Geographic Variation of Amyotrophic Lateral Sclerosis Incidence in New Jersey, 2009–2011

Kevin A. Henry, Jerald Fagliano, Heather M. Jordan, Lindsay Rechtman, and Wendy E. Kaye

Department of Geography and Urban Studies, College of Liberal Arts, Temple University, Philadelphia, Pennsylvania (Kevin A. Henry); Department of Epidemiology, Rutgers School of Public Health, Piscataway, New Jersey (Kevin A. Henry); Environmental and Occupational Health Surveillance Program, New Jersey Department of Health, Trenton, New Jersey (Jerald Fagliano, Heather M. Jordan, Lindsay Rechtman); and McKing Consulting Corporation, Atlanta, Georgia (Heather M. Jordan, Lindsay Rechtman, Wendy E. Kaye)

Abstract

Few analyses in the United States have examined geographic variation and socioeconomic disparities in amyotrophic lateral sclerosis (ALS) incidence, because of lack of population-based incidence data. In this analysis, we used population-based ALS data to identify whether ALS incidence clusters geographically and to determine whether ALS risk varies by area-based socioeconomic status (SES). This study included 493 incident ALS cases diagnosed (via El Escorial criteria) in New Jersey between 2009 and 2011. Geographic variation and clustering of ALS incidence was assessed using a spatial scan statistic and Bayesian geoadditive models. Poisson regression was used to estimate the associations between ALS risk and SES based on census-tract median income while controlling for age, sex, and race. ALS incidence varied across and within counties, but there were no statistically significant geographic clusters. SES was associated with ALS incidence. After adjustment for age, sex, and race, the relative risk of ALS was significantly higher (relative risk (RR) = 1.37, 95% confidence interval (CI): 1.02, 1.82) in the highest income quartile than in the lowest. The relative risk of ALS was significantly lower among blacks (RR = 0.57, 95% CI: 0.39, 0.83) and Asians (RR = 0.63, 95% CI: 0.41, 0.97) than among whites. Our findings suggest that ALS incidence in New Jersey appears to be associated with SES and race.
Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease, is a rare and fatal neurological disease characterized by a progressive loss of motor neurons in the brain and spinal cord. Currently the cause of ALS is unknown; however, a small proportion of cases are familial (1). The remainder of the cases, accounting for 90%–95% of all observed cases worldwide, are referred to as sporadic ALS. Numerous possible risk factors for sporadic ALS have been studied, including environmental exposures (2–4), occupational exposures (4–6), physical activity and trauma (7), oxidative stress (8), nutritional intake (9), and smoking (10, 11), but results from these studies have thus far been inconsistent and inconclusive.

Reported crude incidence rates of ALS worldwide currently range from 0.3 cases per 100,000 population to 3.6 cases per 100,000 (12). The incidence of ALS increases with age, with the majority of cases being diagnosed at 55–75 years of age (12, 13). Men have higher incidence rates of ALS than women (13, 14), and data suggest a lower incidence of ALS in nonwhites and Hispanics compared with whites and non-Hispanics, respectively (15–17). Geographic areas with higher localized incidence rates of ALS (e.g., geographic clustering) have been reported in specific regions worldwide. The most notable examples include a higher incidence of the Western Pacific form of ALS in the 1950s on the island of Guam (18), on the Kii Peninsula in Japan (19), and in southwestern New Guinea (20).

Motivated by investigations into potential environmental causes of ALS in the Western Pacific and other recent reports of localized clusters of ALS elsewhere in the world (21–30), researchers are increasingly using spatial analysis methods to map geographic variations in ALS incidence and to identify localized clusters of ALS (31). The main goal of these types of investigations has been to locate geographic clusters of ALS and develop hypotheses about possible environmental risk factors responsible for the clusters (31).

While spatial analysis of disease rates provides a logical starting point for developing hypotheses about potential geography-based environmental risk factors, studies about socioeconomic variations in disease rates are also useful for formulating hypotheses about the role that environmental, social, and behavioral risk factors play in the development of disease (32, 33). For some chronic diseases, such as some cancers, associations between disease risk and socioeconomic status (SES) have been consistently shown (34–36). Surprisingly, there have only been 3 studies of the association between ALS incidence and SES. These studies were conducted in Finland (37), the United States (38), and Florence, Italy (39) more than 30 years ago, and the results were inconsistent. It remains unclear whether ALS is associated with SES.

To date, only a limited number of population-based studies examining geographic variation and socioeconomic disparities in ALS incidence have been completed in the United States, because of lack of data. In this investigation, we utilized ALS incidence data collected as part of a surveillance project funded by the Agency for Toxic Substances and Disease

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Registry (40) to map the geographic variation in ALS risk in New Jersey and identify any evidence of geographic clustering. In addition to the spatial analysis, a secondary objective of this investigation was to examine whether ALS risk varies by area-based SES. To our knowledge, this is the first geographic analysis of ALS to have been completed for New Jersey and one of only a handful from the continental United States that have used population-based ALS incidence data rather than mortality data.

