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Spatial analyses of ALS incidence in Denmark over three decades

Veronica Vieira^{a,*}, Johnni Hansen^b, Ole Gredal^c, and Marc G. Weisskopf^d

^aProgram in Public Health, College of Health Sciences, University of California, Irvine, California, USA

^bDanish Cancer Society Research Center, Copenhagen, Denmark

^cNational Rehabilitation Center for Neuromuscular Disorders, Copenhagen, Denmark

^dDepartments of Environmental Health and Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Abstract

Objective: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of the motor neuron with very few known risk factors. We conducted a spatial epidemiologic analysis of ALS incidence in Denmark to assess the contribution of sociodemographic determinants to geographic variation.

Methods: We analyzed 4249 ALS cases (1982–2013), each with 100 controls matched on sex and birth year. Odds ratios and 95% confidence bands at birth and diagnosis/index locations were calculated using generalized additive models. We included a bivariate spatial smooth for location in our conditional logistic regression adjusted for socioeconomic status and marital status. We also conducted analyses adjusted for both birth and diagnosis addresses to separate location effects.

Results: We observed significantly elevated ALS odds near Copenhagen for both the birth and diagnosis period analyses. Sociodemographic factors did not explain the observed patterns. When we further adjusted our spatial analyses by including both birth and diagnosis addresses, the significant area of elevated male ALS odds by birth address shifted to northwest Denmark away from Copenhagen, and there was little evidence of variation among women. Geographic variation at diagnosis differed between male and females, suggesting that patterns are not just due to regional variation in case ascertainment.

Conclusions: ALS incidence in Denmark is associated with both location at birth and diagnosis, suggesting that geographic variation may be due to exposures occurring at birth or closer to diagnosis, although the latter could relate to case ascertainment issues.

*Correspondence: Program in Public Health, AIRB 2042, 653 East Peltason Drive, University of California, Irvine, CA 92697, USA. vvieira@uci.edu.

Declaration of interest

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Keywords

Amyotrophic lateral sclerosis (ALS); spatial analysis; generalized additive models

Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease of the motor neurons that results in usually rapidly progressive paralysis and death, usually from respiratory failure. The incidence of ALS in Europe is around 2–3/100,000 person-years and the median survival time with ALS is about 3 years (1,2). ALS typically strikes people in their 60's and 70's although it can occur at earlier ages as well. Great strides have been made in the genetics of ALS, but only an estimated 10% of cases are genetically inherited (3–5). This fact, and other lines of evidence have led to the suspicion that environmental factors may contribute to ALS risk (4,6). However, the identification of non-genetic risk factors for ALS has proven difficult.

The early identification of very high, but rapidly decreasing rates of an ALS complex in the western pacific is one of the pieces of evidence suggesting the possible involvement of environmental factors in the development of ALS (7,8). Similar hot spots for this complex have been identified on the Kii peninsula of Japan, Irian Jaya, and Groote Eylandt, Australia (9–11). In other parts of the world, the exploration of the distribution of ALS has suggested statistically significant geographic differences in the incidence of ALS (12–25). However, because of methodological differences and different levels of ALS awareness, these data should be interpreted cautiously. Nonetheless, even in studies of smaller more homogeneous regions, some spatial differences in ALS have been noted (13–31), although many had very small case numbers. Most of these studies have examined the distribution at the time of ALS diagnosis or death. However, it has been suggested that the etiology of ALS—including the involvement of environmental factors—may begin earlier than we typically think (4), although the evidence for this is limited (17,18, 32–34).

Differences in the spatial distribution of ALS by place of birth would not only add to the suggestion of a possible involvement of environmental factors in ALS etiology, but also suggest very early origins for the pathogenesis. Only four studies of which we are aware have examined the spatial distribution of ALS by place of birth. One was a proportional mortality study in the US and found a northwest to southeast gradient by state of birth (17). Three others were conducted in Finland. One looked at 1,000 ALS deaths between 1985 and 1995 in Finland and found evidence for clustering by place of birth (18). Another found an excess of ALS cases in southeastern Finland among a total of 81 ALS cases (19). The third found an excess prevalence of ALS among evacuees of land ceded to Russia after World War II compared with non-evacuated populations living in later life in the same areas as the evacuees (20). Only this latter study accounted for residence at time of diagnosis, which could be related to case ascertainment issues. However, this latter study could not rule out other factors related to being a war evacuee.

