 (11.6)	1609 (22.9)	2.0
	65-74	684 (24.4)	654 (43.1)	1.8
	≥ 75	132 (43.9)	145 (67.6)	1.5
Other Races	25-44	459 (1.7)	145 (6.9)	4.0
	45-54	315 (3.5)	152 (16.5)	4.7
	55-64	138 (12.3)	77 (24.7)	2.0
	65-74	26 (23.1)	42 (33.3)	1.4
	≥ 75	11 (45.5)	10 (90.0)	2.0

[a] North American Research Committee on Multiple Sclerosis

causes were major cardiovascular disease and cancer, although causes of death in the Other category were responsible for about 21% of deaths. Overall, the age, race, sex and cause-adjusted standardized mortality rate (SMR) using the United States general population was 1.401 (95% CI 1.34-1.47) indicating about 40% excess mortality in the NARCOMS cohort compared to the U.S. general population.

The distribution of UCOD differed markedly by age group (Table 5) reflecting the increase in the impact of comorbidities on mortality with age. MS as the UCOD declined by approximately 45% in both sexes for the participants 75 years and above in comparison to those aged 25-39 years. Cancer and cardiovascular causes became more frequent with increasing age while suicides decreased, becoming nonexistent (or not reported) in the older age groups for females and under 1% for males.

Breaking down the UCOD by age, sex and race provided additional information on cause-specific mortality. Supplemental Table 2 provides the expected number of deaths and observed number of deaths by age, race, and sex for NARCOMS enrollees. This table shows the age, race and sex-specific expected number of deaths when the general U.S. population mortality rates are applied to the NARCOMS population. The categories in the table can

Table 3.
Mortality rates by age group at enrollment, sex and PDDS and the ratio of males to females.

PDDS Level	Age Group	Female		Male		Female	Male	Ratio M/F
		Alive Years FU	**Dead** Years FU	**Alive** Years FU	**Dead** Years FU	Rate/100,000	Rate/100,000	
0=Normal	**25-39**	20818	66	3491	42	3.16	11.89	3.76
	40-54	8217	84	1780	33	10.12	18.20	1.80
	55-64	1680	23	477	49	13.51	93.16	6.90
	65-74	195	20	63	18	93.02	222.22	2.39
	≥ 75	1	–	20	5	–	200.00	–
1=Mild Disability	**25-39**	12511	15	2826	22	1.20	7.72	6.45
	40-54	7001	141	1918	22	19.74	11.34	0.57
	55-64	2140	101	725	51	45.07	65.72	1.46
	65-74	312	21	287	31	63.06	97.48	1.55
	≥ 75	1	–	24	14	–	368.42	–
2=Moderate Disability	**25-39**	8560	105	1592	73	12.12	43.84	3.62
	40-54	5731	130	1610	45	22.18	27.19	1.23
	55-64	1742	41	475	49	22.99	93.51	4.07
	65-74	213	32	129	21	130.61	140.00	1.07
	≥ 75	5	–	64	16	–	200.00	–
3=Gait Disability	**25-39**	15191	183	4263	68	11.90	15.70	1.32
	40-54	11199	207	4418	218	18.15	47.02	2.59
	55-64	3345	185	1880	133	52.41	66.07	1.26
	65-74	425	68	428	92	137.93	176.92	1.28
	≥ 75	66	3	24	14	43.48	368.42	8.47
4=Early Cane	**25-39**	9686	231	3142	169	23.29	51.04	2.19
	40-54	11114	329	4234	280	28.75	62.03	2.16
	55-64	4348	223	2344	296	48.79	112.12	2.30
	65-74	882	47	560	160	50.59	222.22	4.39
	≥ 75	121	33	66	64	214.29	492.31	2.30
5=Late Cane	**25-39**	6492	184	2239	96	27.56	41.11	1.49
	40-54	8448	439	3743	421	49.40	101.10	2.05
	55-64	4365	378	2175	403	79.70	156.32	1.96
	65-74	1033	177	780	265	146.28	253.59	1.73
	≥ 75	120	64	53	93	347.83	636.99	1.83
6=Bilateral Support	**25-39**	3429	163	1174	190	45.38	139.30	3.07
	40-54	5253	449	2583	404	78.74	135.25	1.72
	55-64	3370	425	1828	345	111.99	158.77	1.42
	65-74	877	222	769	340	202.00	306.58	1.52
	≥ 75	192	57	115	143	228.92	554.26	2.42
7,8=Wheelchair/Scooter and Bedridden	**25-39**	4324	633	1977	471	127.70	192.40	1.51
	40-54	6371	1130	4066	1197	150.65	227.44	1.51
	55-64	4042	982	2735	1114	195.46	289.43	1.48
	65-74	1363	452	1369	942	249.04	407.62	1.64
	≥ 75	263	209	146	239	442.80	620.78	1.40
Total		**175446**	**8252**	**62592**	**8648**	**44.92**	**121.39**	**2.70**

