Original Paper

Neuro
-epidemiology

Neuroepidemiology 2018;51:96–103
DOI: 10.1159/000488891

Received: September 2, 2017
Accepted: March 31, 2018
Published online: July 10, 2018

Amyotrophic Lateral Sclerosis Mortality in the United States, 2011–2014

Theodore C. Larson[a] Wendy Kaye[b] Paul Mehta[a] D. Kevin Horton[a]

[a]Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA; [b]McKing Consulting Corporation, Atlanta, GA, USA

Keywords
Amyotrophic lateral sclerosis · Motor neuron disease · Mortality

Abstract
Background: The International Classification of Disease, 10th Revision (ICD-10) did not include a code specific for Amyotrophic lateral sclerosis (ALS) until 2017. Instead, code G12.2 included both ALS and other motor neuron diseases (MND). Our objective was to determine US mortality rates for ALS exclusively by excluding other MND and progressive supranuclear palsy. ***Methods:*** All mortality data coded as G12.2 under the pre-2017 rubric were obtained for 2011–2014. Deaths without ALS listed in one of the un-coded cause-of-death fields were excluded. ALS death rates per 100,000 persons were age-adjusted to the 2000 US standard population using the direct method. ***Results:*** The proportion of excluded records coded G12.2 but not ALS was 0.21, resulting in 24,328 ALS deaths. The overall age-adjusted mortality rate was 1.70 (95% CI 1.68–1.72). The rate among males was 2.09 (95% CI 2.05–2.12) and females was 1.37 (95% CI 1.35–1.40). The overall rate among whites was 1.84, blacks 1.03, and other races 0.70. For both sexes and all races, the rate increased with age and peaked among 75–79 year-olds. Rates tended to be greater in states at higher latitudes. ***Conclusions:*** Previous reports of ALS mortality in the United States showed similar age, sex, and race distributions but with greater age-adjusted mortality rates due to the inclusion of other diseases in the case definition. When using ICD-10 data collected prior to 2017, additional review of multiple-cause of death data is required for the accurate estimation of ALS deaths.

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare and progressive neurodegenerative disease involving loss of cortical and lower motor neurons in the spinal cord and brain stem [1]. The clinical features of ALS include signs and symptoms of progressive muscle atrophy, fatigue, and problems with swallowing, which typically lead to respiratory failure and death [1]. The insidiously progressive nature of ALS results in death among most patients within 2–5 years of diagnosis [2]. Although rare with an

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Theodore C. Larson
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry
4770 Buford Highway, Atlanta, GA 30341 (USA)
E-Mail TLarson@cdc.gov

estimated US prevalence of 5.0 cases per 100,000 population [2], ALS exacts an immense burden for patients, caregivers, and society [3].

ALS makes up about 70% of cases in a disease class known as the motor neuron disease (MND); other main clinical phenotypes of MND are isolated bulbar palsy (4–8% of cases), progressive muscular atrophy (5%), and primary lateral sclerosis (1–3%) [4]. Although ALS is the most common MND, it did not have its own code in the US prior to the 2017 update of the International Classification of Diseases, 10th Revision (ICD-10) rubric. Prior to this update, the ICD-10 code for MND, G12.2, included both ALS and other MND.

The objective for the present analysis was to determine ALS mortality rates for the entire United States for the period 2011–2014, ascertained using ICD-10 code G12.2 as coded using the pre-2017 rubric, but excluding deaths from other MND and other diseases, including progressive supranuclear palsy (G23.1).

Methods

Multiple-cause mortality data for all deaths involving MND were obtained from the National Center for Health Statistics, Centers for Disease Control and Prevention, for all 50 US states and Washington DC during 2011–2014. This time period was selected to match initial, complete years of data collection conducted by the National ALS Registry, a registry of US cases operated by the Agency for Toxic Substances and Disease Registry [5]. MND-related deaths were defined as the ICD-10 code G12.2. Un-coded causes of death as reported in the medical certification section of the death certificate obtained by National Center for Health Statistics were manually reviewed and records in which ALS was not listed as a cause of death were excluded.