METHODS
Study population

The case data included 493 New Jersey residents diagnosed with ALS from 2009 to 2011 that met the El Escorial criteria (41). Details about ALS case ascertainment in New Jersey and data collection efforts have been previously described (13). Information about patient demographic characteristics, including date of birth, sex, race, and ethnicity, was available. Race was classified into white, black/African-American, Asian, and unknown/other. Ethnicity was classified into Hispanic, non-Hispanic, and unknown.

Geocoding, area socioeconomic measures, and population data

For each ALS case, the patient’s address as provided by the reporting neurologist was geocoded using both ArcGIS 10.1 software (ESRI, Redlands, California) and Google Earth software, version 7.1 (Google Inc., Mountain View, California). ArcGIS successfully geocoded the full addresses of 425 of the 493 cases with a perfect match score, and the remaining 68 addresses were manually geocoded using Google Earth. In total, 5 of the 493 addresses could not be geocoded based on the full address. All geocoded cases were assigned a 2010 census tract, and the remaining cases not geocoded (n = 5) were assigned a census tract based on their zip code using geographic imputation methods described previously by Henry and Boscoe (42).

Census-tract median annual household income was used as the area-based SES measure (43) and was categorized into quartiles (1 = lowest, 4 = highest) on the basis of the statewide distribution among census tracts. A quartile value was assigned to each ALS case based on its census tract. For this analysis, census-tract median income was conceptualized as an area-or neighborhood-based socioeconomic measure. Area-based SES measures describe the neighborhood context in which an individual lives and could affect health through several pathways, including the physical conditions of the neighborhood (e.g., pollution levels), the material resources of the neighborhood (e.g., availability of healthy, affordable food options), and social capital and social networks (e.g., social contagion, similar norms of behavior) (32, 33, 44).

Population counts by age, sex, race, and ethnicity for census tracts used in subsequent analyses were obtained from the 2010 US Census (Summary File 1, tables PCT012A–PCT012H) (45). Because population estimates for census tracts were not available for intercensal years, the 2010 population counts were multiplied by 3 to estimate the population at risk of ALS for the 3-year period 2009–2011.
Statewide incidence

Average annual ALS incidence rates per 100,000 population were age-standardized to the 2000 US Census population (19 age groups) by means of the direct method. Rates are presented as number of cases per 100,000 population, and 95% confidence intervals for incidence rates were calculated as gamma intervals (46). The risk of ALS by quartile of census-tract median income was estimated using a Poisson regression model adjusting for sex, age at diagnosis, and race. Coefficients were exponentiated and interpreted as relative risks, and ALS risk in each of the 3 highest income quartiles was compared with that in the lowest income quartile. The natural logarithm of the tract-level population in each sex, race, and age category was used as an offset in the model. Cases with missing information on race ($n = 27$) were not included in the model. SAS (SAS Institute, Inc., Cary, North Carolina) was used to calculate age-adjusted rates, and SAS Proc Glimmix was used to estimate parameters in the Poisson regression model. All tests of statistical significance and confidence intervals were 2-sided. A $P$ value less than 0.05 was considered statistically significant.

Geographic clustering and mapping

Geographic clustering of ALS was evaluated with a spatial scan statistic using SaTScan software, version 9.3 (47). The spatial scan statistic is used to test whether a disease is randomly distributed over space or whether there is evidence of clustering. Analysis was conducted at the census-tract level using a Poisson model and an elliptical spatial window with the maximum cluster size set to 50% of the population at risk. We also conducted sensitivity analyses of the scan statistic results by setting the maximum cluster size to 10% and 5% of the population at risk, respectively. The ALS incidence rates used in the spatial scan statistic were adjusted for sex and age (19 age groups), followed by subsequent analyses that also adjusted for race. SaTScan reports the geographic area that is the most likely cluster and also tests for statistical significance via Monte Carlo simulations (48). Any secondary clusters whose $P$ values are below the set $\alpha$ level are also reported. The level of statistical significance ($\alpha$) was set at 0.05 (5%), and 9,999 Monte Carlo iterations were used (48). Analyses were completed for all cases combined and for males and females separately.