FU=Follow-up; PDDS=Patient Determined Disease Steps

Table 4.
Underlying Cause of Death among NARCOMS[a] decedents (n=2927).

Underlying Cause of Death	N (%)
Multiple Sclerosis	1212 (41.4)
Other	606 (20.7)
Major Cardiovascular Disease	491 (16.8)
Cancer	334 (11.4)
Pneumonia	123 (4.2)
Septicemia	66 (2.3)
Suicide	48 (1.6)
Accident (Unintentional Injury)	47 (1.6)

[a] NARCOMS=North American Research Committee on Multiple Sclerosis

be combined to compute different subgroup comparisons. For example, we observed fewer accidents than expected based on U.S. population rates for those below 55 years and more than expected after 55 years. The risks were reduced more for females than males and substantially more for African Americans than other races. Cancer-related deaths appeared to be increased slightly before the age of 55 years, but fewer cancer-related deaths than expected in those over the age of 55 years. Again, the reductions were larger for females than males, but did not differ between races. Major cardiovascular deaths were increased at all ages except those 75 years and over in both sexes, but African Americans had slightly fewer cardiovascular deaths than expected. Deaths from pneumonia and septicemia were higher at all ages, but the excess declined with age. Other causes of death were higher until age 65 years and then they were lower than expected with slight differences between males and females and only African Americans showed fewer deaths from other causes than expected.

4. Discussion

We compared overall and cause-specific mortality among U.S. NARCOMS participants to the U.S. population from 1999-2010 stratified by age, race and sex. While the adverse impact of disability on mortality was not surprising, the magnitude of the disability effect matched the increase in death experienced with aging over decades. We have shown that regardless of age or sex, increased disability carries an increased risk of death, possibly due to reduced physical

Table 5.
Underlying Cause-Specific Deaths Among NARCOMS participants, n (% of deaths), for Selected Disease Categories Stratified by Age Group at Enrollment and Sex.

Age Group	Sex	Accidents	Cancer	MS	Major CV	Other	Pneumonia	Septicemia	Suicide
25-39	**Female**	3 (1.0)	21 (7.1)	141 (48.0)	29 (9.9)	72 (24.5)	10 (3.4)	8 (2.7)	10 (3.4)
	Male	6 (3.1)	9 (4.7)	110 (57.6)	23 (12.0)	24 (12.6)	6 (3.1)	7 (3.7)	6 (3.1)
40-54	**Female**	9 (1.8)	69 (14.0)	214 (43.3)	61 (12.3)	105 (21.3)	11 (2.2)	16 (3.2)	9 (1.8)
	Male	10 (2.3)	33 (7.7)	199 (46.4)	73 (17.0)	81 (18.9)	14 (3.3)	13 (3.0)	6 (1.4)
55-64	**Female**	4 (1.0)	64 (16.1)	147 (37.0)	71 (17.9)	88 (22.2)	15 (3.8)	5 (1.3)	3 (0.8)
	Male	9 (2.2)	52 (12.5)	161 (38.7)	76 (18.3)	81 (19.5)	20 (4.8)	5 (1.2)	12 (2.9)
65-74	**Female**	2 (1.1)	32 (16.8)	62 (32.5)	41 (21.5)	41 (21.5)	7 (3.7)	6 (3.1)	−(−)
	Male	3 (0.9)	39 (11.8)	123 (37.2)	76 (23.0)	61 (18.4)	23 (7.0)	4 (1.2)	2 (0.6)
75+	**Female**	−(−)	3 (4.4)	19 (27.5)	17 (24.6)	20 (29.0)	8 (11.6)	2 (2.9)	−(−)
	Male	1 (0.9)	12 (10.4)	36 (31.3)	24 (20.9)	33 (28.7)	9 (7.8)	−(−)	−(−)