In order to address this issue further at a smaller geographic scale and with a larger dataset, we explored the spatial distribution of ALS incidence between 1982 and 2013 by place of

birth as well as residence at the time of diagnosis throughout Denmark using generalized additive models (GAMs). GAMs are a form of semi-parametric regression with the ability to smooth longitude and latitude to create spatially continuous response surfaces of individual-level outcomes while adjusting for covariates. This approach is especially useful for assessing the contribution of spatial confounders like socioeconomic status to geographic variation.

Methods

Study Population

The data for the spatial analyses were obtained from the Danish National Patient Register (NPR) system. Cases of ALS were diagnosed between January 1, 1982 and December 31, 2013. We restricted case ascertainment to individuals older than 19 years, and did not include cases in the first 5 years of the NPR in order to avoid prevalent cases at the start of the Register. ALS cases included anyone with an inpatient or outpatient International Classification of Diseases (ICD)-8 discharge diagnosis of 348.0 before 1993 or ICD-10 discharge diagnosis of G12.2 starting in 1994. In a validation study, we found the positive predictive value for this case definition compared with medical record review to be 92.5% (35). We matched 100 controls to each of the cases by sex and year of birth using the Danish Civil Registration System (CRS), which includes administrative records on all Danish residents since 1968. Controls were assigned an index year corresponding to the diagnosis year of their matched case and were spatially selected at random to represent the underlying population distribution that gave rise to the cases (36).

Covariates

In a spatial analysis, the exposure variable of interest is location. We collected geographic information at two time periods: birth and diagnosis (or index) date. Births within Denmark were geocoded to 2181 unique parish level centroids; addresses at diagnosis/index date were geocoded to 983 unique postal code centroids. The most important risk factor known to also vary geographically and act as a spatial confounder is socioeconomic status (SES), which is available in the Danish CRS at the individual level based on job titles from income tax forms. Individuals with the highest SES include corporate managers and academics; those with the lowest SES include unskilled workers. Spouse's SES was used if it was higher than the participant's SES. If the participant was unemployed, or job status was unknown, and there was no information for spouse's job available, then the participant was categorized as unknown job title. Marital status was also included in the analysis as a proxy measure of SES to capture residual confounding due to unknown job title. As housewives were more likely to have missing job titles, including their marital status would indicate whether they were supported by a husband's salary.

Statistical Analysis

We modeled crude and adjusted odds ratios (ORs) for ALS using generalized additive models with a bivariate smooth term for longitude and latitude (36–40). We analyzed birth address and address at time of diagnosis/index year in separate models. The MapGAM library (41, 42) was used to run conditional logistic regression spatial models and create

resulting maps in R Software Version 3.3.2 (Vienna, Austria). A loess smooth with an *a priori* span size of 0.3 was used to account for variable population distributions throughout Denmark, yet still identify local spatial patterns (36). Spans represent the proportion of data contributing information to the estimation of risk at an unmeasured location and adapts to population density. Regions with greater population distributions would smooth data from a smaller geographic area than regions with sparse populations. Previous simulation studies evaluated the type I error rate and power of several GAM hypothesis testing methods and showed that GAMs performed well for analyzing spatial patterns of various shape and sizes including non-circular clusters (43–48).

To assess the contribution of spatially-varying risk factors to ALS incidence, we adjusted for marital status (married, divorced, widowed, never married) and SES (the higher of the two SES levels among participant and spouse was used). We also performed stratified analyses to examine effect modification by sex and secondary analyses that included both birth and diagnosis addresses to separate the effects of the two locations on ALS incidence. In the latter, two bivariate smooth terms for longitude and latitude of birth and diagnosis addresses were included in the model. Risks associated with the two locations adjusted for the other are presented in separate maps where the ORs for one location are mapped for the continuous study area while holding the other location constant.