ALS death rates per 100,000 persons were then age-adjusted to the 2000 US standard population using the direct method [6]. Population estimates used in SEER*Stat software [7] were a modification of the annual time series of July 1 county population estimates by age, sex, and race/ethnicity determined by the US Census Bureau [8]. Modifications included bridged single-race estimates derived from original, multiple race categories in the 2000 and 2010 Censuses [9] and accounted for known issues in certain counties [8]. The modified county-level population estimates, summed to the state and national levels, were used as denominators in rate calculations [8].

For the rate calculations, ages were grouped in 5-year intervals to 84 and 85 years and older. Corresponding 95% CIs were calculated as a modification of intervals based on a gamma approximation for rates and an approximation of the F distribution for rate ratios [10]. Death rates were examined by sex, age, race (black, white, or other), Hispanic origin, year of death, and place of residence at death (state, Census division, and state tier). A map showing the geographic distribution of age-adjusted death rates used the 25th, 50th, and 75th percentiles of state rates as cut points. For further rate calculations, state of residence was aggregated into tiers and Census divisions. The northern tier includes states generally north of 41–42 degrees north latitude; the southern tier consists of those states lying south of 37 degrees north latitude; and the middle tier consists of the remaining states. All rates and average annual percent change (APC) in rates were calculated using SEER*Stat software [7].

Results

There were 30,804 deaths in the United States coded as G12.2 during the study period. Of those deaths, 6,476 (21%) were excluded from this analysis. Among the excluded decedents, other MND or neurologic disorders frequently appeared as a cause of death: 5,039 with progressive supranuclear palsy; 558 bulbar palsy; 331 primary lateral sclerosis; 80 progressive muscular atrophy; 351 with a nonspecific term for MND; and 117 with some other cause. After exclusions, 24,328 ALS deaths remained for 2011–2014. The majority of ALS decedents were white (n = 22,245; 91%) and deaths among men predominated (n = 13,611; 56%). The age range of the decedents was 14–102 years (4 decedents were younger than 20 years). Age-adjusted rates, expressed per 100,000 population, were stable between years (Table 1) with an annual percentage change that was not statistically significant ($p > 0.05$).

The overall rate for all 24,328 ALS deaths was 1.70 (95% CI 1.68–1.72); for male decedents, the rate was 2.09 (95% CI 2.05–2.12); and for female decedents, the rate was 1.37 (95% CI 1.35–1.40; Table 1). The overall rate ratio for males was 1.52 (95% CI 1.48–1.56), and a similar ratio between sexes was seen across age groups (Fig. 1).

Overall rate ratios for race were 2.64 for whites and 1.48 for blacks compared with other races (Table 1). The rate ratio for non-Hispanics compared to that of the decedents of Hispanic origin was 1.85 (Table 1). Similar patterns by race and by Hispanic origin were observed across age groups (Figs. 2, 3, respectively). The overall rate for decedents aged 0–49 years was 0.22 and increased with age through the 70–79 years category (rate = 9.71) and decreased among those aged ≥80 years (Table 1). Figure 2 shows a similar pattern in the age-adjusted rates using 5-year age categories, reaching a maximum rate in the 70–79 years category (overall rate in this age category = 10.59; male rate = 12.46; female rate = 9.12). The APC for rates by sex, race, Hispanic origin, and age was not statistically significant.

The choropleth in Figure 4 visually displays rates by state and suggests states at greater latitudes are associated

Table 1. Characteristics and age-adjusted rates of ALS-associated deaths in the United States during 2011–2014

