

# Race/ethnicity, socioeconomic status, and ALS mortality in the United States

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## ABSTRACT

**Objective:** To determine whether race/ethnicity and socioeconomic status are associated with amyotrophic lateral sclerosis (ALS) mortality in the United States.

**Methods:** The National Longitudinal Mortality Study (NLMS), a United States–representative, multistage sample, collected race/ethnicity and socioeconomic data prospectively. Mortality information was obtained by matching NLMS records to the National Death Index (1979–2011). More than 2 million persons ( $n = 1,145,368$  women,  $n = 1,011,172$  men) were included, with 33,024,881 person-years of follow-up (1,299 ALS deaths, response rate 96%). Race/ethnicity was by self-report in 4 categories. Hazard ratios (HRs) for ALS mortality were calculated for race/ethnicity and socioeconomic status separately and in mutually adjusted models.

**Results:** Minority vs white race/ethnicity predicted lower ALS mortality in models adjusted for socioeconomic status, type of health insurance, and birthplace (non-Hispanic black, HR 0.61, 95% confidence interval [CI] 0.48–0.78; Hispanic, HR 0.64, 95% CI 0.46–0.88; other races, non-Hispanic, HR 0.52, 95% CI 0.31–0.86). Higher educational attainment compared with < high school was in general associated with higher rate of ALS (high school, HR 1.23, 95% CI 1.07–1.42; some college, HR 1.24, 95% CI 1.04–1.48; college, HR 1.10, 95% CI 0.90–1.36; postgraduate, HR 1.31, 95% CI 1.06–1.62). Income, household poverty, and home ownership were not associated with ALS after adjustment for race/ethnicity. Rates did not differ by sex.

**Conclusion:** Higher rate of ALS among whites vs non-Hispanic blacks, Hispanics, and non-Hispanic other races was not accounted for by multiple measures of socioeconomic status, birthplace, or type of health insurance. Higher rate of ALS among whites likely reflects actual higher risk of ALS rather than ascertainment bias or effects of socioeconomic status on ALS risk.

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## GLOSSARY

**ALS** = amyotrophic lateral sclerosis; **CI** = confidence interval; **CPS** = Current Population Surveys; **HR** = hazard ratio; **ICD-9** = *International Classification of Diseases-9*; **ICD-10** = *International Classification of Diseases-10*; **NDI** = National Death Index; **NLMS** = National Longitudinal Mortality Study; **SES** = socioeconomic status.

Amyotrophic lateral sclerosis (ALS) is a degenerative neurologic disorder with few identified risk factors. Even fundamental demographic associations with ALS, including race/ethnicity and socioeconomic status (SES), are not well-understood. In the United States, few studies have tested race/ethnic differences,<sup>1</sup> and studies of SES have focused almost exclusively on occupation.<sup>2–4</sup> Moreover, for the most part, studies of race/ethnicity and ALS have not accounted for SES, and studies of SES have not accounted for race/ethnicity.

Apparent differences in ALS risk by race/ethnicity and SES may be driven in part by underascertainment of ALS due to poorer access to health care among minorities or persons of low

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SES, or because immigrants who develop ALS may return to their birth country when symptoms emerge. If ALS risk differs by SES, this would suggest that ALS risk is affected by factors commonly associated with SES, including health behaviors,<sup>5</sup> environmental stressors,<sup>6</sup> and workplace exposures.<sup>7</sup> Thus, it is critical to jointly examine race/ethnicity, SES, access to health care, and immigrant status, which no studies to date have done.<sup>8–13</sup>

In the present study, we examined the association of ALS mortality with race/ethnicity and SES in a very large United States–representative study<sup>14</sup> with multiple measures of SES and data on health insurance and birthplace collected prospectively.

**METHODS Study population.** The National Longitudinal Mortality Study (NLMS) comprises US Census Bureau Annual Social and Economic Supplements (March 1973 to March 2011), Current Population Surveys (CPS, February 1978, April 1980, August 1980, December 1980, and September 1985), and one 1980 Census cohort.<sup>14–16</sup> Surveys gather data about the noninstitutionalized US population, are conducted in-person and via telephone interview, and emphasize the topics of employment, education, and income. The response rate is approximately 96%. So that NLMS participants' reported SES more accurately reflected their adulthood circumstances, we restricted the sample to the 1,011,172 men and 1,145,368 women who were 25 years or older at the time of their survey.

