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Association of multiple sclerosis with risk of mortality among a nationally representative sample of adults in the United States

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Abstract

Background: Multiple sclerosis (MS) has been associated with increased mortality ratios, but few studies have investigated the independent association of MS with mortality.

Objective: To examine the prospective association of MS with risk of mortality in a nationally representative sample of U.S. adults.

Methods: This prospective study included 23,053 adults aged 45–79 years who participated in the National Health Interview Survey in 2002 and 2008. Physician-diagnosed MS was reported by participants during household interviews. These participants were linked to death records from survey date through December 31, 2015.

Results: Among the 23,053 participants included in this study, 120 reported a physician's diagnosis of MS, with a higher prevalence in females (0.85%) than in males (0.31%). During on average 9.4 years (maximum 13.8 years) of observation, 4208 deaths occurred. After adjustment for age, sex, race/ethnicity, socioeconomic factors, lifestyle factors, and BMI, participants with MS had an 80% higher risk of mortality (HR 1.80; 95% CI, 1.11–2.92), compared with those without MS. The association remained significant (HR 1.75; 95% CI, 1.07–2.87) after further adjustment for baseline diabetes, cardiovascular disease, chronic lung disease, and cancer.

Conclusion: In this nationally representative sample of U.S. adults, MS was associated with an increased risk of mortality.

Keywords: Multiple sclerosis, mortality, epidemiology

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Introduction

Multiple sclerosis (MS) is a complex, neurodegenerative disease characterized by demyelination of neurons[1] that affects nearly an estimated one million people in the United States.[2] Because a demyelinating event can occur anywhere in the central nervous system, there is considerable heterogeneity in symptoms and disease progression among people with MS.[3] This leads to high healthcare costs and poor outcomes. In the U.S., the total medical costs for patients with MS increased from $116 million in 2002 to $198 million in 2013, rising at a rate of $7.34 million annually.[4] In addition, people with MS have a higher rate of death compared with the general population.[5] Studies show that the median survival for people with MS is up to 10 years shorter compared to the general population.[6] The reason for the survival discrepancy between people with MS and the general population remains unclear.

People with MS experience a variety of symptoms including pain, fatigue, and changes in vision, cognition, and movement,[7] and have considerable comorbidity burden.[8] In addition, MS-specific mortality differs by race and age.[9] These factors may partially explain the discrepancy in survival between people with MS and the general population. A recent meta-analysis of standardized mortality ratios

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indicated that people with MS have higher mortality risk compared to the general population.[10] However, the included studies lacked information about potential confounders and therefore the independent association between MS and risk of mortality could not be estimated. To date, only two case control studies in the United Kingdom and Canada found that MS is associated with a 130–140% increase in risk of death when controlling for several factors.[11,12] Because mortality trends in MS may differ based on geographic location,[5] studies that aim to repeat these findings in different populations are urgently needed.

Therefore, the objective of this study is to examine the association of MS with risk of mortality independent of demographic, socioeconomic, lifestyle factors, and several comorbidities in a nationally representative sample of adults in the U.S.

Methods

Study population

This is a prospective cohort study based on nationally representative data from the National Health Interview Survey (NHIS), a leading health survey in the United States. The NHIS is conducted annually by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC). Since its inception in 1957, it has become the principal source of information on the health status of U.S. population.[13] The NHIS uses a multistage probability sampling that permits nationally representative sampling of the civilian noninstitutionalized population in the United States. The annual sample size is about 35,000 households containing about 87,500 persons, including adults and children. The NHIS collects data on a broad range of health topics through in-person household interviews. A detailed description of the survey design, methods, and sample weights in the NHIS was published elsewhere.[14] The NHIS was approved by Research Ethics Review Board of the NCHS and U.S. Office of Management and Budget. All respondents provided oral consent prior to participation.

In this study, we included only participants from NHIS 2002 and 2008, because information about MS was only ascertained in these two cycles. We linked all participants to mortality outcome data through the end of 2015, allowing approximately 10 years of observation for mortality outcomes. Few deaths occurred during follow-up among participants <45 years of age in the 2008 NHIS cycle (<2%) and the vast majority of MS cases in NHIS (99%) were <80 years of age; therefore, the study sample was defined as adults aged 45–79 who had enough information to be eligible for mortality analysis. Thus, all ineligible participants in the study sample were excluded from the analyses but their sampling weights were maintained for the analysis.

Exposure assessment

In 2002 and 2008, NHIS respondents were asked whether they had ever been told by a doctor or other health professional that they had MS. Approximately 99.9% of the NHIS adult participants in 2002 and 2008 responded to this question.