The MapGAM library allows for calculation of standard errors for the point estimates of the risk map. Geographic areas where the confidence interval excludes one are indicated on the map with black contour lines. Regions along the borders of the Denmark study area may not have connecting contour lines. The absence of these contours indicates that the odds ratios outside of these areas were not statistically significant. Resulting maps were plotted using the same OR scale to allow for direct comparisons between analyses. Covariates were held fixed so that the spatial ORs surface represented predictions at the reference level for categorical covariates (highest SES, married) and the median value for continuous covariates (longitude, latitude). For example, maps for birth address analyses show how the predicted ORs vary depending on where a resident was born but assuming all other covariates are the same for everyone. This separates the effects of SES, marital status, and diagnosis location from the effect of birth location. The Institutional Review Boards of the University of California at Irvine (Irvine, California), the Harvard T.H. Chan School of Public Health (Boston, Massachusetts) and the Danish Data Protection Agency approved the research.

Results

From 1982–2013, 4603 ALS cases were identified from the Danish NPR, along with 460,300 matched controls. We excluded individuals with missing or invalid geographic data (1.5% cases; 1.9% controls), those born in Greenland, Bornholm island or outside Denmark (5.0% cases; 4.9% controls), and those with diagnosis postal codes in Greenland or Bornholm island (1.2% cases; 1.2% controls). We also excluded 4 controls with missing information on marital status. Our final dataset included 4249 cases and 423,474 controls. The distribution of SES and marital status by gender and case status are presented in Table 1. Females were more likely than males to be widowed. This also results in more women having an unknown job title as they did not have a husband's SES available and were more

likely during this time period to not have a job of their own. A quarter of the participants moved more than 80km between birth and year of diagnosis. Mobility patterns were similar among males and females with no differences by case status. Figure 1 shows the geographic distribution of participant locations at time of birth, with a high density near Copenhagen.

Areas of decreased ALS ORs were observed in the crude analysis of birth location in the southern and southwestern regions of Denmark (Figure 2a). Note that in the southern region, the contour line for significant decreased ORs is a half-circle in the center, south of Odense, that includes small areas to the east and west. ORs were highest north of Copenhagen, reaching a magnitude of 1.35, and lowest in southwest Denmark, with a minimum OR of 0.80. Adjusting for socioeconomic and marital status did not change these patterns (Figure 2b, Table 2). Statistically significant decreased ALS ORs in relation to birth location were largely driven by risk among males (Figure 2c), but statistically significant increased ORs north of Copenhagen were observed for both males and females (Figures 2c and 2d).

Likewise, crude and adjusted analyses did not substantially differ for ALS ORs associated with location at diagnosis/index year (Figures 3a and 3b, Table 2). Compared to the birth address analysis, the ORs for address at diagnosis continued to be statistically significant and elevated in the Copenhagen area and to its north, albeit attenuated compared to the ORs of birth address, with a maximum magnitude of 1.26. The ORs in the southwestern region of Denmark remained significantly decreased but with a slightly lower minimum OR of 0.69. The spatial distribution of ALS ORs for address at diagnosis was strikingly different between males and females (Figures 3c and 3d).

Figure 3 shows the results of the spatial analyses adjusted for both birth and diagnosis addresses. When we compared maps of ALS risk associated with birth address with and without diagnosis addresses, we observed differences by sex. While results for females were attenuated north of Copenhagen and generally null, the highest risk patterns for males shifted from the Copenhagen region to northwest of Denmark (Figures 4a and 4b). These results show the ORs predicted for varying birth location, but the same diagnosis location, held constant at the median longitude and latitude of the study area. Differences in ALS risk associated with diagnosis address adjusted for birth address were also greater for males, with elevated risk extended across a larger area surrounding Copenhagen (Figure 4c vs. 3c), whereas patterns for women remained the same (Figures 4d vs. 3d). These maps show the effect of diagnosis address predicted at the same fixed birth location.

