Mortality trends of amyotrophic lateral sclerosis in Norway 1951-2014: an age-period-cohort study

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Abstract

Recent studies suggest that the incidence and mortality of amyotrophic lateral sclerosis (ALS) are increasing. Changing environmental factors could influence disease risk differently throughout life span, and also between genders, birth cohorts and seasons of birth. We aimed at describing long term ALS mortality trends in Norway between 1951 and 2014 by using age-period-cohort analysis. The Norwegian Cause of Death Registry provided ALS mortality data that were age- and sex-adjusted through direct standardization. Poisson regression analyses were used for identification of mortality trends and potential month of birth effects. We identified 5345 ALS cases, of which 54.7 % were men. ALS mortality increased throughout the whole period ($p<0.001$), with a mean annual increase of 1.14%. The increase was confined to those older than 60 years, but rates consistently dropped amongst the absolute oldest. The increase was mainly driven by birth cohort effects that increased from 1860 until 1934 ($p<0.001$). No month of birth effect or change in sex ratio were found. The continuous increase in ALS mortality since 1951 is best explained by long-term changes in exposure to risk factors or in case ascertainment, affecting men and women equally in the generations born since 1860 and at least into 1934.

Keywords:

ALS, MND, neuro-epidemiology, mortality, age-period-cohort model, neurodegenerative disorders

Introduction

Despite advances in the understanding of the genetics of amyotrophic lateral sclerosis (ALS), the etiology is still largely unknown [1]. Several environmental and life style risk factors such as smoking, physical trauma, athleticism and low intake of polyunsaturated fatty acids have been suggested [2]. The susceptibility periods for these are not known, and exposure is likely to vary across generations. As mortality rates for ALS closely reflects incidence [3], better understanding of long term trends in age- and sex-specific mortality rates may provide clues to disease etiology. Where standardized rates have the advantage of simplicity, age-period-cohort analyses provides more details on time effects for vital rates [4]. This analytical tool aims at distinguishing between changes resulting from birth cohort effects, period effects and age effects. Cohort effects reflect variations in disease risk that applies to all individuals born in the same period, and are associated with long-term exposures affecting different generations being exposed to different risks. Period effects result from external factors that equally affect all age groups at a particular calendar time. The age effect provides information on the rates of the disease in terms of different age groups. Earlier age-period-cohort analyses of ALS are limited, but findings lean towards cohort effects best explaining increase in rates [5-7]. No age-period-cohort analyses have been conducted on ALS in Norway.

For ALS and other complex diseases, studies have suggested an association between month of birth and risk for disease [8-12]. Such an effect could be of minor magnitude, but never the less of great interest from an epidemiological perspective.

With a relatively stable population, each person given a unique personal identification number and equal access to well-developed public health services, Norway is ideal for register-based studies. The Norwegian Cause of Death Registry (NCoDR) provides digitalized data for all deaths in Norway since 1951. NCoDR is based on death certificates (DCs) that are examined and controlled to ensure the diagnoses are plausible given the person's age and gender. Given the characteristics of ALS, mortality data has proven fairly reliable [3,13], and has previously shown an increasing trend from 1961 to 1994 in Norway [13].

The aim of this study was to describe the mortality trends from ALS in Norway during the period 1951-2014, including potential age, period, cohort and month of birth effects.

Materials and methods

Data collection

NCoDR collects and processes all information from all DCs. The direct, contributing and underlying cause of death is coded using the international classification of diseases (ICD). The following ICD systems have been used: ICD 6: 1951-57, ICD 7: 1958-68, ICD 8: 1969-85, ICD 9: 1986-95 and ICD 10: 1996-onwards. We searched all DCs in Norway from 1951 to 2014 containing codes corresponding to ALS mentioned anywhere on the DC. We used following corresponding codes for ALS: ICD 6 and 7: 356.0, 356.1, ICD 8: 348.0, 348.1, 348.2, ICD 9: 335.2, ICD 10: G12.2. Variables obtained for each case were gender, age (5-year bins), year of death (5 year bins), year of birth (1-year bins), county and month of birth. General population data for the same period were obtained from Statistics Norway.

To validate the data from NCoDR, we searched all electronically available hospital files at Akershus University Hospital (2004-2013) and Haukeland University Hospital (2001-2005), for patients diagnosed with ALS (ICD 10: G12.2), and examined whether those deceased within 2014 be were coded as G12.2 in their respective DCs. Together, these hospitals provide neurological services to 20% of the population in Norway

Statistical analysis

For the purpose of graphical presentation the mortality rates were age-sex standardized using the 2010-14 population as reference.