A geographically smoothed relative risk map of ALS for New Jersey was developed using a structured additive regression model based on a fully Bayesian approach. The ALS case counts by census tract were modeled as a Poisson random variable. The model included sex, age at diagnosis (categorized into 19 age groups), the structured spatial effects, and the unstructured random effects (census tracts). The spatial smoothness “prior” was specified based on Markov random fields with geographic neighbors defined as those census tracts that shared a common boundary. The offset was the natural logarithm of the tract-level population in each sex and age category from 2009 through 2011. Positive hyperparameters ($a = b = 0.001$), which are assumed to have an inverse gamma distribution, were chosen to ensure the propriety of the joint posterior. The model was fitted by full Bayesian inference using Markov chain Monte Carlo simulation methods that allow for random samples to be drawn from posterior distributions. A total of 25,000 iterations were run, with the first 5,000 samples used as the burn-in period, and a final sample of 1,000 was used for posterior estimates. The posterior distribution was used to obtain the 95% credible intervals, and the
posterior mean value for each tract was exponentiated to obtain the relative risk of ALS. Credible intervals, which are analogous to confidence intervals in frequentist statistics, describe the range in which a posterior probability estimate is likely to reside and can be used to determine whether the relative risk at a specific geographic location is significantly different from the statewide risk of ALS (e.g., clustering of high rates). Bayesian analysis was performed using the free software BayesX, version 2.1 (Ludwig-Maximilians University Munich, Göttingen, Germany) (49), and tract relative risk estimates were mapped using ArcGIS 10.1.

RESULTS

A total of 493 ALS cases were diagnosed between 2009 and 2011. The crude ALS incidence rate for the study period was 1.87 cases per 100,000 population, and the direct age-standardized incidence rate was 1.67 cases per 100,000 population. ALS incidence rates increased with age up to age 79 years (Table 1), and age-adjusted incidence rates were statistically significantly higher for men than for women ($P < 0.05$) (Table 2). The overall age-adjusted incidence rate for whites (1.80 cases per 100,000 population, 95% confidence interval (CI): 1.62, 1.97) was statistically significantly higher than that for blacks and Asians ($P < 0.05$). Age-adjusted incidence rates were highest in the highest income quartile and decreased for each lower quartile of median income (Table 2).

Table 3 shows the results from the Poisson regression models examining the association between ALS risk and census-tract median income. In the crude model and in the model adjusted only for age, the risk of ALS was significantly higher in the highest income quartile compared with the lowest (relative risks were 1.65 (95% CI: 1.25, 2.18) and 1.55 (95% CI: 1.18, 2.05), respectively). After adjustment for age, sex, and race, the relative risk of ALS was attenuated slightly but remained significantly higher in the highest income quartile versus the lowest (relative risk = 1.37, 95% CI: 1.02, 1.82). The fully adjusted model also showed that the risk of ALS was significantly higher among men compared with women and lower among blacks and Asians compared with whites.

Using the spatial scan statistic, analysis of geographic clustering of ALS indicated no statistically significant geographic clusters of elevated ALS risk in New Jersey, either for all cases combined or for males and females separately. Furthermore, sensitivity analyses of the spatial scan statistic results using smaller spatial windows also indicated no significant clusters. The age-adjusted smoothed relative risk map of ALS for New Jersey by census tract showed that ALS incidence varied within and across counties. Age-adjusted smoothed relative risk estimates ranged from 0.75 to 1.42 (Figure 1). Generally, the relative risk of ALS was below 1.0 (lower risk than the statewide average) in lower-income areas of the state (Trenton, Camden, Atlantic City, Newark, and Jersey City) and above 1.0 (higher risk than the statewide average) in higher-income areas of the state (parts of Bergen, Morris, and Monmouth counties) (Figure 1). The 95% credible interval from the Bayesian structured additive regression models also indicated that there were no areas where the relative risk of ALS was higher than the statewide average (i.e., no significant clustering of ALS).
DISCUSSION

To our knowledge, this is the first statewide population-based study completed in the United States to have assessed geographic clustering of ALS and to have described the relative risk of ALS by geography and area-based SES. The geographic cluster analysis did not identify any places in New Jersey where the relative risk of ALS (observed number of cases vs. expected number of cases) was statistically significantly high; however, the smoothed relative risk maps did identify distinct regional differences in ALS risk throughout the state. The results from the multivariable regression models indicated a statistically significant association between area-based median income and ALS risk in New Jersey independent of age, sex, and race. ALS risk was highest among persons living in areas of the state with the highest median income compared with those living in areas with the lowest median income.

Not finding any statistically significant geographic clustering of ALS cases in New Jersey is in contrast to many population-based studies completed in other parts of the world (23–26, 29, 50), including one in the United States that found geographic clustering of ALS (21, 27, 28). There are several possible reasons why there was no evidence of geographic clustering of ALS in New Jersey. First, environmental exposures or other risk factors could be present in the other study regions that are not present in New Jersey. Second, the ALS cases in our study were more contemporary incident cases diagnosed between 2009 and 2011, while many other studies used ALS cases or deaths from earlier time periods. It is possible that there may be period and cohort effects where the risk of ALS may vary by time period or year of birth, which could coincide with shifts in exposure to risk factors over time. For example, in Guam, rates of ALS were extremely high among its indigenous people, the Chamorro, in the 1950s (estimated to be 50–100 times higher than worldwide rates), followed by decades of significant decline, with rates today that are only slightly higher than those worldwide (18). It has been suggested that the decline in ALS rates in Guam was related to modernization, which resulted in the elimination of the environmental factors that had triggered the high rates (18).

