AMYOTROPHIC LATERAL SCLEROSIS is a neurodegenerative disorder characterized by loss of upper and lower motor neurons. The incidence of ALS shows small variation worldwide, ranging from 1 to 2 per 100,000 person-years.\(^1\)\(^-\)\(^4\) Over the last decades, increasing mortality due to ALS in Sweden and other countries has been reported.\(^5\)\(^-\)\(^8\) Two studies showed a similar trend in the incidence of ALS in Ireland\(^2\) and the United States.\(^9\) In addition to a real increase in ALS incidence, the observed trends might also be attributable to improved disease awareness and more resources for the diagnosis of ALS. Prolonged observation in these defined populations in recent calendar periods, when these alternative explanatory factors are relatively stable, is thus warranted to verify the earlier observed increasing trend.

Epidemiologic studies have explored the potential roles of demographic factors, including area of residence,\(^2\)\(^,\)\(^3\)\(^,\)\(^10\)\(^,\)\(^11\) season of birth,\(^12\)\(^-\)\(^14\) and socioeconomic status\(^15\)\(^-\)\(^18\) on the risk of ALS; however, the findings are inconsistent. Sweden is a country that provides all citizens equal access to health care. The availability of several nationwide registries and the Population and Housing Censuses conducted by Statistics Sweden provides a unique opportunity to study both the temporal trend of ALS incidence and possible incidence variations according to various demographic variables. To follow up earlier studies of ALS in Sweden,\(^5\)\(^,\)\(^6\)\(^,\)\(^10\) in the present study, we focused our analysis on the period between January 1, 1991, and December 31, 2005.

METHODS

SWEDISH INPATIENT REGISTER

The Swedish Inpatient Register, as described previously,\(^19\) was initiated by the Swedish National Board of Health and Welfare in 1964-1965 primarily for administrative purposes. Its coverage has increased, including 60% of all residents in the country in 1969, 85% in 1983, and 100% since 1987. The register data include the

Objectives: To investigate the temporal trend of amyotrophic lateral sclerosis (ALS) incidence in Sweden between January 1, 1991, and December 31, 2005, and to explore incidence variations according to major demographic factors.

Design: Population-based study.

Setting: Academic research.

Participants: All incident cases of ALS identified through the Swedish Inpatient Register between January 1, 1991, and December 31, 2005.

Main Outcome Measure: Age-standardized incidence rates were calculated by applying the observed age-specific incidence rates to the age distribution of the Swedish population in 1991. A linear regression model was used to assess the potential trend of the incidence during calendar years. We also followed up the entire population in 1991. A linear regression model was used to assess the potential trend of the incidence during calendar years. We also followed up the entire population registered in the 1990 Population and Housing Census for incidence of ALS. Relative risk and 95% confidence interval of ALS associated with demographic variables were estimated using Poisson regression models.

Results: The age-standardized incidence rates increased from 2.32 per 100,000 person-years in 1991-1993 to 2.98 per 100,000 person-years in 2003-2005, representing an annual increase of approximately 2% during the 15 years (P value for trend, .002). The age-specific incidence rates increased in all age groups except those younger than 50 years. The observed increase remained significant when restricting the analysis to individuals born in Sweden (P value for trend, <.001). Compared with individuals born from April through June, those born from October through December were at 11% increased risk of ALS (95% confidence interval, 1.01-1.23).

Conclusions: The incidence of ALS has been increasing during the last 15 years in Sweden. Further studies are warranted to explore the underlying reasons for this observed trend.

Arch Neurol. 2009;66(4):515-519

Author Affiliations:
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (Drs Fang, Valdimarsdóttir, Bellocco, Sparén, Fall, and Ye); Centre for Public Health Sciences, University of Iceland, Reykjavík (Dr Valdimarsdóttir); Department of Statistics, University of Milano-Bicocca, Milan, Italy (Dr Bellocco); Department of Neurology, Karolinska Hospital, Stockholm, Sweden (Dr Ronnevi); and Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts (Dr Fall).
national registration number (a unique identifier of all Swedish residents), up to 8 discharge diagnoses, and times of hospital admission and discharge. Inasmuch as private inpatient medical care is rare in Sweden, the Inpatient Register effectively includes almost all incident cases of ALS in patients who had ever been hospitalized either because of ALS specifically or for any other reason. Although there are no data on the quality of ALS diagnosis to date, the Inpatient Register has both high completeness and accuracy in general.20,21 During the study, the International Classification of Diseases, Ninth Revision (ICD-9; 1991-1996, code 333.C) and Tenth Revision (ICD-10; 1997-2005, code G12.2), were used for ALS diagnosis in this registry.