Poisson regression modeling was used for inference of longitudinal age and gender-specific trends. The following model was specified:

$$\log(\mu_{ijk}) = \log(personyears_{ijk}) + \beta_0 + \beta_1 gender_i + \beta_2 year_j + \beta_3 age_k + \beta_4 age_k^2 + \beta_5 age_k^3$$

where μ_{ijk} is the expected number of ALS deaths for gender *i* (0 for female, 1 for male) in year *j* for persons of age *k*. In this model the 5 year periods were coded on a continuous scale so that the regression coefficient $\beta_2$is interpreted as the annual change in mortality over the whole study period. The same was done for the variable age. The second and third degree terms for age are included to capture the non-linear age distribution of ALS. To test if there is a trend after the last reported observation (13), the model was also fitted using data from after 1994 only.

To test whether there were longitudinal changes in mortality rates for gender or age, the model was extended to include interaction between age and year, and gender and year (compared with the basic model using Likelihood Ratio test).

Age-Period-Cohort analysis was performed for the whole study period only, and followed the methodology described in Carstensen [14]. The Epi R package was used for the analysis. For identification constraints we used 1980 as reference period and 1920 as reference cohort, with period effects set to be 0 on average.

Data for birth months were tabulated in 5-year periods from 1886 to 1960. To test the hypothesis of a month of birth effect the following Poisson regression model were specified:

$$\log(\mu_{ik}) = \log(births_{ik}) + \beta_0 + \beta_1 birthperiod_i + \beta_2 birthperiod_i^{\,2} + \beta_{3k} mob_k$$

where μ_{ik} is the expected number of ALS deaths for persons born in period *i* and month *k*. The birth period variable is used as a continuous variable. The second order term were included to capture longer non-linear trends observed in the data, assumed to be an effect of low mortality in the more recent birth cohorts. The month of birth is a categorical variable with 12 levels.

Results

A total of 5345 ALS cases were identified from 1951-2014, of whom 2922 (54.7%) were men and 2423 (45.3%) were women. Out of 182 ALS cases diagnosed at Akershus University Hospital (2004-2013) and Haukeland University Hospital (2001-2005), 174 (96%) were retrieved in the NCoDR.

The overall standardized mortality rate per 100,000 person years is given in figure 1. The average rates, standardized for sex and age, were 1.3 in 1951-1954, 1.9 in 1970-1974, 2.4 in 1990-1994 and 2.8 in 2010-2014. Crude rates were 1.0, 1.7, 2.3 and 2.8 correspondingly.

ALS-related mortality increased consistently and significantly during the whole period ($p < 0.001$). This trend was almost identical in the two counties with fully developed neurological departments throughout the study period (Oslo and Hordaland including Bergen), compared to the rest of Norway (supplementary figure 1). Mean annual increase was 1.14%. Also after 1994, the latest reported observation [13], the increase was significant ($p=0.016$), with a mean annual increase of 0.88%. The standardized increase in ALS mortality over the whole period was 97% for men and 141% for women. Men had 46% greater mortality rate than women over the entire study period ($p < 0.001$), but the increasing trend over time was not significantly different between the genders ($p=0.270$). The male/female ratio ended in 1.33 (2010-2014).