**Standard protocol approvals, registrations, and patient consents.** The Institutional Review Board of the Harvard T. H. Chan School of Public Health approved this work.

**Case ascertainment.** Mortality information for 1979 through 2011 was obtained by matching NLMS records to the National Death Index (NDI).<sup>17</sup> ALS, like many noninfectious diseases, is not a reportable disease in the United States. Therefore, mortality is often used as a surrogate for ALS incidence. The NDI contains death certificate data and is managed by the National Center for Health Statistics.<sup>18</sup> Cause of death was obtained from the NDI and coded using the ICD-9 (deaths in or before 1998) or ICD-10 (deaths after 1998). Deaths with either the underlying or a contributing cause listed as ICD-9 code 335.2 or ICD-10 code G12.2 were considered ALS cases. In studies in the United States and other industrialized nations, death certificates have had good validity for ALS mortality.<sup>19</sup>

**Measures.** The head or responsible adult for each household responded for all household members. Participants self-reported their ethnicity as Hispanic or non-Hispanic and self-reported their race as white, black, or other races (including Asian, Pacific Islander, Aleut, Eskimo, and Native American). Education was in 5 levels: less than high school, high school graduate, some college, college graduate, postgraduate, or missing. Household income was coded as less than \$20,000, \$20,000–\$35,000, \$35,000–\$50,000, \$50,000–\$75,000, and more than \$75,000 dollars per year, or missing. Current home ownership was coded *yes/no/missing*. Place of birth was coded as in the United States, Puerto Rico, or within an outlying possession of the United States; not one of these places; or

missing. Type of health insurance was Medicare, Medicaid, private, employer, government health, no insurance, or missing. Presence of a Social Security number on Census records in the matches to the NDI was coded as *yes* or *no*.

### **Statistical analyses. Race/ethnicity and ALS mortality.**

To examine the association of race/ethnicity with risk of ALS mortality, we estimated hazard ratios (HR) using proportional hazards models adjusted for sex, with age as the time scale in order to closely control for age. To ascertain whether associations of race/ethnicity with ALS differed in women and men, we compared models with and without sex-by-race/ethnicity interaction terms using the likelihood ratio test.

To calculate the extent to which SES might account for racial/ethnic differences in risk of ALS, we further adjusted for indicators of SES, including educational attainment, household income, household income in relation to the poverty line, and home ownership. Presence and type of health insurance coverage may have affected ascertainment of ALS, and emigration of participants to their country of birth following onset of ALS symptoms may have resulted in underascertainment of ALS mortality among immigrants. We therefore further adjusted for presence and type of health insurance coverage and 2 indicators of immigrant status: birthplace (United States or non–United States) and presence or absence of a Social Security number on Census records in the matches to the NDI. We additionally examined rates of ALS death by race/ethnicity restricted to US-born persons in which a Social Security number was used in the matches to the NDI. As an association of military service with rate of ALS has previously been found in this cohort,<sup>20</sup> we conducted sensitivity analyses that further adjusted for military service, coded as *any* or *none*.

We also conducted sensitivity analyses to examine the association of race/ethnicity and SES with ALS under restrictions that may have improved the ascertainment of ALS and SES. As ALS cases are less reliably diagnosed in death certificates for persons at older ages,<sup>21</sup> we restricted follow-up to age 75. We next implemented exclusions that may have improved the ascertainment of SES. First, as ALS symptoms may have led to unemployment or lower income, we excluded the first 5 years of follow-up and the first 8 years of follow-up. A detailed natural history study of ALS found that by 5 years after first symptom, 80% of patients had died and by 8 years after first symptom, 96% of patients had died.<sup>22</sup> Second, as occupation is less stable in younger vs older persons and may therefore less accurately reflect adulthood income, we restricted analyses to persons ages 35–75 at enrollment. To ensure that missing data on SES were not reducing its explanatory power to account for race/ethnic differences in ALS, we

restricted to participants with complete data on SES and estimated models of race/ethnicity as a predictor of ALS mortality unadjusted and adjusted for all SES measures. In addition, to check on the possibility of differences in competing risks by race/ethnicity accounting for differences in ALS mortality, we also conducted analyses restricting follow-up to age 67 (roughly the median age at ALS death among minorities) since effects of competing risks would be expected to be less at younger ages.