Discussion

Our spatial analyses of ALS incidence in Denmark suggest differences in geographic variation depending on where participants lived at the time of birth and address at diagnosis that cannot be explained by socioeconomic factors. Those born north of Copenhagen had significantly elevated odds of ALS compared to their counterparts born in southwestern Denmark. Sex differences were observed, with only males experiencing lower odds if born in southern Denmark. When we compare birth analyses to analyses of residence at diagnosis or index year, we note changes in both the location and magnitude of significant ALS odds. The maximum OR values in the diagnosis address analyses are attenuated and the regions of

significantly low ORs are only in the west. Most notable is the difference between ALS spatial patterns among males and females at diagnosis address. This may suggest that variation in ALS odds is not due to regional differences in ALS case ascertainment, as increased diagnoses resulting from differences in case ascertainment might be expected to be similar among males and females. Furthermore, the areas of highest odds were not centered on the main cities of Denmark (Copenhagen, Aarhus, Odense), which may also suggest that differences in case ascertainment are not driving the geographical pattern. If that was the case, higher odds would likely have been expected in the major cities because of things like a higher density of neurologists or better (possibly faster) recognition of the condition.

When we further adjusted our spatial analyses by including both birth and diagnosis addresses, the significant area of elevated male ALS odds by birth address shifted to northwest Denmark and was no longer near Copenhagen, and there was little evidence of variation among women. This may suggest that factors related to the address at diagnosis influenced the elevated odds by birth address to the north of Copenhagen seen in the crude analyses. The risk by diagnosis address expanded south of Copenhagen for men, but didn't change appreciably for women. By including both birth and diagnosis address in the model, we can isolate the associations with each independently of the other. The increased ALS incidence in northwestern Denmark and decreased incidence in the southeast in the male birth address analyses adjusted for diagnosis address suggests a possible involvement of environmental factors early in the pathogenesis of ALS and warrants further investigation. Similarly, the variation of risk by address at diagnosis does not appear compatible with a simple effect of case diagnosis differences and also warrants further investigation.

The sex differences we observed are intriguing. While our spatial analysis cannot identify specific causes of these differences, metabolic differences by sex are known. Men and women differ in the balance between metabolism and conjugation of some xenobiotic chemicals. For example, estrogen up-regulates some cytochrome P450 enzymes without altering detoxifying enzymes (49). Such differences could mean that the same exposures could lead to different ALS risk by sex, which was in fact proposed as a possible explanation for the sometimes seen difference by sex in the association between cigarette smoking and ALS (50).

To our knowledge, our analyses are the first to investigate spatial variation in ALS using individual-level data to assess both birth and diagnosis addresses. A spatial analysis of ALS conducted in Finland between 1985 and 1995 also found evidence for clustering by place of birth but did not account for diagnosis address (18). By using GAMs to smooth the effect of location, we were able to identify regions of statistically significant increased and decreased ALS incidence that were not restricted to census or postal code boundaries. We also included over 30 years of data, which allowed for sufficient sample size for a robust nationwide spatial analysis. Data linkage in Denmark made it possible to control for socioeconomic factors which are known to spatially vary. By stratifying our models by sex, we identified important geographic differences between males and females in ALS incidence at diagnosis address.

Although advanced statistical methods were applied, these spatial analyses have some potential limitations. Data were geocoded to birth parish or postal code of diagnosis rather than street address. While the impact of this on a national-scale geographic analysis is small, it could affect the exact delineation of statistically significant areas. GAMs may exhibit biased behavior at the edges of the data, but our past work indicated little bias when loess smoothers are used (36, 40). Nonetheless, we are cautious in interpreting data in these regions if data are sparse.

Although we controlled for an individual-level SES indicator, marital status, and stratified by sex, it is possible that observed patterns are the result of residual confounding. Our SES indicator is based on occupation and has been used widely in Denmark, for example showing strong associations with mortality of different kinds (51, 52). Nonetheless, additional differences between individuals in aspects of SES or other factors may still be important. Identifying the source of such residual confounding could give important insight into ALS etiology. Furthermore, we do not have data available on genetics or gene-environment interactions to determine their role in the spatial variability of ALS incidence in Denmark. However, we optimized the spatial data that was available using the MapGAM library in R and expanded on previous geographic ALS analyses. In addition, our use of administrative data to identify ALS cases does not allow for consideration of details of the ALS that would be available, for example, in many ALS registries. Therefore, we could not look at differences by, for example, bulbar or spinal ALS. However, the trade off is the advantage of the very large size of our study that facilitates spatial mapping.

