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Multiple Sclerosis Mortality and Patterns of Comorbidity in the United States from 1990 to 2001

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Abstract
Multiple sclerosis (MS) is a neurodegenerative condition that can result in cognitive and physical disability and shortened life expectancy. However, population-based information is lacking regarding the mortality burden from MS in the United States. We investigated trends in MS mortality rates and examined important comorbidities in the United States from 1990 to 2001. MS deaths were matched by age, sex, and race/ethnicity with randomly selected deaths from other conditions for matched odds ratio comparisons. The overall age-adjusted mortality rate from MS was 1.44/100,000 population. MS mortality rates increased throughout the study period. MS mortality rates were higher in whites than in any other racial/ethnic group, followed by Blacks, Hispanics, American Indians/Alaska Natives, and Asians and Pacific Islanders. Observed mortality rates were more than 10 times lower in Asians and Pacific Islanders than in whites. The odds of pressure ulcers, urinary tract infections, and pneumonia/influenza being reported on the death certificate were higher in MS deaths than in matched controls.

Introduction

Multiple sclerosis (MS) is an autoimmune disease causing demyelination of the central nervous system. While many individuals with MS experience mild symptoms, MS can result in severe disability from a variety of symptoms, including memory loss, cognitive dysfunction, depression, fatigue, urinary incontinence or retention, vision loss, poor muscle control and coordination, muscle spasticity and muscle weakness [1–3]. Ultimately, MS can cause early death and has been estimated to shorten life expectancy by 6–7 years [4, 5].

Recent estimates place the prevalence of multiple sclerosis in the United States (US) between 58 and 85 cases per 100,000 persons and the incidence at 3.2 cases per 100,000 person years [6–8]. MS incidence and prevalence are known to be higher in females than males [6, 8]. Genetic factors play an important role in determining an individual's risk of developing MS [9, 10]. However, the pattern of inheritance is not Mendelian, and it is thought that genetic factors predisposing certain individuals to MS may be turned on by environmental exposures [9, 10]. Several exposures have been suggested as risk factors, including lack of exposure to ultraviolet radiation, low vitamin D_3 levels, dietary fat/fatty acid consumption, viral infection, smoking, exposure to organic solvents, and dairy milk consumption [11–16].

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Although projections of the mortality burden from MS have been published, little population-based information is available on the incidence and mortality burden of MS in the US [17]. It is important to understand trends in MS mortality in order to better understand the impact of MS on the health of Americans and to identify groups at highest risk of death. Mortality trends may reflect trends in MS incidence or in treatment effectiveness. In addition, understanding important comorbidities contributing to death may allow interventions which prolong survival. We used national vital records data to examine trends in MS mortality in the US from 1990 to 2001.

Methods

Deaths due to MS in the US were identified using national multiple cause of death (MCOD) data [18]. For each of the 50 states and the District of Columbia, completion of death certificates is required by law, including the assignment of a cause of death or sequence of events leading to death as determined by a physician. MCOD files used ICD-9 codes to describe causes of death from 1990 to 1998, and ICD-10 codes from 1999 to 2001 [19, 20]. Deaths due to MS were defined as any deaths for which ICD-9 code 340 or ICD-10 code G35 was reported for the underlying cause of death or any of the contributing causes of death. Demographic information (age, sex, race/ethnicity, state of residence), month and year of death as well as comorbid causes of death were obtained from MCOD files for all deaths which met the case definition.

Information about the size and demographic breakdown (by age, sex, and race/ethnicity) of the US population for each year from 1990 to 2001 was obtained from censal and intercensal year estimates with bridged race data [21–23]. We divided the US population into 5 racial/ethnic categories: non-Hispanic White, Hispanic, non-Hispanic Black, non-Hispanic Asian/Pacific Islander, and non-Hispanic American Indian/Alaska Native.

Crude MS mortality rates per 100,000 population were calculated for each age group (<1, 1–4, 5–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, 85+), gender, and racial/ethnic group. Non-US residents were excluded from rate calculations. Age-adjusted mortality rates and rate ratios were calculated by gender and race/ethnicity using the age distribution of the 2000 US population as a standard [24]. Small cells (less than 5 observations) were collapsed into larger cells in age-adjusted rate and rate-ratio calculations to stabilize the variance. Poisson regression analysis was used to examine temporal trends in MS mortality rates. Temporal trends were examined in both genders and by racial/ethnic group and geographic region. Boundaries for geographic regions of the US were taken from *Health, United States, 2004* [25]. Non-MS deaths in the US from 1990 to 2001 were randomly selected and matched to MS deaths on age, sex, and race/ethnicity (using 1:1 matching) for matched odds ratio comparisons of the relative involvement of comorbid causes of death. Comorbidities examined included leading causes of death in the general population and conditions known to be associated with MS. All analyses were conducted using SAS 8.2 software.

