Environmental Research 147 (2016) 102–107

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

No association between soil constituents and amyotrophic lateral sclerosis relative risk in Ireland

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ARTICLE INFO

Article history:
Received 28 October 2015
Received in revised form
30 December 2015
Accepted 25 January 2016

Keywords:
Amyotrophic lateral sclerosis
Soil minerals
Spatial risk
Epidemiology

ABSTRACT

Introduction: We have recently mapped ALS spatial risk in Ireland using Bayesian and cluster analysis methods at electoral division (ED) and small area (SA) levels. As a number of metal elements (both minerals and toxins) have been proposed as risk factors for ALS, here we extend this analysis to include soil constituents from the Irish National Soils Database as Bayesian conditional auto-regression covariates to determine associations with small area ALS risk.
Methods: Data on 45 different soil parameters were obtained under license from National Soils Database (via Irish EPA). We interpolated average values of each soil constituent for each small area using ordinary kriging. All cases of ALS in Ireland from January 1995 to December 2013 were identified from the Irish ALS register and observed and age and gender standardised expected cases were calculated for each SA. Besag-York-Mollié (BYM) models were then built including each parameter from the national soils database in turn as a Bayesian covariate in the BYM model. Models were compared using the deviance information criterion (DIC) and separate models were built for ALS subtypes.
Results: 1701 ALS patients were included – 959 (56%) were male, 938 (55%) had limb onset ALS. 315 Bayesian models were built in total. Of the 315 models built, only one resulted in a coefficient that did not overlap zero. For limb onset cases, total magnesium had a mean coefficient of 0.319 (credible interval 0.033–0.607).
Discussion: We report the first spatial analysis of potential association between ALS and soil minerals using a population-based dataset collected over 18 years. Our sole non-zero finding is likely a random finding due to the high number of models built. We did not find any evidence to support soil mineral and toxin levels as risk factors for ALS. However as soil parameters are an ecological assessment of exposure in a given area, individual level measures of exposure are required.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative condition with a median survival in Ireland of 2.39 years from symptom onset (Rooney et al., 2013). Despite this bleak prognosis, progress in identifying the causes of ALS has been slow. Current theories postulate that multiple genes and environmental factors may in combination result in clinical disease (Al-Chalabi and Hardiman, 2013), with recent epidemiological analysis suggesting a 6 step process leading to clinical disease (Al-Chalabi et al., 2014). Several disease causing mutations have been identified (most notably C9orf72) to date, and familial disease is present in up to 16% of cases (Byrne et al., 2013). However, progress toward identifying environmental factors has been slow, with some preliminary evidence for higher risk in those occupationally exposed to pesticides (Kamel et al., 2012; Malek et al., 2012), and conflicting results regarding physical exercise (Pupillo et al., 2014; Huisman et al., 2013).

Exposure to heavy metals has been proposed as a risk factor for ALS, particularly lead and mercury, and elemental nutrients for example selenium (Sutedja et al. 2009), with the possibility that metal-gene and metal-epigenome interactions could also play a role (Eum et al., 2014; Callaghan et al., 2011; Rooney, 2011).

We have recently mapped ALS spatial risk in Ireland using Bayesian and cluster analysis methods at electoral division (ED) and small area (SA) levels (Rooney et al., 2015). Here we extend

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http://dx.doi.org/10.1016/j.envres.2016.01.038
0013-9351/

Table 1
Summary of soil parameters from the National Soils Database.