Our study is only one of a few to investigate both place of birth and diagnosis addresses, and the only analysis to isolate the contribution of diagnosis address from the risk due to birth address. While different geographic patterns between males and females suggests that spatial variation in ALS incidence is not likely due to regional inequalities in case ascertainment alone, additional research is needed to identify which environmental or social factors may be influencing the observed geographic differences.

References

1. Logroscino G, Traynor BJ, Hardiman O, Chio A, Mitchell D, Swingler RJ, et al. Incidence of amyotrophic lateral sclerosis in Europe. *J Neurol Neurosurg Psychiatry* 2010;81(4):385–390. [PubMed: 19710046]
2. Chio A, Logroscino G, Hardiman O, Swingler R, Mitchell D, Beghi E, et al. Prognostic factors in ALS: A critical review. *Amyotroph Lateral Scler* 2009;10(5–6):310–23. [PubMed: 19922118]
3. Dion PA, Daoud H, Rouleau GA. Genetics of motor neuron disorders: new insights into pathogenic mechanisms. *Nat Rev Genet* 2009;10(11):769–82. [PubMed: 19823194]
4. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. *Nat Rev Neurol* 2013;9(11):617–28. [PubMed: 24126629]
5. Ajroud-Driss S, Siddique T. Sporadic and hereditary amyotrophic lateral sclerosis (ALS). *Biochim Biophys Acta* 2015;1852(4):679–84. [PubMed: 25193032]
6. Factor-Litvak P, Al-Chalabi A, Ascherio A, Bradley W, Chio A, Garruto R, et al. Current pathways for epidemiological research in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14 Suppl 1:33–43. [PubMed: 23678878]
7. Plato CC, Galasko D, Garruto RM, Plato M, Gamst A, Craig UK, et al. ALS and PDC of Guam: forty-year follow-up. *Neurology* 2002;58(5):765–73. [PubMed: 11889241]