Table 1. Total deaths from MS and crude MS mortality rates per 100,000 population in the US by demographic group, 1990–2001

	Frequency	Crude rate
Sex		
Male	15,822 (35.4%)	1.01
Female	28,815 (64.6%)	1.76
Race/ethnicity		
White	39,687 (88.9%)	1.70
Hispanic	826 (1.9%)	0.23
Black	3,944 (8.8%)	1.01
Asian/Pacific Islander	114 (0.3%)	0.10
Native American/Alaska Native	66 (0.2%)	0.26
Age group, years[1]		
<1	3 (0.0%)	0.01
1–4	3 (0.0%)	0.00
5–14	19 (0.0%)	0.00
15–24	126 (0.3%)	0.03
25–34	979 (2.2%)	0.20
35–44	4,591 (10.3%)	0.90
45–54	9,601 (21.5%)	2.49
55–64	10,374 (23.2%)	3.89
65–74	10,863 (24.3%)	4.88
75–84	6,735 (15.1%)	4.93
85+	1,342 (3.0%)	2.99
Total	44,637	1.39

[1] Age information was missing for one individual.

Results

A total of 27,572,153 deaths were reported in the US from 1990 to 2001. MS was reported as a cause of death for 44,637 persons (0.2%). For 27,319 MS deaths (61.2%), MS was reported as the underlying cause of death. The age-adjusted mortality rate from MS from 1990 to 2001 was 1.44 deaths per 100,000 population.

Mortality rates increased with age, reaching a peak in individuals aged 75–84 years, then dropping slightly in individuals ≥85 years (table 1). The mean age of death from MS was 60.9 years, and the majority of deaths from MS occurred in persons less than 65 years old (median age = 61, lower quartile = 51, upper quartile = 72). The majority of MS deaths were observed in females (table 1).

Poisson regression analyses showed an increase (fig. 1) in overall age-adjusted mortality rates from MS during 1990–2001 (coefficient = 0.0214, SE = 0.0014, 95% CI = 0.0187–0.0241). Mortality rates also increased in both males and females, in whites, Hispanics, and Blacks (for Asians/Pacific Islanders and American Indians/Alaska

Table 2. Results of Poisson regression analysis of time trends in age-adjusted MS mortality rates in the US by geographic and demographic groups from 1990 to 2001

	Coefficient	SE	95% CI
Sex			
Male	0.012	0.0023	0.008–0.017
Female	0.027	0.0017	0.024–0.030
Race/ethnicity			
White	0.024	0.0015	0.021–0.027
Hispanic	0.027	0.0103	0.007–0.047
Black	0.027	0.0047	0.018–0.036
Geographic Area			
Midwest	0.024	0.0026	0.019–0.029
Northeast	0.015	0.0028	0.010–0.021
South	0.034	0.0028	0.028–0.039
West	0.014	0.0029	0.009–0.020

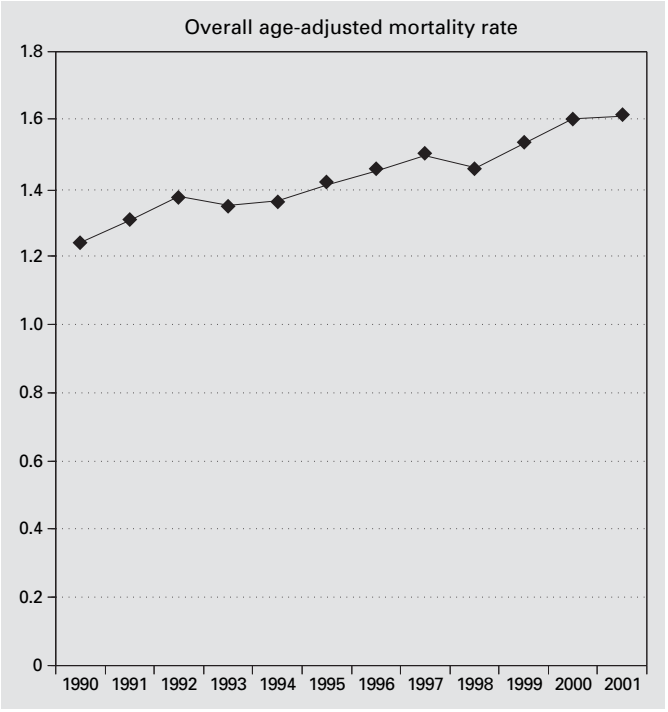

Fig. 1. MS mortality rates per 100,000 population by year in the US 1990–2001.