NATIONWIDE ANALYSIS

Using the Inpatient Register, we identified all hospitalization records with ALS as either the primary or secondary diagnosis at discharge between January 1, 1991, and December 31, 2005. The age-specific incidence rates of ALS were calculated in 13 age groups (<29 years, 5-year groups between 30 and 84 years, and ≥85 years). We further calculated the age-standardized incidence rates of ALS during calendar periods (1991-1993, 1994-1996, 1997-1999, 2000-2002, and 2003-2005) by multiplying the observed age- and calendar period-specific incidence rates in this registry to the age distribution of the Swedish population in 1991 (ie, standard population). Linear regression models were used to test changes during calendar periods, with age-standardized rates as the dependent variable and calendar year as the independent variable. A linear trend of male-to-female–rate ratio during calendar periods was similarly tested. To further clarify whether the temporal trends in ALS incidence varied by age group, we also calculated the incidence rates stratified by 5 age groups (<49, 50-59, 60-69, 70-79, and ≥80 years) and 5 calendar periods (1991-1993, 1994-1996, 1997-1999, 2000-2002, and 2003-2005).

To allay potential concern of case underascertainment by using only hospitalization data, we also conducted a sensitivity analysis by accruing ALS cases identified from the Causes of Death Register between January 1, 1991, and December 31, 2005 (ie, deaths with ALS as the underlying cause). Age-standardized mortality was calculated as described for incidence rates.

CENSUS-BASED ANALYSIS

To explore roles of demographic factors on ALS incidence, we conducted a cohort study based on the 1990 Population and Housing Census containing 8,587,177 persons. Twenty-four individuals were excluded from follow-up because of incomplete birth date information. Through cross-linkages to the Causes of Death Register, Migration Register, and Inpatient Register, the remaining individuals were followed up from January 1, 1991, to the date of first ALS diagnosis, death, emigration from Sweden, or December 31, 2005, whichever occurred first. The date of ALS diagnosis was defined as the date of first admission to a hospital with ALS as either the primary or secondary diagnosis as recorded in the Inpatient Register. Another 300 individuals (<0.1%) in whom ALS was diagnosed before enrollment in the cohort and 141,256 individuals (1.6%) who had other inconsistent information uncovered in record linkage during follow-up (ie, death or emigration recorded before enrollment in the cohort) were further excluded, leaving 8,445,396 individuals (98.4%) for the final analysis.

To address potential concern about the effect of immigrants on the temporal incidence changes of ALS, we tested potential trends of ALS incidence rates during calendar periods by country of birth (Sweden and others). Incidence variations by area of residence (northern, central, and southern Sweden), season of birth (January-March, April-June, July-September, and October-December), and socioeconomic status (white-collar worker, self-employed, blue-collar worker, farmer, and others) were also tested. Because being born in April-June had been reported earlier as associated with the highest risk of ALS,22,23 we used this season as the reference group. To investigate the role of birth cohort effect on the association between season of birth and ALS risk, we further stratified the analyses by birth cohorts (1920 or before, 1921-1930, 1931-1940, and 1941 or after). Poisson regression models were used to estimate the relative risk of ALS with the demographic variables as the independent variables and their corresponding observed number of cases as the dependent variables. Age at follow-up (as a categorical variable in 13 groups: ≤29 years, 5-year groups between 30 and 84 years, and ≥85 years), sex, and area of residence were adjusted for in all models. The logarithm of accumulated person-years served as the offset variable. The Pearson χ² test was applied to check the goodness of fit of the models. A scale parameter, the square root of the Pearson χ² divided by the degrees of freedom, was used to correct overdispersion, if applicable.