**SES and ALS mortality.** To investigate which, if any, measures of SES were associated with ALS mortality, we first estimated HRs using proportional hazards models with age as the time metamer, adjusted for sex, for each SES measure separately (educational attainment, household income, household percent of poverty line, and home ownership). We next added race/ethnicity to these models to determine the extent to which race/ethnicity accounted for possible differences in ALS mortality by SES factors. To determine whether SES measures were associated with ALS independently of one another, and as health insurance may affect ALS ascertainment, we mutually adjusted for all SES measures and health insurance in a final model. As smoking has been associated with increased risk of ALS,<sup>23</sup> we considered smoking as a possible confounder. Smoking was queried only in a subset of surveys and data were available on 501,233 participants in our sample (23.2%). We ascertained the association of race and SES with ALS adjusted for smoking status in this subsample.

We created missing data indicators for missing data (<5% missing for all covariates except type of health insurance, for which 28.2% was missing). Follow-up time was measured from the time of the survey or, for those surveyed before 1979, from January 1, 1979 (the start of electronic NDI data), until death or until the last date of NDI linkage. All analyses were conducted using weighted data in SAS (SAS Institute, Cary, NC). NLMS weights are derived from the original CPS weights adjusted so that the survey records in the NLMS represent the noninstitutionalized US population at the time of the survey. For specific analytic purposes, these weights are first adjusted using a ratio adjustment to account for the different survey sizes among the NLMS cohorts and then adjusted to represent the sample size. In this way, we maintain the proper record interrelationships for adjustments of oversampling and undersampling for age, sex, race, Hispanic origin, and state of origin, established in the original CPS weights, but adjusted so that proper estimates of variance can be obtained.

**RESULTS** White participants in our sample were slightly older at enrollment, had higher levels of education, were more likely to be home owners,

and had higher incomes compared with minority race/ethnicities (table 1). Black and Hispanic participants were substantially more likely to have no health insurance compared with white participants. Hispanic participants and persons of other race/ethnicities were born outside the United States far more often than white participants (47.9% and 47.7% vs 4.0%, table 1).

**Race/ethnicity and ALS mortality.** Race/ethnicity was strongly associated with risk of ALS. Compared with non-Hispanic white participants, non-Hispanic black, Hispanic, and non-Hispanic persons of other race/ethnicities were at substantially lower risk of ALS mortality (table 2, model 1). This association did not differ by sex ( $\chi^2_{df=4} = 2.7, p = 0.60$ ). In models further adjusted for all SES measures and type of health insurance, risk for Hispanic and Black participants were slightly attenuated (table 2, model 2). In models additionally adjusted for birthplace and presence of a Social Security number, risk for Hispanic and non-Hispanic persons of other race/ethnicities were further attenuated but remained substantial (table 2, model 3).

In the sample with follow-up limited to age <75 years, as expected, the mean age of participants was younger in all race/ethnic groups and the difference in age between groups was somewhat attenuated compared to the full sample (white, mean = 46.2; black, mean = 45.4; Hispanic, mean = 41.9; other race/ethnicities, mean = 43.9 years). Associations of race/ethnicity with ALS mortality were very similar in models restricting follow-up to age <75 years ( $n = 2,001,071$ , no. cases = 829), in persons 35–75 years at enrollment ( $n = 1,486,746$ , no. cases = 1,145), and excluding the first 5 and 8 years of follow-up ( $n = 1,703,980$ , no. cases = 1,033;  $n = 1,430,181$ , no. cases = 871, respectively). Race/ethnic differences in ALS mortality were similar in participants with complete SES data, and, as in the main analyses, adjusting for SES accounted for very little of the race/ethnic differences in ALS mortality in this subgroup. The association of ALS with race/ethnicity was nearly unchanged after further adjustment for military service. In a model restricted to US-born respondents with Social Security numbers used in matches to the NDI, risk estimates were similar to those in the whole sample, though confidence intervals (CIs) were wider due to the reduced sample size (non-Hispanic black, HR 0.48, 95% CI 0.33–0.70; Hispanic, HR 0.66, 95% CI 0.39–1.12; non-Hispanic other race/ethnicities, HR 0.32, 95% CI 0.10–1.11). Further adjustment for smoking did not alter the association of race/ethnicity with ALS in the subsample with data on smoking. In analyses limiting follow-up to age 67, the HR for non-Hispanic