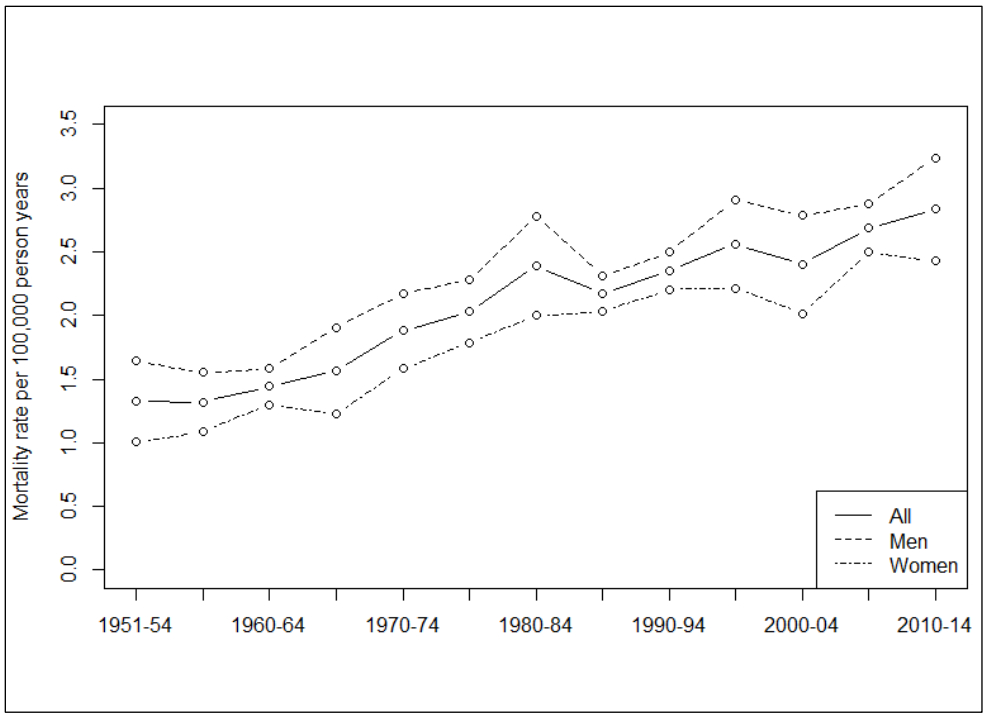

Fig.1 Amyotropchic lateral sclerosis mortality rate in Norway, 1951-2014. The rates are directly age -and sex standardized, using the Norwegian 2010-2014 population as reference

As shown in figure 2 A, ALS-related mortality was greater amongst men in all age groups, it peaked at 75-79 years for both genders, and declined markedly thereafter. The rise in period-specific rates was restricted to age-groups older than 60 years, and after 1969 to age-groups older than 70 years (fig 2 B). Hence, mean age at death of ALS increased from about 62 years in 1951-54 to about 71 years in 2010-2014. Meanwhile, mean general life expectancy in Norway increased from 71 to 82 years.

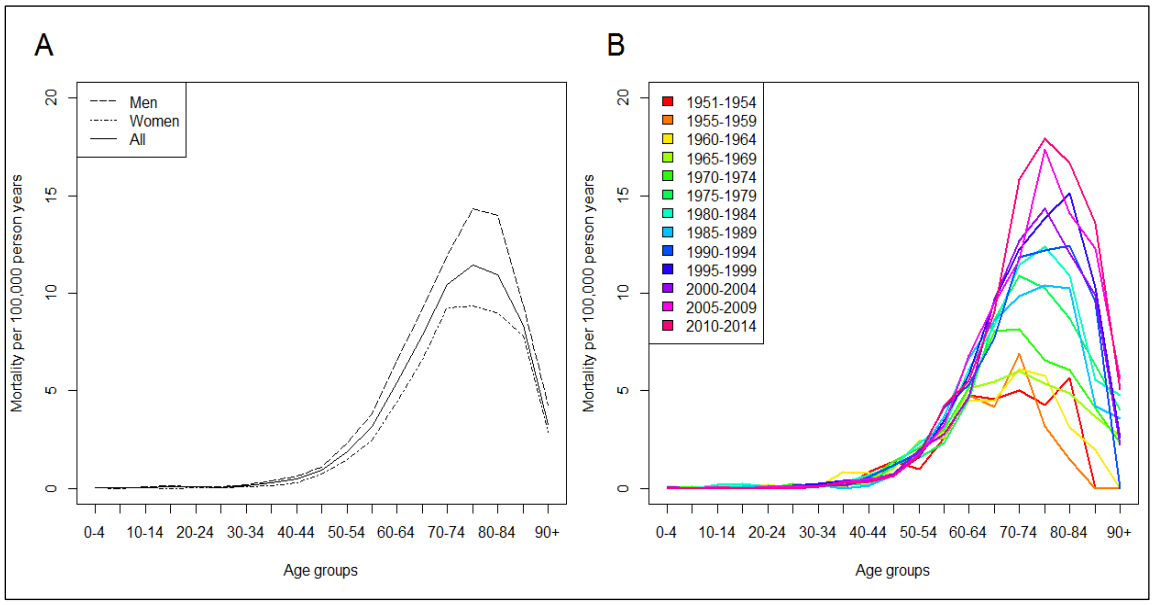

Fig.2 Amyotrophic lateral sclerosis mortality rates in Norway, 1951-2014, connected within genders in panel A, and within time-period of death in panel B

Figure 3 displays age-dependent rates by birth cohort and by period of death. In older cohorts, mortality rates increased more with successive birth years than in recent cohorts (3 A). During the study period, the mortality rates remained more or less unchanged for those aged less than 65 years, indicated by horizontal lines (panel 3 B). For age-groups older than 65, and particularly for those older than 75 years, the rates increased steadily (3 B). Taken together, this indicates disproportional changes in mortality rates, depending on both year of birth and period of death.