Outcome ascertainment

We used the NHIS Public-Use Linked Mortality File through December 31, 2015, which was linked by the NCHS to the National Death Index (NDI) with a probabilistic matching algorithm to determine mortality status of each NHIS adult participant.[15] National Death Index is an NCHS centralized database of all deaths in the United States. Crude mortality rates are reported as deaths per 100 persons with 95% confidence intervals (CIs). In addition, rates were standardized by age to the 2000 U.S. standard population with the direct method. Follow-up time for each participant was calculated as the difference between the NHIS survey time and the last known date alive or censored from the linked mortality file. Because NDI reports the quarter which death occurred instead of the month, we assumed that death occurred in the middle of the recorded quarter.

Covariate assessment

Data on age, sex, race/ethnicity, education, family income, body weight and height, and history of diabetes, cardiovascular disease or cancer diagnosis were collected using a standardized questionnaire. The participants self-reported their race and Hispanic origin in response to specific interview questions. In this analysis, race/ethnicity was categorized into Hispanic, non-Hispanic white, non-Hispanic black, and other. Family income to poverty ratio (IPR) is a measure of family income relative to poverty guidelines specific to the survey year. Family income levels were classified into four categories: < 1.0, 1.0–1.9, 2.0–3.9, and ≥ 4.0. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, and then classified as <18.5, 18.5–24.9, 25–29.9, and ≥ 30 kg/m2. Participants were asked whether they had ever been told they have asthma,

emphysema, or chronic bronchitis, an answer of 'yes' to any of these conditions was coded as having a chronic respiratory disease. Missing data was coded into its own category for each variable.

Statistical analysis

Survey weights were adjusted to pool the two NHS samples according to NHIS guidelines,[16,17] to account for unequal probabilities of selection, oversampling, and non-response in the complex survey. Therefore, the results were representative of the civilian, non-institutionalized U.S. population.

Means and proportions of baseline characteristics were compared using linear regression for continuous variables and logistic regression for categorical variables. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% CIs for the associations between MS and risk of mortality. In the main model, we adjusted for age, sex, race/ethnicity, education, family income level, smoking status, alcohol intake, physical activity, and BMI. In addition, we further adjusted for baseline disease status (i.e. diabetes, cardiovascular disease, chronic lung disease, and cancer) in a separate model, because these conditions might be mediators for the associations with mortality. Furthermore, we performed stratified analyses and interaction analyses by sex to explore whether there were sex differences in the associations. All statistical analyses were conducted using survey modules of SAS software version 9.4 (SAS Institute, Cary, North Carolina). Two-sided P value < 0.05 was considered statistically significant.

Results

We included 23,053 adults aged 45–79 years (mean age 58.2 years, 52.4% female) in this study. Among them, 120 participants reported a physician's diagnosis of MS, with a higher weighted prevalence of MS in females (0.85%) than in males (0.31%; $P < 0.001$). During on average 9.4 years (maximum 13.8 years) of observation, 4208 deaths occurred. The mean ($\pm$ SE) age of death was 65.2 ± 0.9 among the people with MS and 67.6 ± 0.09 among people without MS ($P = 0.008$). Participants with MS were more likely to be younger, female, non-Hispanic white, have chronic respiratory disease, and they have lower physical activity levels and BMI (Table 1).

Participants with MS had higher crude and age-standardized mortality rates compared to those without MS (Table 2). In addition, participants with MS were at a higher risk of death during the follow up (Table 3; Supplementary Table 1). In the main model adjusting for age, sex, race/ethnicity, socioeconomic factors, lifestyle factors, and BMI, participants with MS, compared with those without MS, had a 80% higher risk of all-cause mortality (HR 1.80; 95% CI, 1.11–2.92). After further adjustment for baseline disease status (diabetes, cardiovascular disease, chronic lung disease, and cancer), the association was slightly attenuated but remained significant (HR 1.75; 95% CI, 1.07–2.87).

Stratified analyses by sex showed that the adjusted HR of all-cause mortality associated with MS was 1.19 (95% CI, 0.51–2.78) among males and 2.21 (95% CI, 1.27–3.86) among females (Table 3), although the interaction by sex was not statistically significant (P for interaction, 0.28). A sensitivity analysis restricting to non-Hispanic whites, who consist of the majority (i.e. 97 out of 120) of the MS cases, showed that the adjusted HR of all-cause mortality associated with MS was 2.16 (95% CI, 1.31, 3.55; Supplementary Table 2). We could not estimate the risk of mortality other race/ethnicity groups due to limited number of MS cases (12 in Hispanics, 9 in non-Hispanic black and 2 in other groups) among these groups.

Discussion

In a nationally representative sample of U.S. adults, we found a significant association of MS with a higher risk of all-cause mortality. This association persisted after adjustment for demographic, socioeconomic variables, lifestyle factors, BMI, and several comorbidities.

