Age-Period-Cohort Analysis of Trends in Amyotrophic Lateral Sclerosis in Denmark, 1970–2009

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Amyotrophic lateral sclerosis (ALS) is a disease of the motor neuron with poorly understood etiology. Recent studies have suggested that the incidence rate of ALS and the rate of death from ALS are increasing, but it is unclear whether this is due to changing exposures or improvements in diagnosis. We used age-period-cohort models to investigate trends in ALS incidence (hospitalization) from 1982 to 2009 and ALS mortality from 1970 to 2009 in Denmark. Among those 45 years of age or older, 4,265 deaths (incidence rate = 5.35 per 100,000 person-years) and 3,228 incident diagnoses (incidence rate = 5.55 per 100,000 person-years) were recorded. Age-adjusted mortality rates increased by an average of 3.0% annually between 1970 and 2009 and by an average of 2.1% annually after 1982. Age-period-cohort analyses suggested that the full age-period-cohort model provided the best fit to the mortality data \((P < 0.001)\), although restriction to the post-1982 period suggested that the age-cohort model provided the best fit. Age-adjusted incidence rates increased by 1.6% annually after 1982 \((P < 0.001)\), which was best explained by the age-period model, with borderline significant cohort effects \((P = 0.08)\). A consistent finding regardless of parameterization or data subset appeared to be an increase in ALS incidence and mortality rate with later birth cohorts, up to a birth year of at least 1910.

age-period-cohort model; amyotrophic lateral sclerosis; brain disorders; neurodegenerative disorders; neuroepidemiology

Abbreviations: ALS, amyotrophic lateral sclerosis; APC, age-period-cohort; ICD-8, International Classification of Diseases, Eighth Revision; ICD-10, International Classification of Disease, Tenth Revision.

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder of unknown etiology. Although many studies have documented an apparent increase in incidence and mortality rates over time (1–5), it is unclear whether this is due to improved case ascertainment or to a genuine increase in incidence (6). Given the lack of known risk factors apart from age and possibly male sex (7), the latter hypothesis is important in that a genuine increase in incidence could signal the presence of environmental or occupational risk factors that have changed over time.

Age-period-cohort (APC) techniques are a tool to examine rates of an outcome over time and, when changes are observed, to distinguish between changes that result from birth cohort effects and those that result from period effects in the presence of a known age dependence (6, 8, 9). Birth cohort effects are those that affect entire birth cohorts and change their risk for some outcome over their entire life-course, relative to surrounding birth cohorts. Period effects are generally those that affect an entire population at a given moment in time, changing (either transiently or permanently) the risk of some outcome across all age groups—for example, newly introduced air or water pollutants (10). We know of only 2 studies in which APC analyses were applied to ALS population data (4, 5). An analysis in France from 1968 to 2007 of 37,624 deaths showed an increase in mortality rate that was better explained by a birth cohort effect than either a period or period-cohort effect (5). In an analysis in Switzerland from 1942 to 2008 of 5,027 deaths, researchers concluded that the increase was best explained by agespecific period effects, with steep increases limited to 1981 onward, although they could not rule out cohort effects (4). No
study has analyzed both incidence rate and mortality rate in the same population over the same years. To determine whether a birth cohort effect is a likely explanation for the apparent increase in ALS incidence and mortality rates, we analyzed incidence and mortality data in Denmark starting in 1970 (mortality rate) and 1982 (incidence rate) through 2009.

MATERIALS AND METHODS

Data source

We obtained death records from the Danish Cause of Death Registry, which has been kept electronically since 1970 (11). Deaths in Denmark were coded according to the International Classification of Diseases, Eighth Revision (ICD-8) before 1994, after which the International Classification of Diseases, Tenth Revision (ICD-10) was used. Cases of ALS were defined as persons with underlying or contributing causes of death with ICD-8 code 348.0 or ICD-10 code G12.2. The inclusion of contributing causes is generally considered the best practice, particularly for capturing ALS diagnoses in the elderly (12).

We obtained data on hospitalizations from the Danish National Hospital Registry, which has collected nationwide data on all somatic hospital admissions since January 1, 1977 (13). Incident cases were defined as first inpatient discharge diagnoses with the aforementioned ICD-8 or ICD-10 codes. To avoid prevalent cases, we included patients only from 1982 and later. Date of first inpatient discharge was considered the case date. Date of birth was obtained from the Central Person Register, which is linked to hospital and death registries through a personal identification number (14). We excluded all deaths from ALS (n = 123) and diagnoses of ALS in men and women less than 45 years of age (n = 204). Age- and sex-specific population denominators in 1-year, 1-age bins were obtained from Statistics Denmark (14).