**Table 1** Participant characteristics by race/ethnicity, National Longitudinal Mortality Study, 1973–2011 (n = 2,156,540)

	White, non-Hispanic (n = 1,593,523)		Black, non-Hispanic (n = 200,280)		Hispanic (n = 216,922)		Other race/ ethnicities, non-Hispanic (n = 100,141)		Missing (n = 45,674)	
	%	No.	%	No.	%	No.	%	No.	%	No.
<b>Sex</b>										
Female	52.68	839,433	58.10	116,364	52.53	113,941	53.64	53,717	47.98	21,913
Male	47.32	754,090	41.90	83,916	47.47	102,981	46.36	46,424	52.02	23,761
Age at enrollment, y, mean (SD)	48.70	(16.01)	47.45	(15.65)	43.16	(14.13)	45.55	(14.83)	48.6	(16.6)
<b>Education</b>										
< High school	17.79	283,431	30.79	61,657	43.01	93,303	17.45	17,478	29.26	13,364
High school	36.15	576,051	33.88	67,860	28.49	61,796	27.54	27,583	34.54	15,774
Some college	21.59	344,094	21.21	42,474	17.25	37,425	21.17	21,203	15.70	7,170
College graduate	15.29	243,676	9.20	18,416	7.64	16,566	20.94	20,973	9.92	4,533
Postgraduate	9.16	146,041	4.90	9,820	3.59	7,787	12.86	12,882	5.88	2,687
Missing	0.01	230	0.03	53	0.02	45	0.02	22	4.70	2,146
<b>Home ownership</b>										
Owner	77.94	1,241,958	55.19	110,531	53.75	116,600	63.31	63,403	70.73	32,303
Renter	21.64	344,789	44.37	88,867	45.98	99,745	36.41	36,463	23.34	10,660
Missing	0.43	6,776	0.44	882	0.27	577	0.27	275	5.94	2,711
<b>Percent poverty</b>										
≤200	23.54	375,037	45.17	90,460	45.96	99,698	29.54	29,582	29.38	13,417
201-300	18.51	294,999	17.40	34,841	19.59	42,499	16.71	16,738	21.53	9,832
301-500	27.28	434,657	19.43	38,909	19.44	42,164	24.37	24,409	25.24	11,526
>500	26.05	415,156	12.86	25,761	12.00	26,022	26.32	26,362	19.12	8,735
Missing	4.62	73,674	5.15	10,309	3.01	6,539	3.05	3,050	4.74	2,164
<b>Household income</b>										
<\$20,000	25.74	410,148	46.94	94,002	40.57	88,013	28.59	28,635	30.55	13,952
\$20,000–\$35,000	23.33	371,766	23.51	47,079	26.30	57,057	21.03	21,062	24.44	11,164
\$35,000–\$50,000	18.66	297,399	13.29	26,624	15.15	32,867	16.34	16,363	17.18	7,845
\$50,000–\$75,000	19.05	303,589	10.37	20,768	11.51	24,957	17.97	17,996	13.53	6,181
>\$75,000	11.49	183,098	4.81	9,632	5.97	12,954	15.34	15,365	6.85	3,129
Missing	1.73	27,523	1.09	2,175	0.50	1,074	0.72	720	7.45	3,403
<b>Insurance</b>										
No insurance	7.20	114,756	13.46	26,952	27.10	58,791	15.54	15,557	5.69	2,600
Medicare	13.26	211,246	14.02	28,085	9.38	20,350	11.18	11,199	12.70	5,799
Medicaid	1.87	29,849	6.72	13,465	6.47	14,035	4.69	4,699	1.27	579
Government	0.94	14,931	1.30	2,596	0.86	1,873	1.55	1,550	2.87	1,309
Employer	43.71	696,575	37.64	75,395	41.23	89,430	49.18	49,245	29.59	13,516
Private	4.78	76,183	2.57	5,145	3.04	6,596	4.93	4,940	3.65	1,665
Missing	28.24	449,983	24.29	48,642	11.92	25,847	12.93	12,951	44.24	20,206
<b>Birthplace</b>										
In United States	92.77	1,478,275	89.54	179,339	47.78	103,651	47.07	47,132	91.63	41,849
Not in United States	4.02	64,016	6.24	12,504	47.93	103,979	48.78	48,851	2.89	1,321
Missing	3.22	51,232	4.21	8,437	4.28	9,292	4.15	4,158	5.48	2,504