The positive association between area-based SES and ALS risk is an intriguing finding, but the underlying factors that may account for this association are unknown. It is possible that area-based median income could be correlated with specific behavioral risk factors that modify the risk of ALS. It is also possible that differences in residential location based on income could account for differential exposures to environmental risk factors that are hypothesized to be associated with ALS, including pesticides (51, 52) or the cyanobacteria-produced neurotoxin β-methylamino-L-alanine (BMAA) (53–56), which is most commonly found in marine and freshwater environments (57). More research is needed to understand what it is about census-tract median income that produces variability in risk of ALS in New Jersey. Because both individual and environmental factors have been suggested as possible causes of ALS, future studies should include both individual and area-level measures of SES, behavior, and environment.

Of the previous 3 studies that examined SES and ALS risk in the United States, Italy, and Finland (37–39), our findings were consistent with only 1: the nationwide study that examined mortality rates for motor neuron disease in the United States (38). In that study,
Bharucha et al. (38) found that SES, as defined by county-level education, was positively associated with motor neuron disease. In the study in Italy, Bracco et al. (39) found that the incidence of ALS was highest among manual workers, but they did not find significant differences based on educational level. Finally, in Finland, Palo and Jokelainen (37) reported that social class was negatively associated with ALS incidence, in contrast with our findings. Variations between the studies carried out in the United States, Italy, and Finland—countries whose social, economic, and demographic profiles vary greatly—make comparisons difficult, and the differences in how SES was operationalized in each one exacerbate the problem. These issues point to the need for additional studies to assess the SES-ALS relationship, as well as to determine whether our finding of a positive association with SES is unique to New Jersey.

A rigorous case ascertainment approach was employed to capture ALS cases for the New Jersey ALS surveillance project; however, it is important to consider potential study biases related to any unreported ALS cases during the study period. As part of the case capture strategy in New Jersey, which has been previously described (13), neurologists in New Jersey and in parts of the surrounding states of New York, Pennsylvania, and Delaware submitted 109% of the expected number of cases for the 3-year reporting period. New Jersey death certificate and hospital discharge data were also used to identify possibly unreported cases. Although approximately 10% of neurologists who said they diagnosed or cared for ALS patients did not submit case reports, the majority of ALS patients are treated at ALS referral centers, and all ALS referral centers in the region reported cases. However, it is possible that a small number of cases may have gone unreported. If the unreported cases were not missing at random or differential by SES, the direction of the potential bias would depend on whether the high- or low-SES groups were more likely to be captured.

In this study, we also investigated the potential for bias to affect estimates of SES and ALS due to the exclusion of 27 cases that either had unknown race or were coded as other race. Of the 27 cases, 38.1% and 26.7% were in the 2 highest SES groups, respectively. The inclusion of these cases would have resulted in a stronger association between SES and ALS, and therefore their exclusion in our analysis biased the result toward the null. We also conducted 2 additional regression analyses by including only whites and mutually exclusive race/ethnicity groups in the models. Both analyses found a significant positive association between SES and ALS risk.

There are several limitations to be noted regarding this investigation. First, the geographic locations of the cases might not have been their addresses at the time of diagnosis, as neurologists were instructed to report the most recent address that was in the medical record. Therefore, if patients moved after diagnosis and neurologists updated the medical records, it is possible that some addresses might not have represented the case’s address at the time of diagnosis. Second, using only residential address at the time of diagnosis limits a study’s ability to assess clustering based on past exposures, which may be measured through previous residential locations. This is especially important for a disease such as ALS, where some studies have suggested a lag time between exposure to a causative agent and the development of clinical symptoms (58, 59). To better assess geographic exposures over
time, future investigators should consider lifetime residential histories when conducting spatial analysis.

In conclusion, no statistically significant geographic clusters of ALS were found in this study. However, ALS risk did vary geographically throughout New Jersey and appeared to be associated with area-based SES and race. Men and women living in the wealthiest or highest-income areas of the state had a higher risk of ALS than those living in lower-income areas. The variations we observed in incidence rates by race, area-based SES, and geography could be indicative of differential exposures to relevant environmental factors, with respect to person or place. Further research is needed to clarify the area-based SES-ALS relationship and to determine what other factors, including behavioral, environmental, occupational health risk factors, might be contributing to the observed geographic variation in ALS in New Jersey.