Compared to the present study, several previous studies have reported much higher crude mortality ratios or standardized mortality ratios (SMR) in people with MS compared with the general population.[6,18–26] A recent meta-analysis of 15 studies, mostly from Northern Europe and Canada, found that the pooled SMR for all-cause mortality among people with MS, compared with the general population, was 2.61 (95% CI 2.58–2.65).[10] Similarly, a recent analysis of the U.S. Department of Defense database showed a 2.9-fold higher risk of all-cause mortality (mortality rate ratio 2.9, 95% CI 2.7–3.2) among people with MS, compared with non-MS controls.[27] However, these studies were usually based on registry or administrative claims data and therefore lack of data on many important confounding variables to assess the independent association of MS with mortality by accounting for potential confounders. In the present study, due to the rich data collected in the

Table 1. Baseline characteristics of participants aged 45–79 years, NHIS 2002 and 2008.

Characteristics	Without multiple sclerosis	With multiple sclerosis	*P* value
N	22,933	120	
Age, years	58.25 (0.08)	56.79 (0.95)	0.009
Sex, %			
Males	47.74 (0.39)	24.86 (4.53)	<0.001
Females	52.26 (0.39)	75.14 (4.53)	
Race/ethnicity, %			
Non-Hispanic white	76.11 (0.39)	88.24 (2.90)	0.02
Non-Hispanic black	10.20 (0.27)	4.76 (1.80)	
Hispanic	8.80 (0.24)	5.26 (1.92)	
Other	4.89 (0.18)	1.73 (1.22)	
IPR, %			
<1.0	7.20 (0.21)	6.26 (2.19)	0.95
1.0–1.9	11.60 (0.26)	11.13 (3.12)	
2.0–3.9	23.77 (0.37)	26.46 (4.89)	
≥ 4.0	38.84 (0.48)	39.56 (5.17)	
Missing	18.59 (0.39)	16.58 (3.55)	
Smoking status, %			
Never smoking	48.48 (0.41)	47.48 (5.19)	0.79
Former smoking	31.02 (0.39)	28.77 (4.96)	
Current smoking	19.50 (0.33)	22.01 (4.13)	
Missing	0.99 (0.08)	1.75 (1.26)	
Alcohol intake, %			
Non-drinker	19.67 (0.35)	15.49 (3.96)	0.06
Past drinker	19.71 (0.33)	30.91 (5.20)	
Current drinker	58.72 (0.42)	51.34 (5.71)	
Missing	1.90 (0.11)	2.26 (1.31)	
Physical activity, %			
Inactive	40.27 (0.50)	57.93 (5.51)	0.002
Insufficiently active	20.00 (0.32)	17.30 (3.92)	
Sufficiently active	38.22 (0.46)	22.36 (4.30)	
Missing	1.52 (0.12)	2.41 (1.35)	
BMI, kg/m^2, %			
<18.5	1.14 (0.08)	4.96 (2.51)	0.02
18.5–24.9	30.28 (0.36)	31.57 (5.19)	
25.0–29.9	36.04 (0.36)	32.23 (4.97)	
≥ 30	32.54 (0.38)	31.24 (5.38)	
Cardiovascular disease at baseline, %			
No	80.83 (0.31)	76.57 (4.67)	0.32
Yes	19.03 (0.31)	23.43 (4.67)	
Missing	0.14 (0.03)	0	
Diabetes at baseline, %			
No	86.89 (0.27)	92.36 (2.56)	0.10
Yes	13.05 (0.27)	7.64 (2.56)	
Missing	0.07 (0.02)	0	
Cancer at baseline, %			
No	88.20 (0.23)	86.56 (3.48)	0.61
Yes	11.73 (0.23)	13.44 (3.48)	
Missing	0.06 (0.02)	0	

(continued)

Table 1. Continued.

Characteristics	Without multiple sclerosis	With multiple sclerosis	*P* value
Chronic respiratory disease at baseline, %			
No	84.32 (0.29)	74.06 (5.52)	0.02
Yes	15.54 (0.29)	25.94 (5.52)	
Missing	0.14 (0.03)	0	

Values are means (SE) or percentage (SE) and are weighted.

Table 2. Sex-specific crude and age-standardized weighted mortality rates.