Continued

**Table 1** Continued

	White, non-Hispanic (n = 1,593,523)		Black, non-Hispanic (n = 200,280)		Hispanic (n = 216,922)		Other race/ ethnicities, non-Hispanic (n = 100,141)		Missing (n = 45,674)	
	%	No.	%	No.	%	No.	%	No.	%	No.
<b>Social Security number</b>										
<b>Yes</b>	73.81	1,176,103	71.85	143,908	63.93	138,677	76.09	76,195	65.47	29,903
<b>No</b>	26.19	417,420	28.15	56,372	36.07	78,245	23.91	23,946	34.53	15,771

black was somewhat greater (0.73, 95% CI 0.53–1.02), but HRs for other minorities were even lower than with full follow-up.

To explore differences over time, we investigated risk of ALS by race/ethnicity in 2 time periods, 1973–1999 and 2000–2011. Risk for Hispanic participants was slightly higher in the earlier vs later time period, though CIs overlapped considerably (HR<sub>1973–1999</sub> 0.78, 95% CI 0.46–1.31; HR<sub>2000–2011</sub> 0.55, 95% CI 0.37–0.83). Risk for other groups differed only slightly in the 2 time periods.

**SES and ALS mortality.** Measures of SES were moderately associated with ALS mortality rate in models adjusted only for sex, with lower ALS risk among respondents reporting low income and high household poverty compared to respondents with the highest income and least impoverishment (table 3, column 4). Type of health insurance was associated with ALS mortality, with lower rate of ALS for persons with private insurance and for persons missing insurance data. After adjusting for race/ethnicity, associations of income and poverty with ALS were attenuated, while educational attainment remained substantially associated with ALS mortality, with high school, some college, and postgraduate education all associated with

elevated rate of ALS compared with less than high school education (table 3, column 5). In a model further adjusted for all other SES measures as well as type of health insurance, educational attainment remained statistically significantly associated with ALS (table 3, column 6). Further adjustment for smoking did not change the association of educational attainment with ALS.

**DISCUSSION** In this large, US-representative sample, we identified a higher risk of ALS among white participants compared with race/ethnic minority participants that is not accounted for by multiple measures of SES, type of health insurance, or immigrant status. Moreover, adjustment for the 4 measures of SES available in the NLMS data scarcely changed associations of race/ethnicity with ALS, suggesting that further confounding due to imprecise measurement of SES is likely to be small. Prior studies that report ALS risk by race/ethnicity in US samples have in general found that risk of ALS in black participants is substantially less than that of white participants,<sup>11,24</sup> with studies using national data finding risks in black participants to be approximately half that of white

**Table 2** Adjusted hazard ratios (HR)<sup>a</sup> (95% confidence intervals [CIs]) for amyotrophic lateral sclerosis (ALS) mortality by race/ethnicity, National Longitudinal Mortality Study, women and men age 25 years or older, 1973–2011