NARCOMS=North American Research Committee on Multiple Sclerosis; MS=Multiple Sclerosis; CV=Cardiovascular

activity and consequently increased cardiovascular risks. Bronnum-Hansen et al., (2004) This illustrates the mortality toll MS disability exerts, which heretofore has been relatively hidden.

We did not present survival curves by age at death since NARCOMS is a registry population and our population represents a cross-section of participants who are alive to register. This confounds our ability to estimate a true time until death and our survival analyses suffer from an immortal time bias. Suissa (2008) That is, registrants in NARCOMS cannot die at ages younger than their enrollment age. This tends to bias survival upward. However, our findings are consistent with prior studies that have estimated that persons with MS have a reduced life expectancy of five to ten years. Confavreux and Vukusic (2008) Furthermore, we saw the expected differences in mortality by age and sex. (Grytten Torkildsen et al., 2008; Hirst et al., 2008; Koch-Henriksen et al., 1998; Lalmohamed et al., 2012; Smestad et al., 2009; Nielsen et al., 2006; Sadovnick et al., 1991) The early excess mortality in these MS participants appears in essentially every category but accidents. This suggests that the impact of MS on shortening the life expectancy may be greater than that estimated here. Our adjusted standardized mortality ratio showed an excess rate of death of 40%, but the excess varies by age and is less pronounced as common comorbidities increase the mortality rates at older ages.

We also found that NARCOMS participants aged 25 to 54 years had a higher proportion of deaths from cancer while decedents aged over 55 years experienced less cancer deaths than expected. Pneumonia, septicemia, suicide and other causes of death all are increased in MS, but declined relative to the U.S. general population as the population aged and experienced their own consequences of aging. The underlying causes of infection and suicide might also be considered consequences of MS and thus excess mortality from MS spans all ages.

Cardiovascular deaths were elevated relative to the U.S. population, as observed in the Danish MS population. Bronnum-Hansen et al., (2004) However, due to the high mortality rate from MS, a lower PMR for cardiovascular deaths in this cohort compared to a general population is expected. The declining excess of cardiovascular disease mortality as the UCOD is probably not due to risks improving amongst MS patients, but rather the general population aging and catching up with their cardiovascular risk. The early excess of cardiovascular deaths is consistent with reports of increased incidence of cardiovascular disease in European and Canadian MS populations, (Christiansen et al., 2010; Jadidi et al., 2013; Marrie et al., 2013) and may be due to the cumulative effects of decreased physical activity, overweight (Ranadive et al., 2012) and comorbid diseases such as hypertension. Marrie et al., (2008) This suggests greater effort should be directed to evaluating and reducing cardiovascular risks and potentially other comorbidities, such as diabetes, and obesity, that are major causes of death in the U.S., regardless of MS status.

The decline of suicides by age group could be due to underreporting at older ages since it is more difficult to verify amid a number of comorbidities, or due to declining prevalence of mental illness at older ages. Marrie et al., (2008) Attention should focus on potential prevention efforts, as 3% of the deaths in those under 45 years and 1.5% under 55 are still due to clinically relevant risks.

The excess cancer deaths appearing only in the youngest age groups are interesting and important, because they could suggest earlier unmasking of cancer due to drug therapy or treatment-related cancers, although we have not examined treatment-related factors herein. Unlike cancer incidence, which could be influenced by the degree of exposure to medical care and opportunities for ascertainment, cancer mortality should be less subject to ascertainment biases. If there is an excess of cancer deaths in younger persons with MS, better understanding of the reasons may be warranted. Similar to our findings in older ages, studies in Canada, Denmark and the U.S. have reported lower than expected deaths due to cancer. (Koch-Henriksen et al., 1998; Redelings et al., 2006; Sadovnick et al., 1991) These findings could be explained by an age effect in that cancer commonly develops later in life and the decreased life expectancy of participants results in insufficient time for cancer to develop. This is a particularly important consideration when using mortality data to evaluate long-term adverse impacts of disease-modifying therapies (DMT); so that risks are not underestimated. Conversely, the increased mortality found amongst younger MS patients may lead to the appearance of excess mortality due to therapy when it is secondary to another mechanism.