We conducted all analyses using commercially available software (SAS version 9.1; SAS Institute, Cary, North Carolina). The study was approved by the Regional Ethics Committee of Karolinska Institutet, Stockholm, Sweden.

RESULTS

We identified 3,481 individuals (1,903 men and 1,578 women) from the Swedish Inpatient Register who were first diagnosed as having ALS between January 1, 1991, and December 31, 2005. Their mean age at diagnosis was 68.0 years (67.0 years for men and 69.1 years for women). The age-specific incidence rates of ALS are shown in Figure 1. The peak age at diagnosis was 70 to 84 years. Using the Causes of Death Register, we identified 3,485 deceased individuals with ALS as the underlying cause of death during this period, with a mean age at death of 69.9 years (68.6 years for men and 71.3 years for women). Of the 3,485 deceased individuals, 2,740 (78.6%) were also identified in the Inpatient Register.

Figure 2 shows the age-standardized incidence rates of ALS using the Swedish population in 1991 as the standard. The standardized rates increased from 2.32 per 100,000 person-years in 1991-1993 to 2.98 per 100,000 person-years in 2003-2005.
person-years in 2003-2005, indicating an annual increase of approximately 2% during the 15 years (P value for trend, .002). A similar annual increase in age-standardized mortality from ALS was also observed (P value for trend, .002). The increasing trends of incidence and mortality were evident in both men and women. No clear trend was noted for the male-to-female–rate ratio during the study (P value for trend, .83). Figure 3 demonstrates the age-specific incidence rates of ALS by calendar period in 5 age groups. We observed an increasing incidence during calendar periods in most age groups except the youngest (≤49 years; P value for trend, .13).

CENSUS-BASED ANALYSIS

We identified 3390 individuals with ALS (97.4% of the total number identified from the Inpatient Register in the nationwide analysis; 1846 men and 1544 women) in 114,227,395 person-years accrued during follow-up. The crude incidence rate was 2.97 per 100,000 person-years. A total of 91.0% of the cohort members were born in Sweden, 90.9% of 3390 who had ALS. The observed increasing trend of ALS incidence was noted only in individuals born in Sweden (P value for trend, <.001, adjusted for age, sex, and area of residence; Table 1) but not among others (data not shown).

An increasing south-to-north gradient of ALS incidence was suggested; however, a linear trend was not statistically significant (P value for trend, .12, adjusted for age and sex; Table 2). Individuals born in October through December demonstrated an 11% higher incidence of ALS compared with those born in April through June (relative risk, 1.11; 95% confidence interval, 1.01-1.23). Individuals born in January through March and July through September also exhibited a slightly higher incidence of ALS compared with the reference group; however, the differences were not statistically significant (Table 2). Further stratified analysis showed similar seasonal birth patterns in most birth cohorts, in particular in those born in the 1920s and 1930s (data not shown). No clear difference in ALS incidence was observed among different socioeconomic status groups (Table 2). Farmers tended to be at higher risk of ALS compared with white-collar workers; however, the difference was not statistically significant (relative risk, 1.16; 95% confidence interval, 0.89-1.48).

In the present study, we observed an increasing incidence of ALS in Sweden between January 1, 1991, and December 31, 2005. Earlier studies demonstrated that mortality from ALS in Sweden increased continuously from the 1960s to the beginning of 1990s. Compared with mortality, incidence rates based on hospital discharge records are more reliable given the prospective case inception, minimized patient loss, and probably the uniform application of the diagnostic criteria. The shift in use of the ICD code during the study may account in part for the observed trend in our study because the ICD-9 code 355 was specific for ALS, whereas the ICD-10 code G12.2 is used for all motor neuron diseases. However, according to the Causes of Death Register, for example, between 1987 and 1996, other motor neuron diseases (coded as ICD-9 335 excluding 335C) comprised less than 5% of all motor neuron diseases. The observed incidence increase is approximately 30% in our study and thus could not be entirely explained by other non-ALS motor neuron diseases. Further, a similar magnitude of increase was noted between 1994-1996 (ICD-9 in use) and 1997-1999 (ICD-10 in use) and between 2000-2002 and 2003-2005 (ICD-10 in use in both periods). In addition, we observed a continuous increase in men in all periods, with an even stronger magnitude in both the beginning and end of the study, when only ICD-9 or ICD-10 was in use.