Table 3. Age-adjusted mortality rates and rate ratios (95% CI) for MS in the US, 1990–2001

	Age-adjusted mortality rate per 100,000 population	Age-adjusted mortality rate ratio (95% CI)
Sex		
Female	1.72	–
Male	1.13	0.66 (0.64–0.67)[1]
Race/ethnicity		
White	1.58	–
Hispanic	0.39	0.25 (0.23–0.26)[2]
Black	1.28	0.81 (0.78–0.83)[2]
Asian/Pacific islander	0.13	0.08 (0.07–0.10)[2]
Native American/Alaska Native	0.38	0.24 (0.24–0.31)[2]
Total	1.44	–

[1] Using females as the referent group.
[2] Using whites as the referent group.

Natives, insufficient observations were found to show trends over time), and in all 4 major geographical regions of the US (table 2).

Racial/ethnic differences were observed in age-adjusted MS mortality (table 3), with higher mortality rates observed among whites than among any other racial/ethnic group.

MS mortality rates were also considerably higher in Blacks than in Hispanics, Asians/Pacific Islanders, and American Indians/Alaska Natives. Mortality rates were lowest among Asians/Pacific Islanders (using whites as the referent group, rate ratio = 0.08, 95% CI = 0.07–0.10).

Table 4. Frequencies and odds ratios[1] of selected conditions as comorbid causes of death[2] ratios among MS deaths in the US, 1990–2001

	Frequency of condition	Matched odds ratio of condition being reported as a cause of death (95% CI)[2]
Cerebrovascular disease	2,371 (5.3%)	0.62 (0.59–0.66)
COPD	974 (2.2%)	0.48 (0.45–0.52)
Diabetes	2,386 (5.4%)	0.61 (0.58–0.64)
Hypertension	1,366 (3.1%)	0.63 (0.59–0.68)
Ischemic heart disease	4,863 (10.9%)	0.44 (0.42–0.45)
Malignant neoplasms	3,975 (8.5%)	0.16 (0.15–0.17)
Pneumonia/influenza	8,818 (19.7%)	3.70 (3.53–3.87)
Pressure ulcers	1,480 (3.3%)	13.78 (11.32–16.76)
Septicemia	4,488 (10.1%)	2.23 (2.12–2.36)
Suicide	274 (0.3%)	0.17 (0.15–0.20)
Urinary tract infection	3,749 (8.4%)	11.28 (10.08–12.62)

[1] Comparing MS deaths with a randomly selected sample of reported deaths matched by 5-year age group, sex, and race/ethnicity.
[2] Based on death certificate reporting.

Pneumonia/influenza comorbidity was reported in 8,818 (19.8%) of MS deaths (table 4) and was also common (n = 2,027, 20.0%) in MS deaths among individuals less than 50 years of age. Septicemia, urinary tract infections (UTIs), ischemic heart disease, cerebrovascular disease, and diabetes were also reported in a high proportion of MS deaths (table 4). Pressure ulcers, UTIs, pneumonia/influenza and septicemia were more likely to be reported on the death certificate in MS deaths than in randomly selected deaths from other conditions, even after matching for age, sex, and race/ethnicity (table 3). Septicemia was more likely to be reported in MS deaths with reported pressure ulcer involvement (odds ratio = 6.06; 95% CI = 5.43–6.77) or UTI involvement (odds ratio = 3.59; 95% CI = 3.31–3.89) than in MS deaths where pressure ulcers or UTIs were not mentioned on the death certificate.

Discussion

MS is an important cause of death in the US, resulting in nearly 45,000 deaths from 1990 to 2001. MS differs from many other chronic diseases in that the majority of its victims die before the age of 65.

