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The association between ALS and population density: A population based study

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Abstract

We aimed to assess whether rural residence is associated with amyotrophic lateral sclerosis in the south-east of England using a population based register. Previous studies in different populations have produced contradictory findings. Residence defined by London borough or non-metropolitan district at time of diagnosis was recorded for each incident case in the South-East England ALS Register between 1995 and 2005. Each of the 26 boroughs or districts of the catchment area of the register was classified according to population density. Age- and sex-adjusted incidence of ALS was calculated for each region and the relationship with population density tested by linear regression, thereby controlling for the underlying population structure. We found that population density in region of residence at diagnosis explained 25% of the variance in ALS rates ($r = 0.5$, $p < 0.01$). Thus, in this cohort in the south-east of England, people with ALS were more likely to be resident in areas of high population density at diagnosis.

Keywords

Amyotrophic lateral sclerosis; epidemiology; population density

Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, degenerative disease that leads to death within three years of onset in 50% of patients (1). It primarily affects motor neurons, with all of the major symptoms relating to motor function. The aetiology remains

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elusive with findings across disciplines from genetics to epidemiology failing to find a single explanation.

The incidence of ALS is between 0.6 and 2.6 per 100,000 person-years (2) with a lifetime risk of about 1 in 400 (3). The only known and reproducible risk factors for ALS are family history of ALS, increasing age, being male, and mutation in the *SOD1*, *FUS/TLS* or *TARDBP* genes. ALS probably has a complex aetiology involving a number of environmental and genetic factors (4,5). Numerous environmental toxins have been implicated including cigarette smoke (6), lead, aluminium, ionizing radiation, mercury and pesticides (7). The risk of exposure to many of these toxins would be expected to vary in urban or rural areas or with certain occupations. Consistent with this, some studies have shown a preponderance of ALS in certain occupations, including agricultural workers (8) and footballers (9), as well as veterans of the first Gulf War (10). Increased rates of ALS have also been reported in rural areas, with the proposed mechanism being chemical exposure (8). Several genetic studies have found an association between the pesticide detoxification genes *PON1-3* and ALS (11–13) and an interaction between *PON1* and population density has also been reported (14). A recent meta-analysis including data from 4037 cases and 4609 controls showed that there was no relationship between the *PON* genes and ALS (15). However, data on toxin exposure was available in only one of the studies surveyed, leaving open the possibility of gene-environment interactions.

We previously found non-random geographical clustering of ALS in an analysis that took account of underlying population structure. The region with the greatest increase in relative risk of ALS was an area with a high population density within Greater London (16), suggesting that population density might act as a marker for underlying risk factors. We therefore aimed to test the hypothesis that susceptibility to ALS is associated with population density. The South-East England ALS register covers areas of high population density (e.g. London, Canterbury and Brighton) and areas of relatively low population density (e.g. Kent and Sussex), making it ideal to examine this possibility.

Methods

Catchment area

For the purposes of this study, place of residence was defined using pre-existing administrative units. In London these are called boroughs and outside of London these are referred to as non-metropolitan districts or local authorities. The catchment area of the South-East England ALS Register (SEALS register) is defined by postcodes and includes the south-east London boroughs (Lambeth, Southwark, Lewisham, Bexley, Greenwich and Bromley) and the non-metropolitan districts of Brighton and Hove, East Sussex and Kent. The register is described in detail elsewhere (17). The study was ethically approved by the research ethics committees of the participating centres.

Case ascertainment

All incident cases of ALS in the register's catchment area since 1989 were recorded in the database. Patient details were obtained from the tertiary referral centres within the catchment area as well as district general hospitals and specialist services (neurorehabilitation, physiotherapy and specialist nursing). The inclusion criteria were having ALS and residence for more than six months at any of the postcodes within the defined area at any time during the study period. Further details regarding diagnosis and inclusion criteria have been described previously (17). The current study made use of all incident cases between 1995 and 2005.

Population

The population density in each of the 25 boroughs and non-metropolitan districts was obtained from the UK Office of National Statistics (18).

Analysis

The age- and sex-adjusted relative risks for the years 1995–2005 were calculated for each borough and district using indirect standardization. Linear regression was used to test the null hypothesis that the adjusted relative risk of ALS did not depend on population density. Residuals were tested for normality by inspection of histograms and partial plots. Variances were tested for equality with Levene's test. The Mann-Whitney *U*-test was used to test the null hypothesis that there was no difference in adjusted relative risk between any of the categorized population densities. All analyses were carried out using SPSS for Windows, version 15 (SPSS Inc, Ohio).

Results

The total population within the 25 districts was 3,022,356, and the median of district populations 95,562 persons.