Table 1 shows the results from the fit of the age-period-cohort model for mortality rate. For our data, the full age period cohort model provided the best fit, with the cohort factor having greater impact than the period factor.

Results of the full age-period-cohort model are shown in Figure 4. The cohort effect estimated from the full model showed that the relative risk of dying from ALS increased markedly up until birth year 1934, when it again decreased (4 A). The model estimates a 76% bigger risk of dying from ALS if born in 1930 compared to 1880, regardless of age at death (4 A). Between 1934 and 1960 the cohort effect seems to decline, but estimations become more uncertain as few have yet reached the ALS susceptibility age.

The period effect displays a U-formed curve with the chosen reference period (1980) at the bottom (Figure 4 B). There were no changes in the effect of period between early 1970ies and late 1990ies, whereas before and after that, period effects were relatively greater.

Stratifying the data by age (older and younger than 70 years), the full age-period-cohort model provided the best fit for those younger than 70, whilst the age-cohort model fitted data best for those older than 70. The results were unchanged when the data was stratified by gender. Finally, shifting the constraints over to the cohort effect also provided the same qualitative interpretation (data not shown).

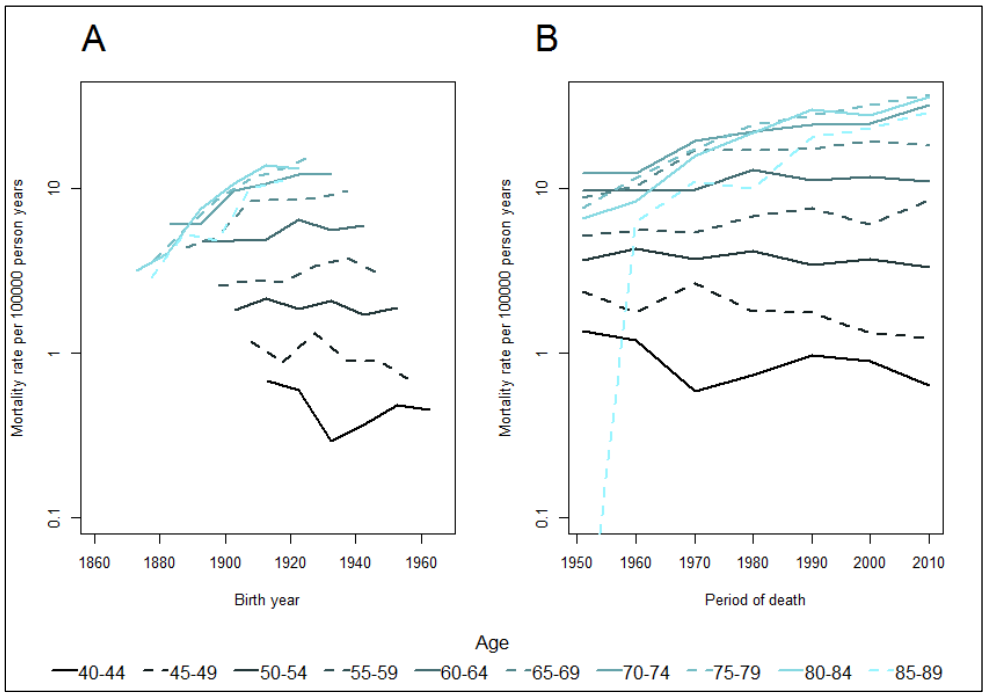

Fig.3 Age-dependent mortality rates from amyotrophic lateral sclerosis in Norway 1951-2014, by birth cohort year (A), and by time period of death (B). Mortality rates are plotted on the logarithmic scale

Fig.4 Age-period-cohort model of amyotrophic lateral sclerosis mortality in Norway, 1951-2014. Average period effect is constrained to be 0. The tilt of the curve is dependent on the constraints, but the curvature is not. Panel A displays estimated cohort effects relative to 1920. Panel B displays estimated period effects relative to 1980. Red-dotted lines indicate 95% confidence intervals (CIs)