8. Zhang ZX, Anderson DW, Mantel N, Roman GC. Motor neuron disease on Guam: temporal occurrence, 1941–85. *Acta Neurol Scand* 1995;92(4):299–307. [PubMed: 8848935]
9. Kuzuhara S, Kokubo Y. 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:S108–13. [PubMed: 16092099]
10. Yase Y The pathogenesis of amyotrophic lateral sclerosis. *Lancet* 1972;2(7772):292–6. [PubMed: 4115029]
11. Foster HD. Amyotrophic lateral sclerosis: two for the price of one? In: Foster HD, ed. *Health, disease & the environment*. London, United Kingdom: Belhaven Press, 1992;439–78.
12. Chancellor AM, Warlow CP. Adult onset motor neuron disease: worldwide mortality, incidence and distribution since 1950. *J Neurol Neurosurg Psychiatry* 1992;55(12):1106–15. [PubMed: 1479386]
13. Mitchell JD, Gatrell AC, Al-Hamad A, Davies RB, Batterby G. Geographical epidemiology of residence of patients with motor neuron disease in Lancashire and south Cumbria. *J Neurol Neurosurg Psychiatry* 1998;65(6):842–7. [PubMed: 9854959]
14. Mitchell JD, Gibson HN, Gatrell A. Amyotrophic lateral sclerosis in Lancashire and South Cumbria, England, 1976–1986. A geographical study. *Arch Neurol* 1990;47(8):875–80. [PubMed: 2375694]
15. Gunnarsson LG, Lygner PE, Veiga-Cabo J, de Pedro-Cuesta J. An epidemic-like cluster of motor neuron disease in a Swedish county during the period 1973–1984. *Neuroepidemiology* 1996;15(3):142–52. [PubMed: 8700306]
16. Taylor JA, Davis JP. Evidence for clustering of amyotrophic lateral sclerosis in Wisconsin. *J Clin Epidemiol* 1989;42(6):569–75. [PubMed: 2738617]
17. Betemps EJ, Buncher CR. Birthplace as a risk factor in motor neurone disease and Parkinson's disease. *Int J Epidemiol* 1993;22(5):898–904. [PubMed: 8282470]
18. Sabel CE, Boyle PJ, Loytonen M, Gatrell AC, Jokelainen M, Flowerdew R, 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]
19. Jokelainen M, Palo J, Wikstrom J. The Distribution of Amyotrophic Lateral Sclerosis in Finland. *Journal of the Neurological Sciences* 1975; 25:473–479.
20. Jokelainen M, Wikstrom J, Palo J. Effect of birthplace on the development of amyotrophic lateral sclerosis and multiple sclerosis: A study among Finnish war evacuees. *Acta Neurol Scandinav* 1979;60:283–288.
21. Sabel CE, Gatrell AC, Loytonen M, Maasilta P, Jokelainen M. Modelling exposure opportunities: estimating relative risk for motor neurone disease in Finland. *Soc Sci Med* 2000;50(7–8):1121–37. [PubMed: 10714932]
22. Caller TA, Doolin JW, Haney JF, Murby AJ, West KG, Farrar HE, et al. A cluster of amyotrophic lateral sclerosis in New Hampshire: a possible role for toxic cyanobacteria blooms. *Amyotroph Lateral Scler* 2009;10 Suppl 2:101–8. [PubMed: 19929741]
23. Caller TA, Field NC, Chipman JW, Shi X, Harris BT, Stommel EW. Spatial clustering of amyotrophic lateral sclerosis and the potential role of BMAA. *Amyotroph Lateral Scler* 2012;13(1):25–32. [PubMed: 22214351]
24. Migliaretti G, Berchialla P, Dalmaso P, Cavallo F, Chio A. Amyotrophic lateral sclerosis in Piedmont (Italy): a Bayesian spatial analysis of the incident cases. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14(1):58–65. [PubMed: 23134503]
25. Scott KM, Abhinav K, Stanton BR, Johnston C, Turner MR, Ampong MA, et al. Geographical clustering of amyotrophic lateral sclerosis in South-East England: a population study. *Neuroepidemiology* 2009;32(2):81–8. [PubMed: 19039239]
26. Alonso V, Villaverde-Hueso A, Hens MJ, Morales-Piga A, Abaitua I, de la Paz MP. Increase in motor neuron disease mortality in Spain: temporal and geographical analysis (1990–2005). *Amyotroph Lateral Scler* 2011;12(3):192–8. [PubMed: 21198417]
27. Uccelli R, Binazzi A, Altavista P, Belli S, Comba P, Mastrantonio M, et al. Geographic distribution of amyotrophic lateral sclerosis through motor neuron disease mortality data. *Eur J Epidemiol* 2007;22(11):781–90. [PubMed: 17874192]