Parameter	Units	Mean value	Std Dev.	Min	Max
Soil pH	n/a	5.33	0.98	3.20	7.70
Soil organic carbon	Percent	13.35	14.01	1.40	55.80
Available Phosphorous	mg/l	10.61	13.77	0.56	316.41
Available Potassium	mg/l	145.42	94.09	4.66	949.23
Available Magnesium	mg/l	218.82	132.16	13.49	1001.97
Aluminium	Percent	3.53	1.93	0.06	9.74
Arsenic	mg/kg	9.05	9.19	0.35	122.70
Barium	mg/kg	233.41	137.54	6.60	1296.90
Calcium	Percent	0.76	1.56	0.03	26.63
Cadmium	mg/kg	0.56	0.70	0.03	15.15
Cerium	mg/kg	34.30	18.55	0.60	136.40
Cobalt	mg/kg	6.86	5.26	0.20	58.70
Chromium	mg/kg	44.49	25.09	2.10	221.70
Copper	mg/kg	19.48	16.76	1.10	272.40
Iron	Percent	1.95	1.33	0.05	19.43
Gallium	mg/kg	9.04	5.05	0.14	25.16
Germanium	mg/kg	1.25	0.50	0.10	2.58
Mercury	mg/kg	0.11	0.14	0.02	3.45
Total Potassium	Percent	0.97	0.54	0.02	2.64
Lanthanum	mg/kg	19.16	9.71	0.50	75.20
Lithium	mg/kg	24.61	17.66	2.00	165.70
Total Magnesium	Percent	0.35	0.23	0.04	2.10
Manganese	mg/kg	703.05	1184.99	7.00	21,077.00
Molybdenum	mg/kg	1.25	1.43	0.07	21.14
Sodium	Percent	0.42	0.32	0.02	2.25
Niobium	mg/kg	6.76	4.16	0.06	38.88
Nickel	mg/kg	20.56	15.50	0.80	176.00
Total Phosphorous	Percent	0.11	0.05	0.01	0.49
Lead	mg/kg	31.40	75.61	1.10	2634.70
Rubidium	mg/kg	55.34	35.39	0.60	222.00
Sulphur	Percent	0.11	0.10	0.01	0.70
Antimony	mg/kg	0.67	0.51	0.05	5.29
Scandium	mg/kg	6.00	3.61	0.12	17.11
Selenium	mg/kg	1.09	1.31	0.08	17.44
Tin	mg/kg	2.03	1.69	0.22	17.84
Strontium	mg/kg	57.99	51.17	9.20	1252.50
Tantalum	mg/kg	0.50	0.27	0.05	2.71
Thorium	mg/kg	4.58	2.42	0.10	11.15
Titanium	mg/kg	2093.44	1169.71	39.00	8704.00
Thallium	mg/kg	0.46	0.25	0.02	2.66
Uranium	mg/kg	2.31	2.85	0.10	64.19
Vanadium	mg/kg	54.22	31.44	2.10	240.30
Tungsten	mg/kg	0.71	0.51	0.10	7.72
Yttrium	mg/kg	11.31	8.04	0.22	111.78
Zinc	mg/kg	70.07	57.60	3.60	1384.40

this analysis to include soil mineral levels from the Irish National Soils Database as covariates in Bayesian conditional auto-regression models to estimate associations with ALS small area risk.

Table 2
Summary of BYM models for all cases including individual soil parameters as a covariates.