	Number*	Rate† (95% CI)	RR‡ (95% CI)	Ratio *p* value
All deaths	24,328	1.70 (1.68–1.72)	–	
Year of death				
2011	5,905	1.72 (1.67–1.76)	1	
2012	6,149	1.74 (1.70–1.79)	1.01 (0.98–1.05)	0.4850
2013	5,982	1.65 (1.61–1.69)	0.96 (0.93–1.00)	0.0316
2014	6,292	1.70 (1.65–1.74)	0.99 (0.95–1.02)	0.5078
Gender				
Male	13,611	2.09 (2.05–2.12)	1.52 (1.48–1.56)	<0.0001
Female	10,717	1.37 (1.35–1.40)	1	
Race				
White	22,245	1.84 (0.64–0.76)	2.64 (2.42–2.89)	<0.0001
Black	1,540	1.03 (0.98–1.09)	1.48 (1.34–1.64)	<0.0001
Other	543	0.70 (0.64–0.76)	1	
Hispanic origin				
Hispanic	1,225	0.96 (0.91–1.02)	1	
Non-Hispanic	23,103	1.78 (1.76–1.80)	1.85 (1.74–1.96)	<0.0001
Age group, years				
0–49	1,761	0.22 (0.21–0.23)	0.09 (0.08–0.09)	<0.0001
50–59	4,461	2.51 (2.44–2.58)	1	
60–69	7,635	5.98 (5.84–6.11)	2.38 (2.30–2.47)	<0.0001
70–79	6,931	9.71 (9.48–9.94)	3.87 (3.73–4.02)	<0.0001
≥80	3,540	7.72 (7.47–7.98)	3.08 (2.94–3.22)	<0.0001
State tier§				
Northern	6,501	1.89 (1.85–1.94)	1.22 (1.18–1.26)	<0.0001
Middle	7,912	1.77 (1.73–1.81)	1.14 (1.11–1.17)	<0.0001
Southern	6,501	1.55 (1.52–1.58)	1	
Census division‖				
West North Central	1,934	2.01 (1.92–2.10)	1.17 (1.10–1.25)	<0.0001
New England	1,403	1.99 (1.89–2.10)	1.16 (1.10–1.25)	0.0001
East North Central	4,096	1.89 (1.83–1.95)	1.10 (1.04–1.17)	0.0010
East South Central	1,501	1.74 (1.65–1.83)	1.01 (0.94–1.09)	0.7442
Mountain	1,700	1.71 (1.63–1.80)	1	
Pacific	3,534	1.63 (1.57–1.68)	0.95 (0.90–1.00)	0.0913
South Atlantic	4,781	1.62 (1.58–1.67)	0.95 (0.89–1.00)	0.0571
West South Central	2,374	1.55 (1.49–1.61)	0.90 (0.85–0.96)	0.0019
Mid Atlantic	3,005	1.53 (1.47–1.58)	0.89 (0.84–0.95)	0.0002

* Number of deaths.

† Average annual mortality rates per 100,000 persons and age-adjusted to the 2000 US standard population.

‡ Rate ratios with 95% CIs.

§ Northern: AK, CT, ID, MA, ME, MI, MN, MT, ND, NE, NH, NY, RI, SD, VT, WI & WY. Middle: CO, DC, DE, IA, IL, IN, KS, KY, MD, MO, NJ, NV, OH, PA, UT, VA & WV. Southern: AL, AR, AZ, CA, FL, GA, HI, LA, MS, NC, NM, OK, SC, TN & TX.

‖ West North Central: IA, KS, MN, MO, NE, ND & SD. New England: CT, ME, MA, NH, RI & VT. East North Central: IN, IL, MI, OH & WI. East South Central: AL, KY, MS & TN. Mountain: AZ, CO, ID, NM, MT, UT, NV & WY. Pacific: AK, CA, HI, OR & WA. South Atlantic: DE, DC, FL, GA, MD, NC, SC, VA & WV. West South Central: AR, LA, OK & TX. Mid-Atlantic: NJ, NY & PA. ALS, amyotrophic lateral sclerosis.

with higher mortality rates. The rate for the northern tier of states was 1.89 with a rate ratio of 1.22 compared with the southern tier ($p < 0.0001$; Table 1). The confidence intervals for rate and rate ratios at each state tier were non-overlapping (Table 1). Stratifying the state tier results by race showed a similar trend among whites but not among blacks and other races (Table 2). Similarly, the rate ratios among Hispanics did not suggest an association between the state tier and ALS mortality in that demographic (Table 2). Comparing other Census divisions, the