Race/ethnicity	Participants				Model 1: Adjusted for sex, HR (95% CI)	Model 2: Further adjusted for socioeconomic status <sup>a</sup> and health insurance, HR (95% CI)	Model 3: Further adjusted for place of birth and presence of a Social Security number, HR (95% CI)
	No.	Person-years	ALS deaths, n	Age at ALS death, y, mean (SD)			
White, non-Hispanic	1,593,523	25,304,899	1,129	70.14 (10.98)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Black, non-Hispanic	200,280	2,805,086	62	64.63 (12.57)	0.58 (0.46–0.73) <sup>b</sup>	0.61 (0.48–0.78) <sup>b</sup>	0.61 (0.48–0.78) <sup>b</sup>
Hispanic	216,922	2,819,176	54	68.72 (11.59)	0.56 (0.41–0.76) <sup>b</sup>	0.60 (0.44–0.82) <sup>c</sup>	0.64 (0.46–0.88) <sup>c</sup>
Other races, non-Hispanic	100,141	1,167,743	20	70.37 (13.00)	0.46 (0.28–0.75) <sup>c</sup>	0.47 (0.29–0.76) <sup>c</sup>	0.52 (0.31–0.86) <sup>d</sup>
Missing	45,674	927,977	34	66.25 (10.49)	0.87 (0.62–1.20)	0.93 (0.67–1.29)	0.93 (0.67–1.29)

<sup>a</sup> Socioeconomic status is measured by (1) income categorized in 5 levels, (2) household income as a percentage of the poverty line in 4 levels, (3) ownership or rental of home, and (4) educational attainment in 5 levels, all at time of survey.

<sup>b</sup> p < 0.001.

<sup>c</sup> p < 0.01.

<sup>d</sup> p < 0.05.

**Table 3** Adjusted hazard ratios (HR)<sup>a</sup> (95% confidence intervals) for amyotrophic lateral sclerosis (ALS) mortality by indicators of socioeconomic status, National Longitudinal Mortality Study, women and men age 25 years or older, 1973-2011

	No.	Person-years	ALS deaths	Adjusted for sex	Adjusted for sex and race/ethnicity	Adjusted for sex, race/ethnicity, and all socioeconomic indicators
<b>Model 1: Education</b>						
< High school	469,233	7,202,488	329	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
High school	749,064	12,359,890	514	1.32 (1.15-1.52) <sup>b</sup>	1.23 (1.07-1.42) <sup>c</sup>	1.20 (1.04-1.28) <sup>d</sup>
Some college	452,366	6,383,012	206	1.33 (1.12-1.58) <sup>c</sup>	1.24 (1.04-1.48) <sup>d</sup>	1.20 (1.00-1.44) <sup>d</sup>
College	304,164	4,265,319	125	1.19 (0.97-1.46)	1.10 (0.90-1.36)	1.06 (0.86-1.32)
Postgraduate	179,217	2,744,359	124	1.42 (1.15-1.75) <sup>c</sup>	1.31 (1.06-1.62) <sup>d</sup>	1.27 (1.01-1.59) <sup>d</sup>
Missing	2,496	69,814	<5 <sup>a</sup>	0.17 (0.00-7.00)	0.17 (0.00-6.90)	0.36 (0.01-15.35)
<b>Model 2: Income</b>						
<\$20,000	634,750	8,748,843	333	0.73 (0.60-0.90) <sup>c</sup>	0.79 (0.64-0.97) <sup>d</sup>	0.79 (0.57-1.09)
\$20,000-\$35,000	508,128	8,104,995	349	0.99 (0.81-1.21)	1.02 (0.84-1.25)	1.05 (0.80-1.38)
\$35,000-\$50,000	381,098	6,266,901	221	0.83 (0.67-1.02)	0.84 (0.68-1.04)	0.87 (0.67-1.12)
\$50,000-\$75,000	373,491	6,176,267	237	0.89 (0.72-1.10)	0.89 (0.72-1.10)	0.91 (0.73-1.13)
>\$75,000	224,178	2,903,184	127	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Missing	34,895	824,691	32	0.58 (0.39-0.87) <sup>c</sup>	0.59 (0.39-0.88) <sup>d</sup>	0.62 (0.40-0.96) <sup>d</sup>
<b>Model 3: Household percentage of poverty line</b>						
≤200%	608,194	8,936,440	299	0.79 (0.67-0.92) <sup>c</sup>	0.86 (0.74-1.01)	1.01 (0.76-1.34)
201% to <300%	398,909	6,406,476	255	0.97 (0.83-1.14)	1.01 (0.86-1.19)	1.03 (0.81-1.30)
301% to <500%	551,665	8,662,715	335	0.90 (0.78-1.05)	0.92 (0.79-1.07)	0.91 (0.75-1.11)
>500%	502,036	7,167,801	325	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Missing	95,736	1,851,450	85	0.96 (0.76-1.22)	0.99 (0.78-1.25)	1.01 (0.82-1.46)
<b>Model 4: Home ownership</b>						
Own	1,564,795	23,825,327	1,062	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Rent	580,524	8,916,024	233	0.88 (0.77-1.02)	0.96 (0.83-1.11)	1.02 (0.88-1.18)
Missing	11,221	283,531	<5 <sup>a</sup>	0.39 (0.16-0.93) <sup>d</sup>	0.40 (0.16-0.96) <sup>d</sup>	0.48 (0.20-1.17)
<b>Model 5: Type of health insurance</b>						
Medicare	218,656	2,482,830	253	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Medicaid	276,679	682,398	18	1.15 (0.74-1.79)	1.31 (0.84-2.05)	1.47 (0.94-2.30)
Government	62,627	293,391	6	0.66 (0.31-1.42)	0.67 (0.31-1.44)	0.69 (0.32-1.47)
Employer	22,259	12,025,480	328	0.86 (0.72-1.03)	0.85 (0.71-1.01)	0.86 (0.71-1.03)
Private	924,161	1,288,926	45	0.70 (0.50-0.97) <sup>d</sup>	0.68 (0.49-0.94) <sup>d</sup>	0.69 (0.50-0.97) <sup>d</sup>
Not covered	94,529	2,615,841	52	0.76 (0.56-1.02)	0.83 (0.62-1.11)	0.88 (0.75-1.03)
Missing	557,629	13,636,016	597	0.85 (0.73-0.99) <sup>d</sup>	0.84 (0.72-0.98) <sup>d</sup>	0.85 (0.63-1.15)