	Without multiple sclerosis			With multiple sclerosis			
	No. of death	Cohort size, person-years	Rate, % (95% CI)	No. of death	Cohort size, person-years	Rate, % (95% CI)	Rate ratio (95% CI)
Crude mortality rate							
All	4186	224,228	16.20 (15.59, 16.80)	22	1082	23.26 (11.84, 34.67)	1.44 (0.77, 1.78)
Males	2093	96,627	18.58 (17.63, 19.54)	7	257	25.08 (5.20, 44.96)	1.35 (0.54, 2.39)
Females	2093	127,601	14.07 (13.30, 14.85)	15	826	22.64 (8.96, 36.32)	1.61 (0.74, 2.03)
Age-standardized mortality rate							
All	4186	224,228	15.80 (15.30, 16.39)	22	1082	25.47 (17.47, 33.45)	1.61 (0.81, 1.87)
Males	2093	96,627	18.49 (17.66, 19.32)	7	257	24.31 (6.06, 42.56)	1.31 (0.54, 2.37)
Females	2093	127,601	13.49 (12.80, 14.17)	15	826	28.03 (19.15, 36.90)	2.08 (0.83, 2.28)

Standardized rates were standardized to the 2000 U.S. population by the direct method.

NHIS, we were able to estimate the adjusted HRs of mortality after adjustment for demographic, socioeconomic variables, lifestyle factors, and major chronic diseases at baseline. Our findings are in agreement with the findings case-control studies that found an independent association of MS with all-cause mortality in Canada (adjusted HR 2.4, 95% CI 2.2–2.6)[12] and the United Kingdom (adjusted HR 2.3, 95% CI 1.8–2.7),[11] notably both studies observe strong attenuation of mortality risk due to comorbidities. These findings provide important evidence to understand the independent role of MS in the risk of mortality.

The major strength of this study was the nationally representative sampling with a large sample size in the NHIS. Therefore, our findings are expected to be generalizable to the general adult population in the United States. There are also several limitations. First, responders to the NHIS survey are thought to be healthier compared to the general population,[28] suggesting that selection bias due to non-responders may influence the results of the present study. Second, the definition of MS in NHIS was ascertained based on self-reported physician diagnosis and is not validated, which might be subject to recall bias or misreporting. However, given the prospective nature of the study design, misclassification of MS at baseline would be non-differential and therefore more likely to have led to underestimation of the true association between MS and mortality risk. This limitation may explain the lower mortality ratios observed in the present study compared to most previous studies. Third, because exposure and covariate data were collected at baseline only, we were unable to determine new incident cases of MS and assess temporal changes in covariates during the follow up. Fourth, the NHIS does not have information on severity of

Table 3. Association of multiple sclerosis with all-cause mortality in U.S. adults aged 45–79 years, NHIS 2002 and 2008.

	Hazard ratios (95% confidence intervals)	
	Without multiple sclerosis	With multiple sclerosis
All participants		
No. of death/person-years	4186/224,228	22/1082
Model 1	1 (reference)	2.07 (1.28–3.35)
Model 2	1 (reference)	1.80 (1.11–2.92)
Model 3	1 (reference)	1.75 (1.07–2.87)
Males		
No. of death/person-years	2093/96,627	7/257
Model 1	1 (reference)	1.23 (0.56–2.67)
Model 2	1 (reference)	1.19 (0.51–2.78)
Model 3	1 (reference)	1.23 (0.56–2.67)
Females		
No. of death/person-years	2093/127,601	15/826
Model 1	1 (reference)	2.85 (1.60–5.07)
Model 2	1 (reference)	2.21 (1.27–3.86)
Model 3	1 (reference)	2.13 (1.17–3.88)

Model 1: adjusted for age, sex (except for stratified analyses by sex), and race/ethnicity.
Model 2: model 1 + family income, smoking status, alcohol intake, physical activity level, and BMI.
Model 3: model 2 + diabetes, cardiovascular disease, cancer, and chronic respiratory disease.

MS or treatments among people with MS. Further investigation is warranted to determine whether and how severity and treatments will affect the association between MS and mortality. Fifth, because MS disproportionally affect females than males, the sample size for males is limited in the present study. Further investigation is needed to replicate our exploratory findings about sex differences in the association between MS and mortality risk. Sixth, because the study population was restricted to adults aged 45–79, we are unable to evaluate mortality across the lifespan. Seventh, this study focused on all-cause mortality and did not have sufficient sample size to allow further analyses of detailed cause-specific mortality (e.g. deaths from cardiovascular disease, cancer, etc.). Several previous studies based on claims data showed that patients with MS, compared with the general population or non-MS controls, had increased rates of death from infection, respiratory diseases, and cardiovascular disease.[27,29] Future studies with a large sample size and detailed data on potential confounders are needed to estimate the adjusted HRs of cause-specific mortality.

In conclusion, among a nationally representative sample of U.S. adults, MS was associated with an increased risk of all-cause mortality. The association was independent of demographic, socioeconomic variables, lifestyle factors, baseline diabetes, cardiovascular disease, chronic respiratory disease, and cancer status. Further studies are needed to determine the impact of comorbidity reduction on MS-related mortality.

Author contributions

Dr Titcomb had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Bao. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Bao, Titcomb. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Du and Titcomb. Supervision: Bao, Snetselaar, and Wahls.

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Supplemental material

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