28. Noonan CW, White MC, Thurman D, Wong LY. Temporal and geographic variation in United States motor neuron disease mortality, 1969–1998. *Neurology* 2005;64(7):1215–21. [PubMed: 15824349]
29. Doi Y, Yokoyama T, Tango T, Takahashi K, Fujimoto K, Nakano I. 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]
30. Rooney J, Heverin M, Vajda A, Crampsie A, Tobin K, Byrne S, et al. An exploratory spatial analysis of ALS incidence in Ireland over 17.5 years (1995–July 2013). *PLoS One* 2014;9(5):e96556. [PubMed: 24867594]
31. Rooney J, Vajda A, Heverin M, Elamin M, Crampsie A, McLaughlin R, et al. Spatial cluster analysis of population amyotrophic lateral sclerosis risk in Ireland. *Neurology* 2015;84(15):1537–44. [PubMed: 25770197]
32. Chio A, Mora G, Moglia C, Manera U, Canosa A, Cammarosano S, et al. Secular Trends of Amyotrophic Lateral Sclerosis: The Piemonte and Valle d'Aosta Register. *JAMA Neurol* 2017; doi:10.1001/jamaneurol.2017.1387.
33. Seals R, Gredal O, Hansen J, Weisskopf MG. Physical Trauma and Risk of ALS: A Population-Based Study. *American Academy of Neurology San Diego, CA*, 2013;P05.072.
34. Seals R, Hansen J, Gredal O, Weisskopf MG. Age-period-cohort analysis of trends in amyotrophic lateral sclerosis in Denmark, 1970–2009. *Am J Epidemiol* 2013; 178(8):1265–71. [PubMed: 24064744]
35. Kioumourtoglou MA, Seals R, Himmelslev L, Gredal O, Hansen J, Weisskopf MG. Comparison of diagnoses of amyotrophic lateral sclerosis by use of death certificates and hospital discharge data in the Danish population. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16:224–9. [PubMed: 25946516]
36. Webster T, Vieira V, Weinberg J, Aschengrau A. Method for mapping population-based case-control studies: An application using generalized additive models. *International Journal of Health Geographics* 2006; 5(1): 26. [PubMed: 16764727]
37. Hastie T, Tibshirani R. *Generalized Additive Models*. London: Chapman and Hall, Publishers; 1990.
38. Kelsall J, Diggle P. Spatial variation in risk of disease: a nonparametric binary regression approach. *J R Stat Soc Ser C Appl Stat*. 1998; 47(4):559–573.
39. Wood S *Generalized Additive Models: An Introduction with R*. London: Chapman and Hall, Publishers; 2006.
40. Vieira V, Webster T, Weinberg J, Aschengrau A, Ozonoff D. Spatial Analysis of lung, colorectal, and breast cancer on Cape Cod: an application of generalized additive models to case-control data. *Environ Health*. 2005; 4:11. [PubMed: 15955253]
41. Vieira VM, Bartell SM, Bliss RY. 2015 MapGAM: Mapping Smoothed Effect Estimates from Individual-Level Data. R package version 0.7–5. <http://CRAN.R-project.org/package=MapGAM>
42. Bai L *Adaptive Statistical Methods for the Analysis of Sequential and Spatial Observation Data* [dissertation]. Irvine, CA: University of California, Irvine; 2016.
43. Bliss RY, Weinberg J, Vieira VM, Ozonoff A, Webster TF. Power of permutation tests using generalized additive models with bivariate smoothers. *J Biomet Biostat* 2010; 1:104.
44. Young RL, Weinberg J, Ozonoff A, Vieira V, Webster TF. Generalized Additive Models and Inflated Type I Error Rates of Smoother Significance Tests. *Computational Statistics & Data Analysis* 2011; 55(1):366–374. [PubMed: 20948974]
45. Young RL, Weinberg J, Vieira V, Ozonoff A, Webster TF. A power comparison of generalized additive models and the spatial scan statistic in a case-control setting. *International Journal of Health Geographics* 2010; 9:37.
46. Bliss RL, Weinberg J, Vieira VM, Webster TF. Adjusted significance cutoffs for hypothesis tests applied with generalized additive models with bivariate smoothers. *Spatial and Spatio-temporal Epidemiology* 2011; 2(4):291–300. [PubMed: 22748227]
47. Bliss R, Weinberg J, Webster T, Vieira V. Determining the probability distribution and evaluating sensitivity and false positive rate of a confounder detection method applied to logistic regression. *J Biomet Biostat* 2012; 3:142.

48. Siangphoe U, Wheller DC. Evaluation of the performance of smoothing functions in generalized additive models for spatial variation in disease. *Cancer Inform* 2015; 14(Suppl 2):107–16. [PubMed: 25983545]
49. Sin DD, Cohen SB, Day A, Coxson H, Pare PD. Understanding the biological differences in susceptibility to chronic obstructive pulmonary disease between men and women. *Proc Am Thorac Soc* 2007; 4:671–4. [PubMed: 18073400]
50. Alonso A, Logroscino G, Hernan MA. Smoking and the risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2010; 81:1249–52. [PubMed: 20639382]
51. Hansen J, Raaschou-Nielsen O, Olsen JH. Increased risk of lung cancer among different types of professional drivers in Denmark. *Occup Environ Med* 1998; 55:115–118. [PubMed: 9614396]
52. Toch-Marquardt M, Menvielle G, Eikemo TA, Kulhánová I, Kulik MC, Bopp M, et al. Occupational Class Inequalities in All-Cause and Cause-Specific Mortality among Middle-Aged Men in 14 European Populations during the Early 2000s. *PLOS ONE* 2014; 9: e108072. [PubMed: 25268702]

Figure 1.