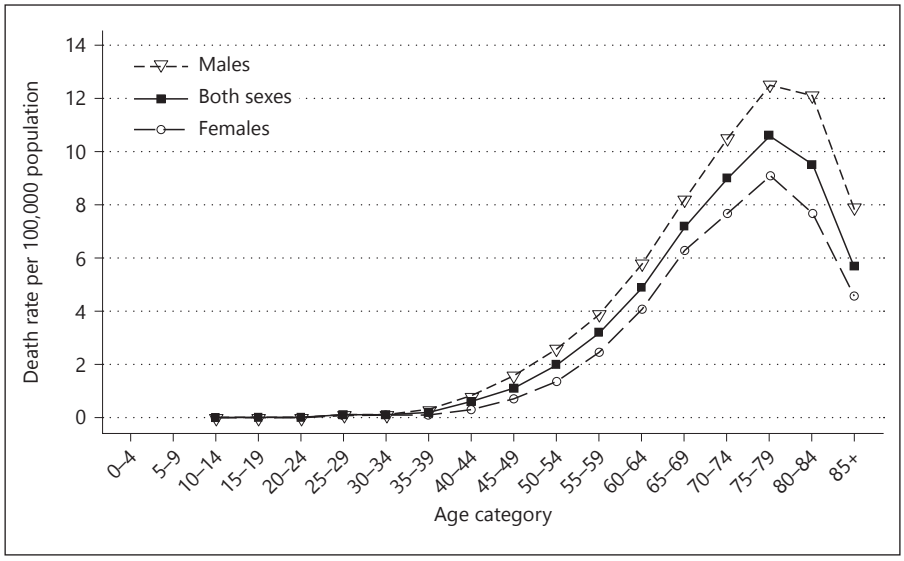


Fig. 1. ALS-associated average annual death rates in the United States by age group and sex, 2011–2014. ALS, amyotrophic lateral sclerosis.

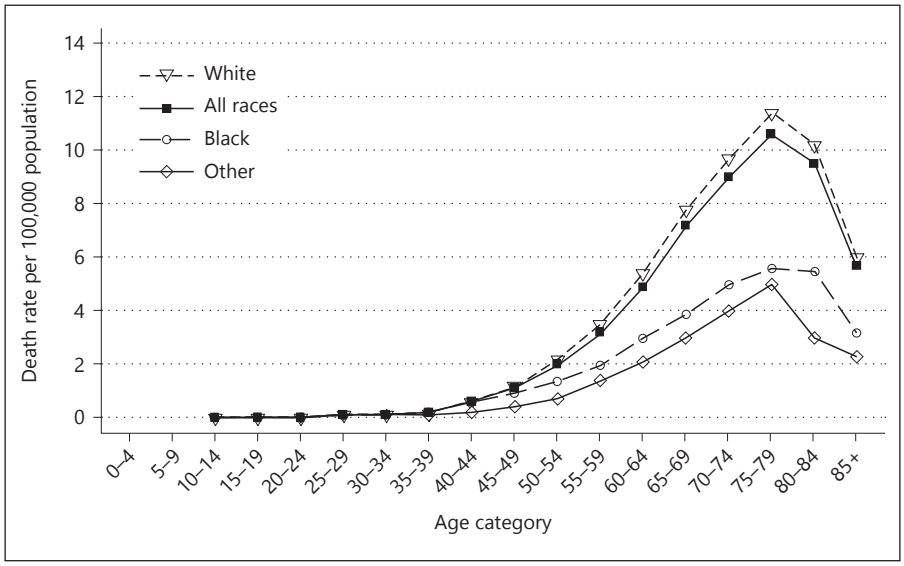


Fig. 2. ALS-associated average annual death rates in the United States by age group and race, 2011–2014. ALS, amyotrophic lateral sclerosis.