Model	Residual df[1]	Residual deviance	Change in df[1]	Change in deviance	p-value
Age	241	677.56			
Age-drift	240	482.17	1	195.38	< 0.001
Age-Cohort	236	314.64	4	167.54	< 0.001
Age-Period-Cohort	232	289.41	4	25.23	< 0.001
Age-Period	236	472.93	-4	-183.52	< 0.001
Age-drift	240	482.17	-4	-9.25	0.055

Table 1 Results and comparison of age-period-cohort models of amyotrophic lateral sclerosis mortality in Norway, 1951-2014. The χ^2 model comparison test is performed sequentially from top to bottom. Decreasing residual deviance indicates a better fit. [1]degrees of freedom

Month of birth

Out of our total 5345 ALS cases, 5129 were born between 1886 and 1960. In the same period 4415823 births were registered. A likelihood-ratio test for the effect of months on the number of ALS deaths was not significant (p=0.472). Supplementary table 1 displays the effect of being born in different months. Being born in May and October seemingly increases risk for ALS with a little less than 8 percent, however not to any statistically significant extent.

Discussion

We find continuously increasing ALS mortality in Norway from 1951 to the end of 2014, but stable sex ratio and no month of birth effect. The increase in mortality is restricted to those above 60 years of age, with a persistent drop amongst the absolutely oldest. Although there is evidence of period effects on ALS mortality particularly before 1970 and after 1990, cohort effects operating at least in generations born before 1934 seem to have the strongest overall impact on the increasing ALS mortality.

Our study extends an earlier study carried out in Norway from 1961-1994 [13], showing that annual mortality rates from ALS increased from 1.52 in 1961 to 2.54 in 1994. An observed levelling off towards 1994 was only temporary; the increasing trend continued into 2014. Increasing mortality rates restricted to older age groups mirror findings in other countries [15,5,6,16-20]. The consistent decrease in period specific rates among the oldest age-groups (>80 years) supports the theory of ALS being an age-dependent disease, more than aging-dependent [21]. Notably, age in this context most likely represents biological age more than chronological age, as mean age at onset of ALS is proportional to life expectancy with a constant factor between different populations [22]. Our finding of a similar increase in mean age of death from ALS and life expectancy in the general population in Norway concur with this notion. This constant relationship may suggest that factors influencing life expectancy also influence ALS onset. For the earliest (1951-54) and latest (2010-2014) observation periods in the current study, mean age at death of ALS relate to mean life expectancy with the following constant proportion: $62/73 \approx 71/82 \approx 0.85$. It can be argued that it exists a subpopulation susceptible to ALS, and when life expectancy increases with time, more susceptible people will reach ages where ALS is expressed [23,24]. This theory is, however, not in conflict with environmental factors potentially influencing both ALS susceptibility and timing of death. It is possible that genetic factors play a relatively great etiological role in people with early debut of ALS, and that these are not affected by environmental factors to the same extent as those with later debut. If so, environmental changes could contribute to the increasing mortality trend restricted to older persons.

Differences in sex-specific mortality rates also reflect findings from other countries [25]. Some studies do however report narrowing of the gap between male to female mortality [26,5,6], and this was also suggested in Norway from 1961 to 1994 (13). Suggested explanations have been that men and women increasingly are being exposed to more similar arrays of environmental factors, alternatively a relative under-ascertainment of female cases in earlier periods. Converging sex-specific rates were not apparent in our study, although there was some fluctuation in the male: female ratio, from 1,12 at the lowest in 1991-1994 to 1,60 at the highest in 1951-1954. Such fluctuations are most likely random, and underscore the need of large data sets and long follow up.

Birth cohort effects affect all individuals in a generation, irrespective of their age of death. Changing environmental exposures could explain such effects. ALS has been modelled as a disease where genes, environment and time work as different burdens up until a threshold for disease [1]. It is possible that environmental risk factors operate at young ages, and that different birth cohorts are unequally affected by such factors in regards to both frequency and intensity. We find increasing cohort effects between 1880 and 1934, indicating a higher risk for developing ALS at any age for those born 1934, compared to those born 1880. Our findings suggest that exposure to environmental factors linked to ALS etiology in both men and women have increased for those being young in the first half of the past century, but thereafter possibly levelled off or even

decreased. ALS mortality data from both France and Denmark [5,6] showed similar results; increasing ALS mortality rates in succeeding birth cohorts from 1880 to 1920.