Spatial distribution of study participants by birth address. Location has been slightly altered for confidentiality. Density is highest near the major cities of Copenhagen, Aarhus, and Odense.

Figure 2. Spatial distribution of (a) crude and (b) adjusted odds ratios associated with location at birth. Analyses were adjusted for SES and marital status and stratified by (c) male and (d) female sex. Black contour lines indicate areas where the upper and lower confidence bands exclude one.

Figure 3. Spatial distribution of (a) crude and (b) adjusted odds ratios associated with location at diagnosis/index year. Analyses were adjusted for SES and marital status and stratified by (c) male and (d) female sex. Black contour lines indicate areas where the upper and lower confidence bands exclude one.

Figure 4. Spatial distribution of (a) male and (b) female odds ratios associated with location at birth address adjusted for diagnosis/index year; and of (c) male and (d) female odds ratios associated with location at diagnosis/index year adjusted for birth address. All models were also adjusted for SES and marital status. Black contour lines indicate areas where the upper and lower confidence bands exclude one.

Table 1.

Characteristics of male and female study participants by ALS case status

	Males				Females			
	Cases (n=2,269)		Controls (n=226,499)		Cases (n=1,980)		Controls (n=196,975)	
	n	%	n	%	n	%	n	%
SES								
1 (high)	256	11.3	23,496	10.4	193	9.7	18,307	9.3
2	291	12.8	26,671	11.8	232	11.7	22,246	11.3
3	438	19.3	43,331	19.1	388	19.6	35,775	18.2
4	638	28.1	67,255	29.7	501	25.3	52,468	26.6
5 (low)	428	18.9	44,563	19.7	352	17.8	38,151	19.4
Job title unknown	218	9.6	21,183	9.4	314	15.9	30,028	15.2
Marital Status								
Married	1,613	71.1	157,750	69.6	1,010	51.0	102,019	51.8
Widowed	197	8.7	19,902	8.8	609	30.8	57,714	29.3
Divorced	222	9.8	22,724	10.0	213	10.8	22,451	11.4
Never Married	237	10.4	26,123	11.5	148	7.5	14,791	7.5
Mobility								
Never moved	385	17.0	42,274	18.7	312	15.8	31,328	15.9
Moved <10km	367	16.2	33,906	15.0	341	17.2	30,425	15.5
Moved 11–25km	446	19.6	45,286	20.0	338	17.1	39,974	20.3
Moved 26–80km	496	21.9	49,565	21.9	458	23.1	44,798	22.7
Moved >80km	575	25.3	55,468	24.4	531	26.8	50,450	25.6

Table 2.

Odds ratios and confidence intervals for non-spatial model covariates

	Males			Females		
Model	Birth	Diagnosis	Both	Birth	Diagnosis	Both
Figure	2c	3c	4c	2d	3d	4d
SES						
1 (high)	Referent	Referent	Referent	Referent	Referent	Referent
2	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)	1.0 (0.9, 1.3)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)
3	1.0 (0.8, 1.1)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)
4	0.9 (0.8, 1.0)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)
5 (low)	0.9 (0.8, 1.1)	1.0 (0.8, 1.1)	1.0 (0.8, 1.1)	0.9 (0.7, 1.0)	0.9 (0.7, 1.0)	0.9 (0.7, 1.0)
Job title unknown	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)
Marital Status						
Married	Referent	Referent	Referent	Referent	Referent	Referent
Widowed	1.0 (0.8, 1.1)	1.0 (0.8, 1.1)	1.0 (0.8, 1.1)	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)
Divorced	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)
Never Married	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)