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Abbreviations

| Abbreviation | Description                  |
|--------------|------------------------------|
| ALS          | amyotrophic lateral sclerosis |
| CI           | confidence interval          |
| SES          | socioeconomic status         |

References

1. Byrne S, Walsh C, Lynch C, et al. Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2011; 82(6):623–627. [PubMed: 21047878]
2. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. Nat Rev Neurol. 2013; 9(11):617–628. [PubMed: 24126629]
3. Brown RC, Lockwood AH, Sonawane BR. Neurodegenerative diseases: an overview of environmental risk factors. Environ Health Perspect. 2005; 113(9):1250–1256. [PubMed: 16140637]
4. Das K, Nag C, Ghosh M. Familial, environmental, and occupational risk factors in development of amyotrophic lateral sclerosis. N Am J Med Sci. 2012; 4(8):350–355. [PubMed: 22912943]
5. Haley RW. Excess incidence of ALS in young Gulf War veterans. Neurology. 2003; 61(6):750–756. [PubMed: 14504316]
6. Park RM, Schulte PA, Bowman JD, et al. Potential occupational risks for neurodegenerative diseases. Am J Ind Med. 2005; 48(1):63–77. [PubMed: 15940722]
7. Beghi E, Logroscino G, Chiò A, et al. Amyotrophic lateral sclerosis, physical exercise, trauma and sports: results of a population-based pilot case-control study. Amyotroph Lateral Scler. 2010; 11(3):289–292. [PubMed: 20433412]
8. Mitumoto H, Factor-Litvak P, Andrews H, et al. ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS): study methodology, recruitment, and baseline demographic and disease characteristics. Amyotroph Lateral Scler Frontotemporal Degener. 2014; 15(3–4):192–203. [PubMed: 24564738]
9. Yanagihara R, Garruto RM, Gajdusek DC, et al. Calcium and vitamin D metabolism in Guamanian Chamorros with amyotrophic lateral sclerosis and parkinsonism-dementia. Ann Neurol. 1984; 15(1):42–48. [PubMed: 6546847]
10. Wang H, O’Reilly EJ, Weisskopf MG, et al. Smoking and risk of amyotrophic lateral sclerosis: a pooled analysis of 5 prospective cohorts. Arch Neurol. 2011; 68(2):207–213. [PubMed: 21320987]

11. Fang F, Valdimarsdóttir U, Bellocco R, et al. Amyotrophic lateral sclerosis in Sweden, 1991–2005. Arch Neurol. 2009; 66(4):515–519. [PubMed: 19364937]

12. Chiò A, Logroscino G, Traynor BJ, et al. Global epimediology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology. 2013; 41(2):118–130. [PubMed: 23860588]

13. Jordan H, Fagliano J, Rechtman L, et al. Population-based surveillance of amyotrophic lateral sclerosis in New Jersey, 2009–2011. Neuroepidemiology. 2014; 43(1):49–56. [PubMed: 25323440]

14. Logroscino G, Traynor BJ, Hardiman O, et al. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. J Neurol Neurosurg Psychiatry. 2008; 79(1):6–11. [PubMed: 18079297]

15. Cronin S, Hardiman O, Traynor BJ. Ethnic variation in the incidence of ALS: a systematic review. Neurology. 2007; 61(13):1002–1007. [PubMed: 17389304]

16. Gundogdu B, Al-Lahham T, Kadlubar F, et al. Racial differences in motor neuron disease. Amyotroph Lateral Scler Frontotemporal Degener. 2014; 15(1–2):114–118. [PubMed: 24067242]

17. Rechtman L, Jordan H, Wagner L, et al. Racial and ethnic differences among amyotrophic lateral sclerosis cases in the United States. Amyotroph Lateral Scler Frontotemporal Degener. 2015; 16(1–2):65–71. [PubMed: 25482100]

18. Plato CC, Garruto RM, Galasko D, et al. Amyotrophic lateral sclerosis and parkinsonism-dementia complex of Guam: changing incidence rates during the past 60 years. Am J Epidemiol. 2003; 157(2):149–157. [PubMed: 12522022]

19. Kuzuhara S, Kobu O. Atypical parkinsonism of Japan: amyotrophic lateral sclerosis-parkinsonism-dementia complex of the Kii peninsula of Japan (Muro disease): an update. Mov Disord. 2005; 20(suppl 12):S108–S113. [PubMed: 16092099]

20. Gajdusek DC, Salazar AM. Amyotrophic lateral sclerosis and parkinsonian syndromes in high incidence among the Auyu and Jakai people of West New Guinea. Neurology. 1982; 32(2):107–126. [PubMed: 7198738]

21. Caller TA, Chipman JW, Field NC, et al. Spatial analysis of amyotrophic lateral sclerosis in northern New England, USA, 1997–2009. Muscle Nerve. 2013; 48(2):235–241. [PubMed: 23881670]