Alternative explanations for the observed trend must also be considered. Aging of the general population, for example, is always of interest when interpreting a temporal trend in ALS incidence because it leaves a growing population at risk. The mean life expectancy of the Swedish population increased from 74.9 years to 78.4 years for men and from 80.5 years to 82.8 years for women during the study period. Thus, the observed increasing ALS inci-
idence could, in theory, be attributable to the aging of the population. However, in the present study, ALS incidence rates in various calendar periods were, by the direct method, standardized to the uniform age distribution of the Swedish population in 1991 to adjust for differential age distributions in different calendar periods. The result from stratified analysis by age group, which showed that ALS incidence rates increased in all age groups older than 50 years, further allays such a concern.

Immigrants from countries with a higher ALS incidence than in Sweden may be another possible explanation. The immigrant population in Sweden has expanded continuously since the 1980s, although the entire population size has not changed much. However, in the analysis restricted to individuals born in Sweden, a similar increasing trend was noted.

Better neurologic service and improved resources for diagnosis of ALS have been claimed as potential explanations for the observed increasing ALS incidence in previous studies and may also contribute to the observed trend in our study. If true, they are likely to have a greater effect in elderly persons and women. Underdiagnosis of ALS in elderly persons is unavoidable in almost all health care systems including Sweden's. However, the Swedish population, regardless of age, has free access to the health care system, and no major reform in the health care system occurred during the study period. The percentage of such underdiagnosis, if it exists, should have been consistent during the study period and thus does not explain the observed trend. In addition, the increasing trend in all age groups but the youngest (not applicable) and the almost parallel trends in the groups aged 70 to 79 years and 80 years or older are reassuring. Previous studies have reported a decreasing male to female ratio in ALS incidence, which suggests improved resources for diagnosis of ALS in women. In our study, however, the increasing trend was evident in both men and women, and we did not observe any clear trend in the male-to-female–rate ratio. The observed temporal trend in ALS incidence might thus be true, and its underlying reasons warrant further studies.

Demographic differences in ALS incidence are valuable in searching for causative clues for the disease. Our data show that neither area of residence nor socioeconomicstatus is associated with risk of ALS. Our findings insofar as season of birth also are different from those reported earlier and do not seem to vary substantially by birth cohorts. Our finding of a higher risk of ALS in individuals born in October through December seems more in agreement with the hypothesis of an infectious cause for ALS because infections (eg, those acquired early in life) often are associated with a similar seasonal pattern. This finding is clearly exploratory and needs confirmation.

We used hospital discharge records rather than death certificate data in our primary analysis to ensure that we identified real incident cases between January 1, 1991, and December 31, 2005. In a previous study, we showed that the mean survival time (ie, from first hospitalization to death) in patients with ALS identified from the Inpatient Register is approximately 2 years, which is similar to the 1- to 3-year mean survival time from ALS diagnosis to death reported by others. The sensitivity analysis based on data from the Causes of Death Register showed similar increasing age-standardized mortality as the incidence rates. Death certificates enable identification of approximately 70% to 90% of ALS cases. Our data are consistent with previous reports because, for example, 77% of ALS cases documented in the Inpatient Register in 1991 were later included in the Causes of Death Register. We thus conclude that the Inpatient Register includes most patients with ALS in Sweden, and probably at an early stage. The lack of detailed diagnosis information in the registry including diagnostic criteria and disease presentation spectrum (eg, bulbar or spinal onset) is another limitation of the present study. This limitation should, however, to some extent be outweighed by the large sample size, nationwide study design, complete follow-up, and unbiased ascertainment of exposures.

In conclusion, in this nationwide study, we found an increasing incidence of ALS in Sweden between January 1, 1991, and December 31, 2005.