Covariate	DIC	Mean	SD	2.5%	Median	97.5%
Strontium (mg/kg)	11,229.1	−0.23	0.227	−0.703	−0.214	0.194
Rubidium (mg/kg)	11,229.3	−0.14	0.097	−0.334	−0.136	0.050
Thorium (mg/kg)	11,229.5	−0.16	0.128	−0.423	−0.160	0.082
Vanadium (mg/kg)	11,230.3	−0.17	0.250	−0.684	−0.158	0.300
Thallium (mg/kg)	11,230.7	−0.11	0.106	−0.323	−0.110	0.095
Aluminium (%)	11,230.7	−0.12	0.119	−0.363	−0.123	0.105
Molybdenum (mg/kg)	11,230.8	−0.10	0.118	−0.339	−0.097	0.126
Lanthanum (mg/kg)	11,230.8	−0.20	0.169	−0.540	−0.202	0.126
Tungsten (mg/kg)	11,231.0	−0.08	0.101	−0.285	−0.079	0.114
Tantalum (mg/kg)	11,231.1	−0.09	0.104	−0.301	−0.093	0.107
Cerium (mg/kg)	11,231.1	−0.12	0.140	−0.405	−0.123	0.145
Chromium (mg/kg)	11,231.2	−0.11	0.147	−0.405	−0.107	0.175
Tin (mg/kg)	11,231.3	−0.06	0.104	−0.266	−0.053	0.144
Germanium (mg/kg)	11,231.4	−0.06	0.135	−0.337	−0.060	0.194
Titanium (mg/kg)	11,231.6	−0.08	0.114	−0.305	−0.075	0.145
Niobium (mg/kg)	11,231.6	−0.08	0.111	−0.303	−0.080	0.135
Potassium (%)	11,231.6	−0.07	0.123	−0.316	−0.068	0.167
Cadmium (mg/kg)	11,231.6	−0.08	0.081	−0.242	−0.080	0.079
Scandium (mg/kg)	11,231.7	−0.08	0.225	−0.536	−0.076	0.351
Basic model (no covariates)	11,231.8	NA	NA	NA	NA	NA
Barium (mg/kg)	11,231.8	−0.10	0.131	−0.361	−0.100	0.155
Zinc (mg/kg)	11,231.9	−0.06	0.129	−0.324	−0.063	0.186
Sodium (%)	11,232.0	−0.03	0.089	−0.213	−0.033	0.139
Available magnesium (mg/l)	11,232.2	−0.32	0.249	−0.809	−0.313	0.177
Soil pH	11,232.2	−0.01	0.548	−1.090	−0.017	1.074
Cobalt (mg/kg)	11,232.2	−0.02	0.131	−0.283	−0.021	0.235
Lithium (mg/kg)	11,232.2	−0.07	0.113	−0.297	−0.074	0.147
Gallium (mg/kg)	11,232.4	−0.12	0.154	−0.419	−0.115	0.185
Iron (%)	11,232.5	−0.06	0.136	−0.326	−0.056	0.209
Available potassium (mg/l)	11,232.6	−0.09	0.286	−0.659	−0.092	0.467
Soil Organic Carbon (%)	11,232.6	−0.12	0.102	−0.324	−0.123	0.079
Sulphur (%)	11,232.6	−0.13	0.137	−0.395	−0.127	0.146
Calcium (%)	11,232.6	−0.05	0.069	−0.190	−0.054	0.082
Magnesium (%)	11,232.6	0.05	0.134	−0.222	0.048	0.309
Lead (mg/kg)	11,232.7	0.01	0.103	−0.193	0.016	0.214
Nickel (mg/kg)	11,232.7	0.01	0.097	−0.186	0.007	0.196
Uranium (mg/kg)	11,232.8	−0.08	0.158	−0.392	−0.083	0.228
Yttrium (mg/kg)	11,232.8	−0.06	0.102	−0.263	−0.062	0.139
Arsenic (mg/kg)	11,232.8	−0.14	0.182	−0.500	−0.144	0.216
Antimony (mg/kg)	11,232.8	0.07	0.086	−0.102	0.071	0.240
Mercury (mg/kg)	11,232.9	−0.03	0.117	−0.260	−0.030	0.200
Manganese (mg/kg)	11,232.9	0.10	0.188	−0.280	0.097	0.458
Available phosphorous (mg/l)	11,233.1	−0.03	0.159	−0.341	−0.024	0.283
Selenium (mg/kg)	11,233.2	−0.01	0.082	−0.167	−0.007	0.153
Copper (mg/kg)	11,233.3	−0.01	0.070	−0.146	−0.008	0.128

Models are ordered by decreasing model fit as assessed by DIC – i.e. the best fitting models are listed first.

2. Methods

ALS case ascertainment was through the Irish ALS Register including patients from 1995 to 2013. Population data were obtained for Small Areas (SAs) from the 2006 census of Ireland via Trutz Haase (Haase and Pratschke, 2012) and Small Area shapefiles were obtained from Ordnance Survey Ireland (OSI, 2013). Calculation of observed and expected ALS cases per small area, and methods for Bayesian smoothing with covariates have been described previously (Rooney et al., 2015). Data on soil concentrations were obtained under license from the Irish EPA (Fay and Zhang, 2007). The National Soils Database contains data on 45 different soil parameters, mainly element and nutrient levels, from 1310 selected sample sites around Ireland (Fay et al., 2007). The sampling strategy for the National Soils Database was designed to ensure 2 samples per 100 km^2 (Fay et al., 2007). Using the *automap* package (Hiemstra et al., 2009) of R ver 3.1.1 (R Core Team, 2014), we interpolated average values of each soil constituent for each SA polygon using ordinary kriging (a geostatistical method to interpolate an unknown parameter at a given location(s) modeled upon known values at known locations and allowing for spatial structure).

2.1. Exploratory approach

Next, Bayesian spatial smoothing was implemented using the Besag-York-Mollié model (Bivand et al., 2008; Besag et al., 1991) via the R-INLA package (Rue et al., 2009; Martins et al., 2013). Separate models were built as baseline reference models for all patients, males, females, age of onset (under or over 55), site of onset (limb or non-limb onset). Subsequent models were then built including each parameter from the national soils database as