Mountain division, the West North Central, New England and East North Central divisions had greater rate ratios ($p < 0.05$) and West South Central and Mid-Atlantic divisions had lesser rate ratios ($p < 0.01$; Table 1). APC for each Census division was not statistically significant with the exception of that of the West North Central division, which had an APC of –4.20 ($p < 0.01$). Annual rates for the West North Central division declined monotonically during the study period (2.13, 2.09, 1.94, and 1.89 for 2011, 2012, 2013, and 2014, respectively). We found no statistically significant change in the APC among states making up this region.

Discussion

We found the ALS mortality rate was 1.70 per 100,000 in the United States. Consistent with the proportion of excluded death records, this rate is about 21% lower than that found by Mehal et al. [11] in a study that did not exclude other MNDs or progressive supranuclear palsy over the period 1999–2009. In the present study, rates by subpopulations showed elevations among males and whites that increased with age until approximately 70–79 years. These subpopulations also had increased rates in previous studies of ALS mortality in the United

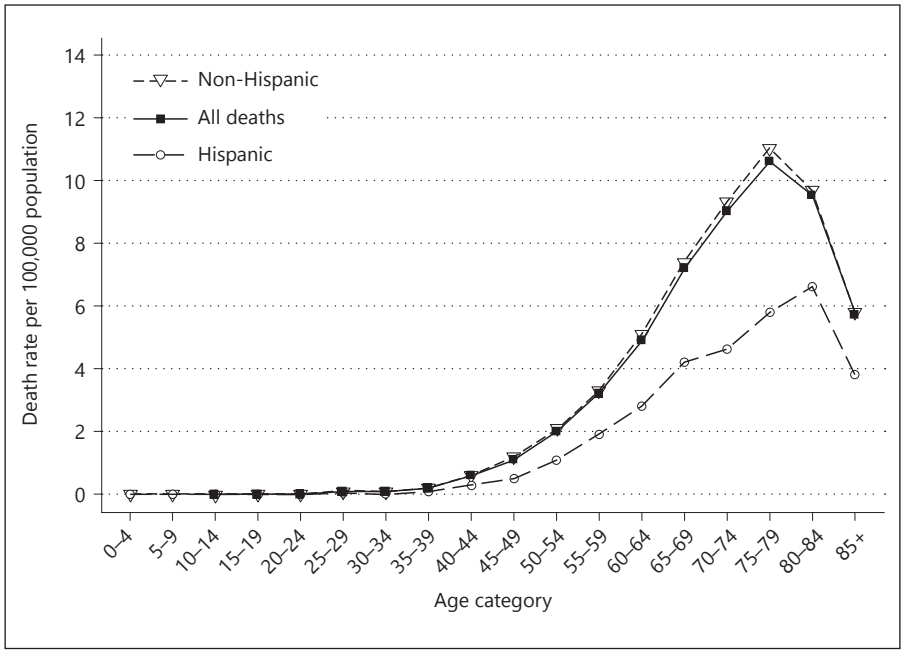
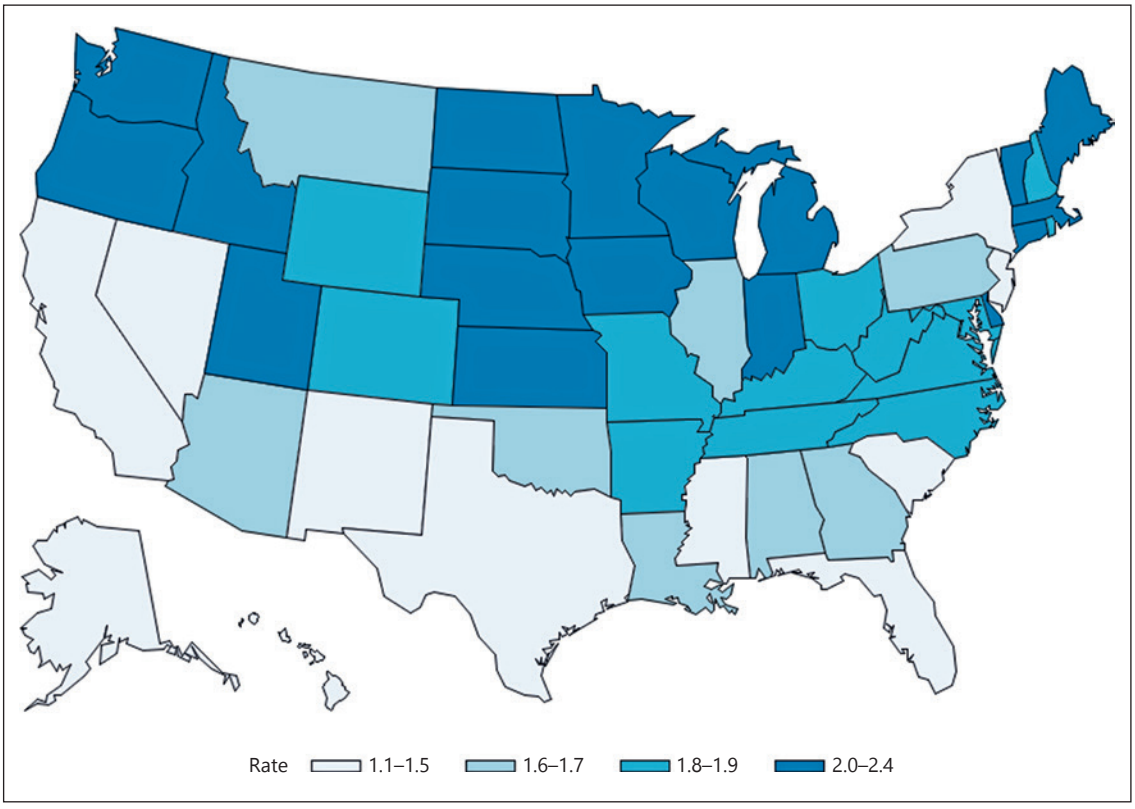