A major strength of this study is that it is one of the largest studies of MS deaths looking at age, sex and race cause-specific mortality with all deaths occurring after the introduction of DMTs. This study was also one of the first that examined both UCOD and AMCOD. Most NARCOMS decedents had more than one disease listed on their death certificate (77%) and the number of diseases listed for all NARCOMS decedents was 2.8, similar to the U.S. population, validating the comparison between the groups (Redelings et al., 2006).

Because this study has methodological limitations, our results should be interpreted cautiously. Our findings were compared to those for the U.S. population, but the large differences raise the question of the impact of the disease-specific selection. NARCOMS is a volunteer registry and may be subject to participation bias resulting in a sample that does not accurately represent the U.S. MS population. However, the cause-specific mortality should be minimally related, if at all to the voluntary enrollment in NARCOMS. Furthermore, the findings are consistent with other mortality studies in the U.S. and abroad. Approximately 85% of NARCOMS participants are initially diagnosed with relapsing-remitting MS. While we did not control for clinical course, the strong relationship of clinical course to disability suggests disease type of MS would show increased risks of death for SPMS or PPMS compared to RRMS if for no other reason than an impact of age on death rates. DMT use was

not controlled for or evaluated in this study.

We showed that U.S. persons with MS registered with NARCOMS who died before the end of 2009 had increased mortality risk at older ages, in males and with higher levels of disability. Suicides declined with age and increased deaths due to cardiovascular disease and cancer occurred at older ages. The cohort had a lower proportion of cardiovascular disease and cancer mortality and a higher proportion of pneumonia and septicemia mortality as the UCOD compared to the demographically similar U.S. population. However, this cohort had increased deaths observed compared to expected deaths based on the general U.S. population for nearly all causes of death in spite of the high proportion of MS deaths.

Funding Acknowledgements

The NARCOMS registry is supported in part by the Consortium of Multiple Sclerosis Centers and its Foundation. This study was supported by Bayer Pharmaceuticals.

Acknowledgements

The authors thank Rachel Tanner, Lindsey Hornung and Jing Wang for their technical assistance.

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.2015.07.008.