Statistical analysis

We used the APC method described by Carstensen (15). Briefly, to solve the identifiability problem inherent in attempting to simultaneously model age, period, and cohort, which are linearly dependent (age = period - cohort), we fixed 2 levels and 1 slope among the 3 effects. We placed no constraints on age, constrained the cohort effect to be relative to 1920, and constrained the period effect to be relative to 1990 and to be 0 on average with 0 slope. In this parameterization, age effects are interpretable as longitudinal rates within the reference cohort (1920) over time. Cohort effects are interpretable as the relative rate from the 1920 reference cohort, in the reference period (1990). Period effects are deviations from the rate predicted by the age-cohort combination; this allows us to test for deviations from linear period effects over time. The estimated effects in this parameterization are dependent on the constraints used to identify them and thus must be interpreted with caution (8). However, testing between models for goodness-of-fit can be performed without additional assumptions. All models were also assessed visually to check for differences in estimated effects between models.

We tabulated 1-year rates for each year of the study. In all modeling we used natural cubic splines, with 6–10 knots for each effect spaced equally at quantiles. All analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria). APC analyses were implemented with the EPI package for epidemiological analysis in R (15).

RESULTS

Mortality rate

Between 1970 and 2009, there were 4,265 deaths attributed to ALS among people 45 years of age or older, for an overall mortality rate of 5.35 ALS deaths per 100,000 person-years. Age-specific male and female mortality rates for the entire study period are shown in Figure 1. Mortality rates peaked between ages 71 and 81 years for both men and women, and in both we observed a drop-off of rates in later years.

Over the course of the study, mortality rate increased an average of 3.0% per year (age-adjusted linear period model; P < 0.001). Restricted to the post-1982 period, the linear trend was a 2.1% increase (P < 0.001).

Mortality rates tabulated by age and year of death (period) are shown in Figure 2A. We stratified crudely for display purposes; in all APC analyses, the 3 factors are treated continuously with splines. Mortality rates increased across all age groups 51 years of age or older and most dramatically in those older than 71 years. Figure 2B shows mortality rates within age groups by birth cohort; in older age cohorts, a greater increase in mortality rates was seen with progressing birth year. Under the null hypothesis of neither a period nor a cohort effect, we would expect both plots to exhibit parallel lines (on the log
That both plots show deviations from parallel indicates that neither the age-period model nor the age-cohort model is sufficient to explain the increase.

Table 1 shows the results from the fit of the APC model for mortality rate, with age, period, and cohort year modeled continuously with splines. Compared with either the age-cohort model or the age-period model, the full APC model provides a significantly better fit to the data. Figure 3 shows the period and cohort effects estimated from the full APC model. The period effect shown here is constrained to be 0 on average with 0 slope for identifiability, but there is a clear deviation from linearity in mortality rate during 1975–1980, when an increase occurred. The cohort effect shows a steadily increasing rate, with a possibly slightly faster increase for those born from 1930 to 1935. Results were unchanged when stratified by sex. When we constrained the cohort effect, rather than the period effect, to be 0 on average with 0 slope, the overall increase over the birth cohorts was (as expected) transferred to the period effect, but the increases in 1975–1980 (period) and before 1910, as well as 1930–1935 (birth cohort), remained (Web Figure 1, available at http://aje.oxfordjournals.org/).

<table>
<thead>
<tr>
<th>Model</th>
<th>Residual df</th>
<th>Residual Deviance</th>
<th>Change in df</th>
<th>Change in Deviance</th>
<th>P Value</th>
</tr>
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</tr>
</tbody>
</table>

Abbreviation: df, degrees of freedom.

* Models are ordered so that adjacent rows provide tests between models, culminating in the age-period-cohort model. Changes in residual df and deviance are used to perform a $\chi^2$ test between adjacent models, where the fuller model is accepted if the test is significant.
When we limited mortality data to the post-1982 period (for comparability to the incidence data), the age-cohort model formally provided the best fit to the data, although the full APC model was only marginally nonsignificant ($P = 0.10$, comparing the age-cohort model with the full model). Plots of the effects from this full APC model (Web Figures 2 and 3) are similar to those from the complete mortality data (Figure 3 and Web Figure 1) for the years they share. Because Denmark switched from ICD-8 to ICD-10 in 1994, we also restricted mortality data to the post-1994 period, and again the age-cohort model was a better fit than the full APC model ($P = 0.78$, comparing the age-cohort model with the full model). In all of the treatments of the mortality data, the increase in ALS with later cohorts before at least birth year 1910 is consistent.