Fig. 3. ALS-associated average annual death rates in the United States by age group and Hispanic origin, 2011–2014. ALS, amyotrophic lateral sclerosis.



Color version available online

Fig. 4. Geographic distribution of average annual age-adjusted ALS mortality rates per 100,000 population in the United States, 2011–2014. The rate for Washington DC is in the 1.1–1.5 category.

Table 2. Age-adjusted ALS death rates stratified by race or Hispanic origin and by state tier

	State tier	Number*	Rate†	RR (95% CI)‡	Ratio *p* value
White	Northern	6,146	2.03 (1.98–2.09)	1.20 (1.16–1.24)	<0.0001
	Middle	7,288	1.89 (1.84–1.93)	1.11 (1.07–1.14)	<0.0001
	Southern	8,811	1.70 (1.67–1.74)	1	
Black	Northern	236	0.92 (0.80–1.05)	0.91 (0.78–1.05)	0.2012
	Middle	516	1.12 (1.02–1.22)	1.10 (0.98–1.23)	0.1162
	Southern	788	1.02 (0.95–1.09)	1	
Other	Northern	119	0.75 (0.61–0.90)	1.10 (0.87–1.37)	0.4409
	Middle	108	0.68 (0.56–0.83)	1.00 (0.79–1.26)	1.0000
	Southern	316	0.68 (0.61–0.76)	1	
Hispanic	Northern	179	0.95 (0.80–1.10)	0.97 (0.82–1.15)	0.7790
	Middle	188	0.95 (0.81–1.10)	0.97 (0.82–1.15)	0.7813
	Southern	858	0.97 (0.90–1.04)	1	
Non-Hispanic	Northern	6,322	1.95 (1.90–2.00)	1.18 (1.14–1.22)	<0.0001
	Middle	7,724	1.81 (1.77–1.85)	1.10 (1.06–1.13)	<0.0001
	Southern	9,057	1.65 (1.62–1.69)	1	

* Number of deaths.
† Average annual mortality rates per 100,000 persons and age-adjusted to the 2000 US standard population.
‡ Rate ratios with 95% CIs.
ALS, amyotrophic lateral sclerosis.