While MS mortality in the US reportedly decreased during the 1970's [26], we observed steady increases in MS mortality in the US from 1990 to 2001. The observed increase in MS mortality was uniform in both sexes and across racial/ethnic groups and geographical regions. MS mortality data may serve as an important proxy for population-based incidence data. Trends in MS incidence in the US have been difficult to track, as incidence studies have tended to focus on US veterans or on small geographic subpopulations of the US (such as counties) [27–29]. The steady increase in MS mortality between 1990 and 2001 (despite improved treatment) may reflect an increase in MS incidence. Though a number of exposures have been hypothesized as risk factors for MS, it is beyond the scope of vital records data to confirm suspected increases in MS incidence or to identify actual causes of observed increases in mortality [11–16].

Nationwide, MS mortality rates were higher in women than in men, reflecting the higher MS incidence in women [6, 30]. MS mortality was higher in whites than in other racial/ethnic groups, followed by Blacks, Hispanics, American Indians/Alaska Natives and Asians/Pacific Islanders. Previous studies have suggested that the prevalence of MS may be considerably lower in Hong Kong, Japan, Taiwan and India than it is in the US [31–34]. The MS mortality rate in Asians/Pacific Islanders was less than one tenth of the observed mortality rate in whites. A difference of this magnitude is important to understand as it may shed light on possible risks or preventive factors for MS. Unfortunately, it is not possible to identify causes of decreased mortality rates from MS in Asians/Pacific Islanders using vital records data. Future research should investigate genetic and lifestyle factors which may protect Asians/Pacific Islanders from MS mortality.

The odds of pressure ulcers being reported on the death certificate was 13 times higher for reported MS deaths than for matched controls. This is consistent with an earlier study which found increased pressure ulcer morbidity in persons with MS [35]. Pressure ulcers are not a common cause of death. Thus, despite the increased odds of pressure ulcer involvement in MS deaths, pressure ulcers were reported as a cause of death for less than 4% of MS decedents. Pressure ulcers are unlikely to act as a cause of death directly, but they can allow for the development of potentially fatal septic infections. A strong association was noted between reported pressure ulcers and reported septicemia in MS deaths.

MS has been reported as a risk factor for UTI [35]. UTIs were noted as underlying or contributing causes of death in nearly 10% of reported MS deaths, and the odds of UTIs being reported on the death certificate were more than 10 times higher in MS deaths than in matched controls. In addition, an association was observed between UTIs and septicemia, suggesting that UTIs may lead to sepsis in individuals with MS. The frequent involvement of UTIs in MS deaths highlights the importance of preventive urological care for MS patients [36–38].

The odds of pneumonia/influenza being reported on the death certificate were higher in MS deaths than in matched controls. Elevated pneumonia/influenza mortality may be associated with the use of immunosuppressive steroid therapies in MS patients [39, 40]. Influenza vaccination is recommended for persons taking immunosuppressive medications and has been shown to generate an immune response against influenza in persons with MS [41]. Despite fears about the safety of vaccinating persons with MS, vaccination has not been found to cause MS relapses [42, 43]. Future research should address the extent to which preventive measures such as influenza vaccination are effective in reducing mortality from pneumonia/influenza in persons with MS.

A recent study suggests that as many as 2% of deaths in persons with MS may be caused by suicide [44]. However, we found that suicide was less likely to be reported in MS deaths than in non-MS deaths. Our data on suicide may be affected by reporting practices. Physicians might be unlikely to list MS as a cause of death for persons with MS who commit suicide if they perceive that MS plays an indirect role in causing suicide deaths. However, it is not possible to confirm this hypothesis using mortality data.

These data must be interpreted with caution for several reasons. Studies based on death certificate data have a unique set of limitations [45, 46]. Physicians typically do not receive training in how to fill out death certificates, and may often be unfamiliar with the decedent's medical history, or may not have time to fill out the death certificate carefully. Thus, reporting error may have introduced significant bias. Observed mortality rates from MS and observed frequencies of comorbid conditions such as pneumonia/influenza may be low due to underreporting. The use of vital records information did not permit us to assess morbidity from MS or to examine certain important variables, including treatment of individuals who died of MS.

MS is an important cause of death in the US, and MS mortality increased steadily throughout the study period. Strong racial ethnic disparities were observed, with mortality rates ten times higher in Whites than in Asians/Pacific Islanders. Future research should investigate the extent to which prevention of pressure ulcers, septicemia, UTIs and pneumonia/influenza in MS patients may help to prevent death from MS.

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