22. Caller TA, Doolin JW, Haney JF, et al. A cluster of amyotrophic lateral sclerosis in New Hampshire: a possible role for toxic cyanobacteria blooms. Amyotroph Lateral Scler 2009; 10(suppl 2):101–108. [PubMed: 19929741]

23. Corcia P, Jafari-Schluep HF, Lardillier D, et al. A clustering of conjugal amyotrophic lateral sclerosis in southeastern France. Arch Neurol. 2003; 60(4):553–557. [PubMed: 12707069]

24. Doi Y, Yokoyama T, Tango T, et al. Temporal trends and geographic clusters of mortality from amyotrophic lateral sclerosis in Japan, 1995–2004. J Neurol Sci. 2010; 298(1–2):78–84. [PubMed: 20804988]

25. Sabel CE, Boyle PJ, Löytönen M, et al. Spatial clustering of amyotrophic lateral sclerosis in Finland at place of birth and place of death. Am J Epidemiol. 2003; 157(10):898–905. [PubMed: 12746242]

26. Scott KM, Abhinav K, Stanton BR, et al. Geographical clustering of amyotrophic lateral sclerosis in South-East England: a population study. Neuroepidemiology. 2009; 32(2):81–88. [PubMed: 19039239]

27. Torbick N, Hession S, Stommel E, et al. Mapping amyotrophic lateral sclerosis lake risk factors across northern New England. Int J Health Geogr. 2014; 13:1. [PubMed: 24383521]

28. Turabelidze G, Zhu BP, Schootman M, et al. An epidemiologic investigation of amyotrophic lateral sclerosis in Jefferson County, Missouri, 1998–2002. Neurotoxicology. 2008; 29(1):81–86. [PubMed: 17950889]

29. Uccelli R, Binazzi A, Altavista P, et al. Geographic distribution of amyotrophic lateral sclerosis through motor neuron disease mortality data. Eur J Epidemiol. 2007; 22(11):781–790. [PubMed: 17874192]
30. Taylor JA, Davis JP. Evidence for clustering of amyotrophic lateral sclerosis in Wisconsin. J Clin Epidemiol. 1989; 42(6):569–575. [PubMed: 2738617]
31. Caller TA, Field NC, Chipman JW, et al. Spatial clustering of amyotrophic lateral sclerosis and the potential role of BMAA. Amyotroph Lateral Scler. 2012; 13(1):25–32. [PubMed: 22214351]
32. Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. Health Aff (Millwood). 2002; 21(2):60–76. [PubMed: 11900187]
33. Robert SA. Socioeconomic position and health: the independent contribution of community socioeconomic context. Annu Rev Sociol. 1999; 25:489–516.
34. Boscoe FP, Johnson CJ, Sherman RL, et al. The relationship between area poverty rate and site-specific cancer incidence in the United States. Cancer. 2014; 120(14):2191–2198. [PubMed: 24866103]
35. Kroll ME, Stiller CA, Murphy MF, et al. Childhood leukaemia and socioeconomic status in England and Wales 1976–2005: evidence of higher incidence in relatively affluent communities persists over time. Br J Cancer. 2011; 105(11):1783–1787. [PubMed: 22027710]
36. Ward E, Jemal A, Kokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin. 2004; 54(2):78–93. [PubMed: 15061598]
37. Palo J, Jokelainen M. Re: “Geographic and social distribution of patients with amyotrophic lateral sclerosis” [letter]. Arch Neurol. 1977; 34(1):724. [PubMed: 911245]
38. Bharucha NE, Schoenberg BS, Raven RH, et al. Geographic distribution of motor neuron disease and correlation with possible etiologic factors. Neurology. 1983; 33(7):911–915. [PubMed: 6683374]
39. Bracco L, Antuono P, Amaducci L. Study of epidemiological and etiological factors of amyotrophic lateral sclerosis in the province of Florence, Italy. Acta Neurol Scand. 1979; 60(2):112–124. [PubMed: 495044]
40. Antao VC, Horton DK. The National Amyotrophic Lateral Sclerosis (ALS) Registry. J Environ Health. 2012; 75(1):28–30. [PubMed: 22866401]
41. Brooks BR, Miller RG, Swash M, et al. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000; 1(5):293–299. [PubMed: 11464847]
42. Henry KA, Boscoe FP. Estimating the accuracy of geographical imputation. Int J Health Geogr. 2008; 7:3. [PubMed: 18215308]
43. Krieger N, Chen JT, Waterman PD, et al. Choosing area based socioeconomic measures to monitor social inequalities in low birth weight and childhood lead poisoning: The Public Health Disparities Geocoding Project (US). J Epidemiol Community Health. 2003; 57(3):186–199. [PubMed: 12594195]
44. Diez Roux AV. Investigating neighborhood and area effects on health. Am J Public Health. 2001; 91(11):1783–1789. [PubMed: 11684601]
45. Bureau of the Census, US Department of Commerce. Census 2010 Summary File 1. New Jersey. Washington, DC: Bureau of the Census; 2010. http://www2.census.gov/census_2010/04-Summary_File_1/New_Jersey/ [Accessed February 1, 2014]
46. Fay MP, Feuer EJ. Confidence intervals for directly standardized rates: a method based on the gamma distribution. Stat Med. 1997; 16(7):791–801. [PubMed: 9131766]
47. Kulldorff M. A spatial scan statistic. Commun Stat Theory Methods. 1997; 26(6):1481–1496.
48. Kulldorff, M. SaTScanTM v9.3: SaTScan User Guide for Version 9.4. Silver Spring, MD: Information Management Services, Inc; 2014.
49. Belitz, C.; Brezger, A.; Kneib, T., et al. [Accessed January 8, 2014] BayesX—Bayesian inference in structured additive regression models [software]. Version 2.1. http://www.statistik.lmu.de/~bayesx/bayesx.html
50. Gunnarsson LG, Lygner PE, Veiga-Cabo J, et al. An epidemic-like cluster of motor neuron disease in a Swedish county during the period 1973–1984. Neuroepidemiology. 1996; 15(3):142–152. [PubMed: 8700306]
51. Deapen DM, Henderson BE. A case-control study of amyotrophic lateral sclerosis. Am J Epidemiol. 1986; 123(5):790–799. [PubMed: 3962963]
52. McGuire V, Longstreth WT Jr, Nelson LM, et al. Occupational exposures and amyotrophic lateral sclerosis. A population-based case-control study. Am J Epidemiol. 1997; 145(12):1076–1088. [PubMed: 9199537]