### Table 1. Temporal Trend of ALS Incidence in Individuals Born in Sweden: A Census-Based Cohort Study in Sweden, January 1, 1991, Through December 31, 2005

<table>
<thead>
<tr>
<th>Calendar Period</th>
<th>No. of Cases</th>
<th>Person-Years</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991-1993</td>
<td>532</td>
<td>22,676,767</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>1994-1996</td>
<td>538</td>
<td>21,795,464</td>
<td>1.01 (0.90-1.14)</td>
</tr>
<tr>
<td>1997-1999</td>
<td>664</td>
<td>20,880,425</td>
<td>1.25 (1.12-1.40)</td>
</tr>
<tr>
<td>2000-2002</td>
<td>631</td>
<td>20,009,979</td>
<td>1.18 (1.06-1.33)</td>
</tr>
<tr>
<td>2003-2005</td>
<td>717</td>
<td>19,246,490</td>
<td>1.32 (1.18-1.48)</td>
</tr>
</tbody>
</table>

### Table 2. RRs and Corresponding 95% CIs for Associations Between Area of Residence, Socioeconomic Status, Season of Birth, and Risk of ALS: A Census-Based Cohort Study in Sweden, January 1, 1991, Through December 31, 2005

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Cases</th>
<th>Person-Years</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in Sweden</td>
<td>765</td>
<td>23,714,894</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Northern</td>
<td>1839</td>
<td>63,841,979</td>
<td>0.95 (0.88-1.04)</td>
</tr>
<tr>
<td>Central</td>
<td>786</td>
<td>26,670,521</td>
<td>0.92 (0.83-1.02)</td>
</tr>
<tr>
<td>Southern</td>
<td>1823</td>
<td>56,175,506</td>
<td>0.91 (0.82-1.01)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White-collar worker</td>
<td>752</td>
<td>26,099,336</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Self-employed</td>
<td>102</td>
<td>2,661,234</td>
<td>0.95 (0.76-1.16)</td>
</tr>
<tr>
<td>Blue-collar worker</td>
<td>668</td>
<td>28,311,918</td>
<td>0.99 (0.89-1.10)</td>
</tr>
<tr>
<td>Farmer</td>
<td>65</td>
<td>979,401</td>
<td>1.16 (0.89-1.48)</td>
</tr>
<tr>
<td>Other</td>
<td>1823</td>
<td>56,175,506</td>
<td>0.91 (0.82-1.01)</td>
</tr>
<tr>
<td>Season of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>January-March</td>
<td>877</td>
<td>29,234,923</td>
<td>1.06 (0.97-1.17)</td>
</tr>
<tr>
<td>April-June</td>
<td>843</td>
<td>30,507,708</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>July-September</td>
<td>820</td>
<td>28,419,089</td>
<td>1.02 (0.92-1.12)</td>
</tr>
<tr>
<td>October-December</td>
<td>850</td>
<td>26,065,673</td>
<td>1.11 (1.01-1.22)</td>
</tr>
</tbody>
</table>
1, 1991, and December 31, 2005, which was evident in both men and women. More studies are needed to verify this finding in other areas and, if confirmed, to explore the underlying reasons.

Accepted for Publication: September 9, 2008.

Correspondence: Fang Fang, MD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, 17177 Stockholm, Sweden (fang.fang@ki.se).

Author Contributions: Drs Fang and Ye had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Fang, Valdimarsdóttir, and Ye. Acquisition of data: Sparén and Ye. Analysis and interpretation of data: Fang, Valdimarsdóttir, Bellocco, Ronnevi, Fall, and Ye. Drafting of the manuscript: Fang and Ronnevi. Critical revision of the manuscript for important intellectual content: Fang, Valdimarsdóttir, Bellocco, Ronnevi, Sparén, Fall, and Ye. Statistical analysis: Fang, Bellocco, and Ye. Obtained funding: Valdimarsdóttir and Ye. Administrative, technical, and material support: Fang. Study supervision: Valdimarsdóttir, Ronnevi, Sparén, Fall, and Ye.

Financial Disclosure: None reported.

Funding/Support: This study was supported by Björklund's Fond 2008-20892 (Dr Ye) and state funding from the University of Iceland (Dr Valdimarsdóttir).

REFERENCES