References

Evans C, Beland SG, Kulaga S, et al. Incidence and prevalence of multiple sclerosis in the Americas: a systematic review. Neuroepidemiology 2013;40:195–210.
Peterson JW, Trapp BD. Neuropathobiology of multiple sclerosis. Neurologic clinics 2005;23 107-29.
Kingwell E, van der Kop M, Zhao Y, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. *Journal of neurology, neurosurgery, and psychiatry*. 2012;83:61–6.
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. *Multiple sclerosis*. 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. *Journal of neurology, neurosurgery, and psychiatry*. 2008;79:1016–21.
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. *Journal of neurology, neurosurgery, and psychiatry*. 1998;65:56–9.
Lalmohamed A, Bazelier MT, Van Staa TP, et al. Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study. European journal of neurology: the official journal of the European Federation of Neurological Societies 2012;19:1007–14.
Leray E, Morrissey S, Yaouanq J, et al. Long-term survival of patients with multiple sclerosis in West France. *Multiple sclerosis*. 2007;13:865–74.
Pittock SJ, Mayr WT, McClelland RL, et al. Change in MS-related disability in a population-based cohort: a 10-year follow-up study. *Neurology*. 2004;62:51–9.
Ragonese P, Aridon P, Mazzola MA, et al. Multiple sclerosis survival: a population-based study in Sicily. European journal of neurology: the official journal of the European Federation of Neurological Societies 2010;17:391–7.
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. *Multiple sclerosis*. 2009;15:1263–70.
Sumelahti ML, Hakama M, Elovaara I, Pukkala E. Causes of death among patients with multiple sclerosis. *Multiple sclerosis*. 2010;16:1437–42.
Wallin MT, Page WF, Kurtzke JF. Epidemiology of multiple sclerosis in US veterans. VIII. Long-term survival after onset of multiple sclerosis. Brain: a journal of neurology 2000;123(Pt 8):1677–87.
Redelings MD, McCoy L, Sorvillo F. Multiple sclerosis mortality and patterns of comorbidity in the United States from 1990 to 2001. Neuroepidemiology 2006;26 102-7.
Kaufman DW, Reshef S, Golub HL, et al. Survival in commercially insured multiple sclerosis patients and comparator subjects in the U.S. Multiple Sclerosis and Related Disorders 2014;3:364–71.
Phadke JG. Survival pattern and cause of death in patients with multiple sclerosis: results from an epidemiological survey in north east Scotland. *Journal of neurology, neurosurgery, and psychiatry*. 1987;50:523–31.
Nielsen NM, Rostgaard K, Rasmussen S, et al. Cancer risk among patients with multiple sclerosis: a population-based register study. International journal of cancer Journal international du cancer 2006;118:979–84.
Sadovnick AD, Eisen K, Ebers GC, Paty DW. Cause of death in patients attending multiple sclerosis clinics. *Neurology*. 1991;41:1193–6.
Bronnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain: a journal of neurology 2004;127:844–50.
Goodin DS, Ebers GC, Cutter G, et al. Cause of death in MS: long-term follow-up of a randomised cohort, 21 years after the start of the pivotal IFNbeta-1b study. BMJ open 2012:2.
Marrie RA, Cutter G, Tyry T. Campagnolo D and Vollmer T. Validation of the NARCOMS registry: diagnosis. *Multiple sclerosis*. 2007;13:770–5.
Consortium of Multiple Sclerosis Centers. NARCOMS Multiple sclerosis registry.
Marrie RA, Goldman M. Validity of performance scales for disability assessment in multiple sclerosis. *Multiple sclerosis*. 2007;13:1176–82.
Learmonth YC, Motl RW, Sandroff BM, Pula JH, Cadavid D. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMC neurology*. 2013;13:37.
National Center of Health Statistics Division of Vital Statistics. About the National Death Index. Hyattsville, MD: National Center for Health Statistics, 1999.
Center of Disease Control and Prevention. Mortality by underlying and multiple cause, ages 18+: US, 1981-2009 National Center for Health Statistics.
Heron M. Deaths: leading causes for 2008. National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System 2012;60:1–94.
Suissa S. Immortal time bias in pharmaco-epidemiology. *American journal of epidemiology*. 2008;167:492–9.
Confavreux C, Vukusic S. The clinical epidemiology of multiple sclerosis. *Neuroimaging clinics of North America*. 2008;18:589–622 ix-x.
Christiansen CF, Christensen S, Farkas DK, Miret M, Sorensen HT, Pedersen L. Risk of arterial cardiovascular diseases in patients with multiple sclerosis: a population-based cohort study. Neuroepidemiology 2010;35:267–74.
Jadidi E, Mohammadi M, Moradi T. High risk of cardiovascular diseases after diagnosis of multiple sclerosis. *Multiple sclerosis*. 2013;19:1336–40.
Marrie RA, Yu BN, Leung S, et al. Prevalence and incidence of ischemic heart disease in multiple sclerosis: A population-based validation study. Multiple Sclerosis and Related Disorders 2013;2:355–61.
Ranadive SM, Yan H, Weikert M, et al. Vascular dysfunction and physical activity in multiple sclerosis. *Medicine and science in sports and exercise*. 2012;44:238–43.
Marrie R, Horwitz R, Cutter G, Tyry T. Campagnolo D and Vollmer T. Comorbidity, socioeconomic status and multiple sclerosis. *Multiple sclerosis*. 2008;14:1091–8.
Redelings MD, Sorvillo F, Simon P. A comparison of underlying cause and multiple causes of death: US vital statistics, 2000-2001. *Epidemiology*. 2006;17:100–3.