We stratified results by age to address the possibility that improved diagnosis in the elderly over time manifests as a cohort effect (an age-period interaction). When persons 81 years of age or older were excluded, results were largely unchanged. The full APC model was still strongly preferred ($P < 0.001$). When persons over 65 years of age were excluded, the period effect failed to reach significance when added to the age-cohort model ($P = 0.18$).

### Incidence rate

Between 1982 and 2009, a total of 3,228 newly diagnosed ALS cases were recorded among people 45 years of age or older, for an overall incidence rate of 5.55 cases per 100,000 person-years. Figure 4 displays age-period and age-cohort plots for incidence rates. Unlike for mortality rate, age-specific incidence rates were approximately linear over the period 1982–2009, with some evidence of a slight increase across all ages. Age-specific incidence rates by birth cohort also exhibited the pattern we would expect from an age-cohort model, with the possible exception of persons who were at least 80 years old. The age-adjusted linear increase in incidence rates over the study period was 1.6% per year ($P < 0.001$).

The APC modeling results (with age, period, and cohort year modeled continuously with splines) formally indicated that the age-period model provided the best fit to the data, although the full APC model was only marginally nonsignificant ($P = 0.08$; Table 2). Plots from full APC models for incidence showed a slight period increase between 1992 and 1996 and a cohort effect of increasing incidence over birth cohorts before 1920 (Figure 5), which mirrored the mortality data, particularly the post-1982 mortality data. As in the mortality data, reparameterizing the model to constrain the cohort effect, rather than the period effect, to be 0 on average with 0 slope did not materially change these results (Web Figure 4), with some of the overall increase being transferred to the period effect. Of note, though, is that even in this reparameterization, the increase with increasing birth cohorts before birth

<table>
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<th>Table 2. Modeling Results From Age-Period-Cohort Model for Amyotrophic Lateral Sclerosis Incidence Rate in Denmark, 1982–2009$^a$</th>
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Abbreviation: df, degrees of freedom.

$^a$ Models are ordered so that adjacent rows provide tests between models. Changes in residual df and deviance are used to perform a $\chi^2$ test between adjacent models, where the fuller model is accepted if the test is significant.
year 1910 was still seen. Results were similar when stratified by sex, although there was evidence of a stronger birth cohort effect among women, particularly among later birth cohorts (after 1940). Because the cohort effect was borderline significant, we also considered the alternative age-period-interaction model (Web Table 1).

**DISCUSSION**

Our results indicate that the increases in both the rate of death from ALS and the incidence of ALS in Denmark have a birth cohort component. If this holds, it suggests the existence of a behavioral or environmental factor driving ALS incidence that occurs in particular age groups at particular times, whether it be early in life (a true “birth” cohort effect—e.g., in utero or childhood exposure), upon entering the workforce, or later in life. These results also suggest that period effects (those that affect the entire population in a given calendar period) are less important in explaining the trends in ALS mortality rate.

Several studies have suggested a possible role of behavioral and environmental factors in ALS (16), but the possibility that exposure to such factors early in life contributes to ALS has not been extensively explored. In 1 report, an increased risk of ALS was found among those who played varsity sports when younger (17), although others have not found associations with early sports activity (18, 19). In a recent study, higher testosterone levels in utero—as assessed by examining the difference in lengths of the second and fourth fingers—were observed to be related to subsequent increased risk of ALS (20).

In 1 prior study of ALS in France, largely similar results were seen: a steep increase in motor-neuron disease mortality rate between birth years 1883–1923, with a subsequent plateau. However, those researchers found that age-cohort models adequately explained the change in mortality rate (5). In contrast, we found that mortality rates were best explained by both cohort and period effects (in addition to age). Although we observed the early cohort increase between birth years 1880 and 1920, we also observed a period increase in ALS mortality rate before 1982. This latter finding replicates results from the United States of an increase in mortality rate before 1983 with a subsequent plateau, although those results were not simultaneously controlled for year of birth (1). In a prior study in Switzerland with records beginning in 1942, researchers concluded that age-specific period effects were a sufficient explanation for the change in mortality rates; this might suggest that improved diagnosis before the 1970s overwhelmed any birth cohort effects that could have occurred later, whereas from the 1970s onward, improvements in diagnoses were less important relative to birth cohort effects (4).
It has been observed in prior studies that rates in men and women have been converging over time (5, 16, 17). We found a similar pattern in mortality rates in Denmark and report for the first time a similar trend in incidence. One possible explanation for this is that environmental and occupational factors, as well as smoking, have become increasingly balanced between sexes, and evidence suggests a causative role of such exposures (7, 21, 22). Alternatively, the convergence could be explained by improved diagnosis among women relative to men, which is unlikely because of free health care for all in Denmark independent of workforce involvement. Also, as for our main findings, any such improved diagnosis would have to affect incidence rate and mortality rate equally because we found similar results for the sex ratio of ALS in incidence and mortality data. Thus, for example, greater improvement in identification of ALS on death certificates for women than for men could not explain our findings. Improved diagnosis of ALS among women, if that also led to a similar improved identification on death certificates, could possibly explain our findings, but that would have to apply to diagnosis at any age because results excluding those older than 65 or 80 years were similar.