The median population density was 10.71 people per hectare (interquartile range = 25.46; a hectare is 10,000 square metres). This figure ranged from 1.68 in the rural districts of Rother and Wealden to 99.24 in the London borough of Lambeth.

The crude incidence of ALS in this area has already been established previously as 1.06 per 100,000, which is at the lower end of the range of incidences noted in a recent European-wide study (19). Many postcode districts within the catchment area have a high proportion of people of non-European ancestry in whom the incidence of ALS is lower (20, 3). We would expect the incidence in the catchment area to reflect this demographic variation. Of the 385 people (157 women) who were registered over this time period, correct postcode data were missing for 17. The study therefore included the remaining 368 whose borough could be identified using the Office of National Statistics website (18).

The age- and sex-adjusted relative risk correlated positively with population density ($r = 0.5$, $p = 0.01$), which means that population density explained 25% of the variance in adjusted relative risk of ALS ($r^2 = 0.25$). Inspection of the data showed two distinct groups falling above or below the 50 people per hectare density (Figure 1). Adjusted relative risks were significantly different for the two groups ($p = 0.001$). Removing the three most densely populated areas from the regression analysis (Lambeth, Southwark and Lewisham) removed the correlation between population density and adjusted relative risk.

Discussion

We have studied a population of nearly three million people over a 10-year period.

Our data support the hypothesis that the age- and sex-adjusted relative risk of ALS in the south-east of England depends on population density. Population density alone explains 25% of the variance in adjusted relative risk for ALS. In particular, residence in an area with a population density greater than 50 people per hectare is associated with increased rates of ALS. Below this level, variation in population density does not seem to be related to ALS risk, suggesting that the relationship between incidence and population density is non-linear. This is also consistent with previous studies on this register that showed clustering of ALS in postcodes in Greater London (16). This study adds to this evidence by suggesting that it is the increased population density underlying the clusters previously noted. A similar

association has been found in an Italian study in which an increased rate of ALS was observed in areas with higher population densities (21). In contrast to these findings, some studies have recorded increased rates in rural areas (2) or a lack of association of ALS with residence type (urban or rural) (22). Rural and urban areas may differ in the presence or absence of environmental risk factors in other countries, and the population density and definition of rural or urban will differ between studies. It may be that it is not rural or urban residence per se that is associated with ALS but some other factor that is sometimes associated with residence. Pesticide exposure is considered an important candidate in environmental studies, with higher rates of ALS reported in agricultural workers (2). The interaction between *PONI* genes and population density previously noted (14) may explain some of the variation in incidence in areas with population densities less than 50 people per hectare where pesticide exposure is more likely. However, this study goes against the hypothesis that pesticides are a major risk factor for ALS, insofar as pesticides tend to be associated with rural rather than urban residence. There are many other unmeasured factors that could explain the observed association, including poverty, exposure to pollution and cigarette smoking.

An alternative explanation is ascertainment or referral bias with more cases being picked up in central London where the register is based and fewer being picked up in rural areas. King's College Hospital, a major ALS tertiary referral centre, is in central London. It is therefore within Southwark and near to Lambeth and Lewisham, the areas in which we have identified a significantly higher risk of ALS. This possibility has been explored previously (16) and is not a likely explanation for several reasons. First, the UK has the National Health Service, a health system providing free access to health care, so access to diagnostic and care services is no better in urban than in rural areas. Secondly, we have previously shown a lower referral rate than average from some postcodes adjacent to King's College Hospital (16). Finally, the register has multiple sources of ascertainment. For example, although there were two other tertiary ALS referral centres from which patients were recruited, in London WC1 and in East Kent, neither of these areas was associated with significantly increased risk, and therefore ascertainment from tertiary referral centres is an unlikely explanation of the association. Nevertheless, such a bias is difficult to rule out completely in a population study of a rare disease.

Migration into more densely populated areas could also underlie the patterns observed in this study. However, there is actually net migration out of Lambeth, Southwark and Lewisham, the areas with the highest risk of ALS (23).

One drawback of this study is that we have only examined residence at diagnosis with ALS, whereas the factors that predispose to ALS may well act many years before symptoms appear. Thus, a migration study examining residence from birth to diagnosis would be preferable although very difficult to achieve. It is also important to note that with any study of this sort the population density is defined based on administrative boundaries, since this is the information available from census data. This means that the density of population used is of necessity an average over the administrative area rather than some sort of moving average centred around each incident case. Nevertheless, the relationship between population density and ALS is clear both from inspection of the scatterplot (Figure 1) and the statistical analysis.

We have identified an increased risk of ALS associated with residence in urban areas. This confirms some previous findings and lends support to the hypothesis that environmental factors associated with urban residence (rather than rural residence) are important in the aetiology of ALS.

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Figure 1.
Scattergraph showing the relationship between population density and adjusted relative risk.