53. Banack SA, Caller T, Henegan P, et al. Detection of cyanotoxins, β-N-methylamino-L-alanine and microcystins, from a lake surrounded by cases of amyotrophic lateral sclerosis. Toxins (Basel). 2015; 7(2):322–336. [PubMed: 25643180]

54. Bradley WG, Borenstein AR, Nelson LM, et al. Is exposure to cyanobacteria an environmental risk factor for amyotrophic lateral sclerosis and other neurodegenerative diseases? Amyotroph Lateral Scler Frontotemporal Degener. 2013; 14(5–6):325–333. [PubMed: 23286757]

55. Cox PA, Banack SA, Murch SJ. Biomagnification of cyanobacterial neurotoxins and neurodegenerative disease among the Chamorro people of Guam. Proc Natl Acad Sci U S A. 2003; 100(23):13380–13383. [PubMed: 14612559]

56. Pablo J, Banack SA, Cox PA, et al. Cyanobacterial neurotoxin BMAA in ALS and Alzheimer’s disease. Acta Neurol Scand. 2009; 120(4):216–225. [PubMed: 19254284]

57. Merel S, Walker D, Chicana R, et al. State of knowledge and concerns on cyanobacterial blooms and cyanotoxins. Environ Int. 2013; 59:303–327. [PubMed: 23892224]

58. Garruto RM, Gajdusek C, Chen KM. Amyotrophic lateral sclerosis among Chamorro migrants from Guam. Ann Neurol. 1980; 8(6):612–619. [PubMed: 7212649]

59. Garruto RM, Gajdusek DC, Chen KM. Amyotrophic lateral sclerosis and parkinsonism-dementia among Filipino migrants to Guam. Ann Neurol. 1981; 10(4):341–350. [PubMed: 7316487]
Figure 1.
Geographically smoothed relative risk map of amyotrophic lateral sclerosis (ALS) in New Jersey, 2009–2011. The map is based on results from a Bayesian geoadditive model with adjustment for age and sex.
Table 1

Age-Specific Crude Incidence Rates of Amyotrophic Lateral Sclerosis for Cases Diagnosed in New Jersey in 2009–2011 (n = 493)

| Age at Diagnosis, years | No. of Cases | %   | Crude IRa |
|-------------------------|--------------|-----|-----------|
| <30                     | 4            | 0.8 | 0.04      |
| 30–39                   | 13           | 2.6 | 0.38      |
| 40–49                   | 40           | 8.1 | 0.98      |
| 50–59                   | 114          | 23.1| 3.06      |
| 60–69                   | 143          | 29.0| 5.73      |
| 70–79                   | 119          | 24.1| 8.33      |
| ≥80                     | 60           | 12.2| 5.57      |