<sup>a</sup> Numbers below 5 are represented as <5 to protect participant confidentiality.

<sup>b</sup>  $p < 0.001$ .

<sup>c</sup>  $p < 0.01$ .

<sup>d</sup>  $p < 0.05$ .

participants.<sup>1,10,12,13</sup> However, all previous US-wide studies and most regional studies have not adjusted for any socioeconomic factors, health insurance status, or immigrant status.<sup>10,12,13</sup>

We found a slight association of low SES, as measured by income, household poverty, educational attainment, and home ownership, with lower ALS risk. However, these associations were attenuated and most

were not statistically significant after adjusting for race/ethnicity, with the exception of educational attainment. Less than high school education in comparison with higher levels of education remained associated with lower ALS risk (with the exception of college education, for which the association was smaller and not statistically significant), even after adjustment for other indicators of SES and health insurance. We did not find

a monotonic association between educational attainment and ALS risk, or with any other measure of SES and ALS. It seems somewhat unlikely that some protective factor was more prevalent only among the lowest education level or that some risk factor was more prevalent among most of the higher education levels.

While to our knowledge, no systematic examination of SES in association with ALS has been conducted, prior studies have suggested that certain jobs, including military service,<sup>2</sup> heavy manual labor,<sup>3</sup> and agricultural work,<sup>4</sup> and job-related exposures, including electric fields or electric shocks, heavy metals,<sup>25</sup> formaldehyde,<sup>26,27</sup> hypoxia, and pesticides,<sup>27,28</sup> may be risk factors for ALS, although findings have been inconsistent<sup>25,27,29</sup> and reviews have concluded that the evidence for an association of ALS with a variety of occupational risk factors is not strong.<sup>30</sup> It is possible that the association we found is due to underascertainment of ALS among persons with low education, even after accounting for their income and type of health insurance. Some evidence suggests that low education can lead to underascertainment of certain diseases, including parkinsonism,<sup>31</sup> autism, and systemic lupus erythematosus.