In our study, period of death also influenced the observed changes in ALS mortality. In contrast to cohort effects, period effects influence people across all ages, irrespective of their birth year. Decreasing period effects before 1970 and an increasing trend after 1995 diverge from period effects found in Denmark [5], but resembles possible period effects found in Switzerland when applying the full age-period-cohort model [7]. It should be noted that the Danish study used both different selection of ICD systems (ICD 9 not included) and ICD codes (only 348.0 within ICD 8), possibly contributing to conflicting results. The factors underlying the observed period effects in the current study is unclear. The introduction of the disease modifying agent Riluzole in 1996, together with establishments of ALS-teams in the same period, may have given neurologists greater motivation for diagnosing ALS. Additionally, emerging possibilities for genetic testing may have improved case ascertainment, although probably not to any extent that influences mortality rates yet. Changes in different ICD versions and revisions of diagnostic criteria also have to be considered. Over the course of our study period, four different ICD versions were used. A more liberal inclusion of motor neuron disease sub-diagnoses within earlier versions (348.9 in ICD 8, 335.0, 335.1 and 335.9 in ICD 9) would have provided 165 additional cases (data not shown). The exclusion of these cases could have contributed to a weaker period effect in the working period of ICD 8 and ICD 9 (1969-1995). However, the cases excluded from ICD 8 and ICD 9 comprises juvenile and adult forms of muscular atrophies, which are not included in G12.2 in ICD 10. Our selection of codes from the different ICDs is considered most consistent [3]. The El Escorial diagnostic criteria were revised in 1998 in Airlie House, including a probable form based on paraclinical data. The impact of these changes are considered small [27].

As for all studies on incidence or mortality time trends, the issue of possible changes in case ascertainment applies for our study. General improvement of case ascertainment over time, especially amongst the oldest, is both possible and plausible. As the population older than 70 years in Norway has increased by 248% throughout the study period, improved case ascertainment among the elderly would have a great impact on our results. A great strengthening of neurological services has taken place during the study period. Thus, practicing neurologists or neurological departments were present in all counties from 1979. However, the increasing rates have continued also in the last two decades, when these factors are less likely to play a significant role. Moreover, there were no differences in mortality rates in the two largest cities (Oslo and Bergen) and in the rest of the country, arguing against a great impact of differences in case ascertainment between rural and urban areas. This, and consistent findings from other countries [5,6,15-19], might substantiate that a real increase in ALS mortality has taken place.

Systematic inaccuracies in recording number of deaths could also contribute to changes in rates. However, both in the current and earlier studies [28,13] ALS incidence data from hospital files match mortality data from NCoDR quite well.

Age-period-cohort analyses have to be interpreted with caution. Because of the linear dependence of the regressor variables (age=period-cohort), it is not possible to attribute separate effects without further constraints [4]. Using different constraints can change not only the magnitude of the parameters, but also the direction of trend for each time factor, thus profoundly influencing the conclusion from an analysis.

An additional model-related problem is that an age-period interaction could mimic a cohort effect. In our case, it is possible that case ascertainment has improved over time, and that this improvement has an age-gradient; more of the elderly being ascertained. This would result in an age-period interaction. The age-period-cohort model cannot separate between a cohort effect and an age-period interaction. The latter must therefore necessarily serve as an alternative explanation. However, restricting the age-period-cohort analysis to those below 70 years did not change the results. Additionally, the observed cohort effect between 1880 and 1934 is largely consistent with previous reports [5,6], altogether suggesting that this finding is valid.

The earlier suggested spring [8]- or late autumn [12] birth effect could not be reproduced in our material. Recent critics stress the need for both birth period- and place adjustment when examining potential seasonal birth effects on adult disease [29,30]. We believe that our model more accurately took into account the confounding from

periodic variations in month of birth distribution. A larger material that allows adjusting for both time and place of birth is needed.

In summary, we find increasing mortality from ALS throughout the whole study period. The effect of birth year on ALS mortality increased from 1860 to 1934, suggesting an effect of changing environmental exposures or life style factors affecting these generations.

Ethical standards:

The study was approved by the Regional Committee for Medical and Health Research Ethics (REC South East).

The manuscript does not contain clinical studies or individual patient data.

Conflicts of interest:

On behalf of all authors, the corresponding author declares that there is no conflict of interest.

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