Abbreviation: IR, incidence rate.
aNumber of cases per 100,000 population.
Table 2
Age-Adjusted Incidence Rates of Amyotrophic Lateral Sclerosis for Cases Diagnosed in New Jersey in 2009–2011 (n = 493), by Sex, Race, Ethnicity, and Census-Tract Income Quartile

| Characteristic                                      | No. of Cases | %    | Age-Adjusted IR | 95% CI     |
|----------------------------------------------------|--------------|------|-----------------|------------|
| Total                                              | 493          | 100.0 | 1.67            | 1.52, 1.82 |
| Sex                                                |              |      |                 |            |
| Female                                             | 228          | 46.2 | 1.42            | 1.24, 1.62 |
| Male                                               | 265          | 53.8 | 1.96            | 1.73, 2.22 |
| Race                                               |              |      |                 |            |
| White                                              | 413          | 83.8 | 1.80            | 1.62, 1.97 |
| Black                                              | 31           | 6.3  | 0.88            | 0.57, 1.20 |
| Asian                                              | 22           | 4.5  | 1.11            | 0.63, 1.60 |
| Other                                              | 6            | 1.2  | NC              |            |
| Unknown                                            | 21           | 4.3  | NC              |            |
| Ethnicityd                                          |              |      |                 |            |
| Hispanic                                           | 30           | 6.1  | 0.93            | 0.58, 1.30 |
| Non-Hispanic                                        | 438          | 88.8 | 1.66            | 1.50, 1.82 |
| Quartile of census-tract area-based SES (average annual income; range) | | | | |
| 1 ($40,283; $11,193–$51,422)                        | 78           | 15.8 | 1.34            | 1.06, 1.67 |
| 2 ($61,370; $51,613–$71,058)                        | 98           | 19.9 | 1.38            | 1.12, 1.68 |
| 3 ($82,104; $71,188–$95,000)                        | 129          | 26.2 | 1.62            | 1.35, 1.93 |
| 4 ($122,329; $95,072–$250,001)                      | 188          | 38.1 | 2.23            | 1.91, 2.58 |

Abbreviations: CI, confidence interval; IR, incidence rate; NC, not calculated; SES, socioeconomic status.

a Directly age-adjusted to the 2000 US Standard Population.

b Incidence rates per 100,000 population were age-standardized to the 2000 US Standard Population by means of the direct method.

c Denominator was not available for estimation of age-adjusted rates.

d Data on ethnicity were missing for 25 cases.
Table 3

Relative Risk of Amyotrophic Lateral Sclerosis for Cases Diagnosed in New Jersey in 2009–2011 (n = 466)\textsuperscript{a}, by Sex, Race, and Census-tract Income Quintile

| Characteristic | Crude RR | 95% CI | Age-Adjusted RR\textsuperscript{b} | 95% CI | Multivariable-Adjusted RR\textsuperscript{c} | 95% CI |
|---------------|----------|--------|-----------------------------------|--------|---------------------------------------------|--------|
| Sex           |          |        |                                   |        |                                             |        |
| Female        | 1        | Referent | 1                                 | Referent | 1                                           | Referent |
| Male          | 1.22     | 1.02, 1.47 | 1.38                              | 1.15, 1.66 | 1.36                                        | 1.14, 1.64 |
| Race          |          |        |                                   |        |                                             |        |
| White         | 1        | Referent | 1                                 | Referent | 1                                           | Referent |
| Black         | 0.38     | 0.26, 0.55 | 0.52                              | 0.36, 0.75 | 0.57                                        | 0.39, 0.83 |
| Asian         | 0.44     | 0.29, 0.68 | 0.65                              | 0.42, 0.99 | 0.63                                        | 0.41, 0.97 |
| Quartile of census-tract area-based SES (average annual income; range) |          |        |                                   |        |                                             |        |
| 1 ($40,283; $11,193–$51,422) | 1 | Referent | 1                                 | Referent | 1                                           | Referent |
| 2 ($61,370; $51,613–$71,058) | 1.13 | 0.83, 1.54 | 1.05                              | 0.77, 1.43 | 0.96                                        | 0.70, 1.31 |
| 3 ($82,104; $71,188–$95,000) | 1.27 | 0.95, 1.71 | 1.16                              | 0.86, 1.55 | 1.02                                        | 0.75, 1.38 |
| 4 ($122,329; $95,072–$250,001) | 1.65 | 1.25, 2.18 | 1.55                              | 1.18, 2.05 | 1.37                                        | 1.02, 1.82 |

Abbreviations: CI, confidence interval; RR, relative risk; SES, socioeconomic status.

\textsuperscript{a}Six cases with race coded “other” and 21 cases with race coded “unknown” were excluded from the analysis.

\textsuperscript{b}RR estimates for sex, race, and census-tract annual household median income were based on 3 separate Poisson regression models adjusting for age at diagnosis only.

\textsuperscript{c}Multivariate Poisson regression model with adjustment for age, sex, race, and census-tract annual household median income.