The major strengths of the present study were its size and time span and the availability of both incidence and mortality data. In addition, the use of APC techniques allowed us to test for the presence of birth cohort effects while simultaneously controlling for shifts in period-specific mortality and incidence rates. Although a strength of using national registries is the size and completeness they provide, problems can arise if diagnostic accuracy is low. The general validity of the Danish Hospital Register is considered to be high (23). Both diagnostic sensitivity and specificity of the Danish Hospital Register are generally reported to be quite high (e.g., 84% or >90%) when hospital discharge codes for ALS are used, although positive predictive value can be slightly lower, with positive predictive value generally being better for mortality data than for hospital discharge data (24–26). In a previous study, however, medical records were obtained for 15 incident ALS cases identified by International Classification of Diseases code in the Danish Hospital Register, and all 15 cases were confirmed as ALS (27). A related limitation is the switch in 1994 from ICD-8, which was unique to ALS, to ICD-10, which includes other motor-neuron diseases. Nevertheless, our analysis of mortality rate limited to post-1994 deaths showed no major difference in results.

Limitations of our study included the requirement for arbitrary constraints to achieve identifiability of the effects of age, period, and cohort. There are no solutions to the problem of identifiability that are entirely free of the constraint problem. However, by examining the range of possible constraints, we can estimate the range of plausible effect estimates. Our exploration of alternative constraints did not change our qualitative findings of a large pre-1920 (birth cohort) increase in both mortality rate and incidence rate. This pre-1920 birth cohort effect did not account for all of the observed rise in ALS incidence and mortality rates, but how much of the remaining rise can be attributed to a cohort or period effect is hard to determine given the results of the 2 parameterizations. The alternative parameterizations also did not change the findings of an increase in mortality rate among those born in 1930–1935 and those living around 1980.

Although the cohort effect was borderline insignificant for incidence data, this could be explained by the difference in calendar years for incidence rate versus mortality rate. The 12 fewer years of incidence data allowed for less power in detecting effects, particularly those effects that manifest in older cohorts—precisely where the most consistent increases with birth cohort were seen, regardless of parameterization choice. Notably, plots of all deaths and deaths restricted to the years of the incidence data (after 1982) were similar, and plots of incidence rate and mortality rate were similar. For these reasons, we emphasize the full APC model for the incidence data, although a plausible alternative is the age-period-interaction model, results of which are shown in Web Table 1. In that case, period effects would be represented by the age-stratified rates as in Figure 4A.

A further limitation inherent in APC analyses is that we could not directly address the hypothesis that ascertainment improved differentially with respect to age—in particular, that diagnosis improved in the elderly over the study period. Such an effect would appear as a cohort effect, though in reality it would be best considered an age-period interaction (with an effect in particular age groups at particular periods). For example, an increase in rates among those who were at least 65 years of age in 2000 could be explained by either a cohort effect (the introduction of an exposure in 1935) or an age-specific period effect (improved case ascertainment among the elderly beginning in 2000). The similarity between our findings for both incidence and mortality rates, however, suggests that any such changes would have to affect both incidence rate and mortality rate and could not be, for example, better recognition of ALS on death certificates among the elderly. They also could not affect men and women differently, inasmuch as we generally found similar patterns for men and women.

In summary, this large national study provides evidence for a substantial increase in ALS incidence and mortality rates in Denmark in succeeding birth cohorts from 1880 to 1920, with a subsequent plateau, and suggests a convergence in risk for men and women by advancing calendar time. These results support an environmental cause of ALS that became more common in the 20th century, in a way that affected successive birth cohorts as whole units, particularly those born before 1920. Given the paucity of known risk factors, these findings could help narrow future research into environmental agents on the basis of their historical use patterns.

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REFERENCES