The lower risk of ALS we found among US non-Hispanic black, Hispanic, and non-Hispanic persons of other race/ethnicities may be due to genetic differences between these groups vs white participants. This possibility raises 2 important issues. First, to what extent does self-identified race/ethnicity correspond to genetic ancestry in the United States? Self-identified race/ethnicity is associated with genetic variation to varying degrees in individuals in the United States. Persons identifying as black or African American, for example, have been found to be on average 69%–74% of West African origin and 11%–19% European–Middle Eastern genetic ancestry, and percentages for individuals vary very widely.<sup>32,33</sup> African Americans have been found to have more heterozygosity in single-nucleotide polymorphisms and fewer probably damaging alleles compared with US whites, due to the genetic bottleneck experienced among European ancestral populations around the time of migration out of Africa,<sup>34</sup> which may be protective against ALS. Ancestral genetic admixture of self-identified Hispanics in the United States has been estimated in different samples as being 62%–71% European, 21%–33% Amerindian, and 6% African genetic ancestry.<sup>33</sup> Thus, on average, US Hispanics have a genetic ancestry that is heavily European, suggesting that genetics alone may not explain the lower risk of ALS we found among Hispanics. It is also possible that having genetic admixture is protective against ALS. A population study of Cuba, a country in which access to health care does not

differ by race/ethnicity, found that persons of mixed race/ethnicity (estimated to be of 55% European and 45% African ancestry) were at substantially lower risk of ALS mortality compared with whites (85% European, 15% non-European ancestry) or blacks (75% West African ancestry).<sup>35</sup> However, we know of no other studies that find genetic admixture protective against disease.

Second, does our understanding of the genetics of ALS support a hypothesis that genetic differences among race/ethnic groups could yield the substantially different rates of ALS by race/ethnicity that we found? Although little ALS genetic research has been conducted in non-European populations, results suggest that the genetic architecture may differ in different geographic regions.<sup>36</sup> Moreover, the heritability of ALS has been estimated at 0.61 (0.38–0.78),<sup>37</sup> indicating that genetics play an important role in ALS risk.

To the extent that our findings of race/ethnic differences in ALS reflect environmental causes of ALS, such as chemical exposures,<sup>25–27</sup> lifestyle and health-related behaviors,<sup>23,38</sup> and stressors,<sup>3</sup> these factors would have to be associated with race/ethnicity and not with the SES measures we included in our analyses. Specific exposures that fit these criteria are challenging to identify, but may include diet, which is heavily patterned by race/ethnicity,<sup>39</sup> although it is also patterned by SES.<sup>40</sup>

Our study has important limitations. We could not validate the ascertainment of ALS in the NDI nor were we able to determine whether ascertainment differs by race/ethnicity or SES. While we cannot rule out ascertainment bias, we adjusted for multiple possible sources of ascertainment bias, including insurance coverage and immigrant status. Furthermore, differences by race/ethnicity were largely similar in the earlier and later decades of the study. As differences in ascertainment by race/ethnicity are likely to have moderated over time, these results may suggest that ascertainment bias is not a primary driver of race/ethnic differences found here. In addition, ALS is more frequently underdiagnosed at older vs younger ages, which may introduce bias. We conducted sensitivity analyses restricted to persons age <75 years, among whom age-related underdiagnosis of ALS would be less prevalent compared with the whole sample. Results were very similar in this subsample.

Our results provide evidence that higher ALS mortality in US whites vs minority race/ethnicities is due to actual differences in risk of ALS in these groups, rather than reflecting socioeconomic differences in ALS risk or underascertainment due to health insurance or immigrant status in race/ethnic minority groups. These differences in race/ethnic risk may in turn reflect underlying differences in genetic risk factors for ALS in US race/ethnic groups.

## AUTHOR CONTRIBUTIONS

Dr. Roberts contributed to designing the analytic plan and led the writing. Dr. Johnson conducted the data analyses and edited the manuscript. Dr. Chen contributed to designing the analytic plan and edited the manuscript. Dr. Cudkowicz contributed to the study design and edited the manuscript. Dr. Weisskopf conceived the study, contributed to designing the analytic plan, and edited the manuscript. All authors approved the submitted manuscript.

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## DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to [Neurology.org](http://Neurology.org) for full disclosures.

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