States [11, 12]. The fact that ALS incidence and prevalence is greater among men has been a consistent finding across studies [13]. This difference between sexes may be due to occupational exposures that historically occurred more commonly among men [14] or a neuroprotective effect of estrogen [15]. ALS incidence has been characterized as increasing with age though age 75 and rapidly declining thereafter [14]. This decline in incidence may be due to difficulties with ascertainment among the elderly. Al-Chalabi and Hardiman note that "older patients are more likely to be referred to non-neurological services, and ALS might be under-recognized in older people because being weak or wasted may be regarded as a normal part of ageing, or may be ignored in someone with multiple medical problems" [13].

Consistent with the race-specific mortality rates that we found, other studies have found lower incidence and mortality rates among non-whites [16, 17]; however, the majority of population-based epidemiologic studies of ALS have been persons of European ancestry [13]. Similarly, other studies have also found lower ALS mortality rates among Hispanics [1, 17]. Lower incidence and mortality among non-whites and Hispanics may reflect under-ascertainment among non-whites or a genetic factor predisposing whites to ALS [17].

We found no statistically significant temporal trend in the overall mortality rate, but perhaps this should be expected given that only 4 years of data were analyzed. Still, Mehal et al. [11] found the overall US mortality rate (for all deaths coded G12.2) was stable during the period 1999–2009.

We found evidence of a tendency for states at more northern latitudes to have greater age-adjusted ALS mortality rates than states at more southern latitudes. This is consistent with previous US mortality studies of MND and ALS [11, 12, 18]. A recent review of global ALS epidemiology showed a trend of ALS incidence to increase with higher latitudes among European countries [19]. These regional differences in ALS rates may be due to patient factors, including environmental exposures and genetic predisposition [19]. Our finding of an association between northern latitudes and increased mortality rates among whites only may be related to such factors (e.g., geographic patterns of European immigrant settlement in the United States). An additional study of patient factors, such as access to health care and socioeconomic sta-

tus, and their relationship to ALS mortality should be considered.

In order to accurately identify ALS, the National ALS Registry submitted a modification request to the committee overseeing the ICD-10 codes in the United States, specifically, the addition of G12.21 for ALS. This change has been made in the 2017 revision and will allow accurate identification of incidence, prevalence, and mortality of ALS in the United States.

This study is limited by the accuracy of death certificates for ALS. However, as the diagnosis of ALS is typically not ambiguous at advanced stages [20], one would expect the rate of false-negative misclassification of ALS as a cause of death to be low. To explore this, we examined mortality data from the Agency for Toxic Substances and Disease Registry's National ALS Registry, 2010–2013. The Registry actively identifies US ALS cases using data from national health services programs (Medicare, Medicaid, and medical assistance programs administered by the Veteran's Administration) and passively via a web portal [5]. Using National Index Data to determine the multiple cause of death for deceased cases, the true positive rate was 0.865 (i.e., among 17,642 registrant deaths, 15,252 had ICD-10 code G12.2 appearing as a cause of death; 95% CI 0.859–0.870). This suggests that death certificate accuracy for ALS in the United States is good and approximately in the middle of the range of published true positive rates for ALS on death certificates [21]. In addition, when comparing our results to those from other countries, one should be mindful of international differences in ICD-10 rubrics (e.g., ICD-10 Clinical Modification in the United States, ICD-10 Australian Modification, etc.). Differences between rubrics may be seen in the 5th position of specific disease codes [22], which is the position that differentiates between different clinical phenotypes of MND.

In summary, compared with other MND subtypes, ALS is the most malignant with shortest survival [4]. Excluding deaths from other MNDs and progressive supranuclear palsy in data coded using the pre-2017 ICD-10 rubric reduces the total number of deaths attributed to ALS and the adjusted death rate by about 21%. Consistent with other studies, ALS mortality rates with these exclusions were greater among men and whites and generally increased with age. There is evidence of an association between higher latitudes and increased ALS mortality. Although rare, ALS is a devastating disease that imparts large economic impact to patients and society [23]. In addition to ongoing ALS mortality surveillance, the National ALS Registry monitors ALS prevalence in the United States [5]; such Registry data are important for trend analysis and the identification of possible risk factors.

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