

Epidemiology of ALS in Italy

A 10-year prospective population-based study



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ABSTRACT

Objective: To describe the temporal patterns of incidence and demographic characteristics of amyotrophic lateral sclerosis (ALS) in Piemonte and Valle d'Aosta, Italy, in the 10-year period 1995 through 2004.

Methods: The Piemonte and Valle d'Aosta Register for ALS (PARALS) is a prospective register collecting all cases of ALS incident in two regions of northwestern Italy (population: 4,332,842) since 1995. The cases are identified using several concurrent sources. ALS diagnosis is based on El Escorial criteria.

Results: During the 10-year period of observation, 1,347 residents in the study area were diagnosed with ALS. In 1,260 of these cases, a diagnosis of definite or probable ALS was made at presentation or during the follow-up. The mean annual crude incidence rate was 2.90/100,000 population (95% confidence interval [CI], 2.72 to 3.09). The crude prevalence rate (December 31, 2004) was 7.89 (95% CI, 7.09 to 8.75)/100,000 population. According to the capture-recapture estimation, 27 patients were unobserved, thus increasing the annual observed crude incidence to 2.96/100,000 population. The incidence rate did not show any relevant variation during the 10-year period of the study and was constantly higher among men. The demographics and clinical features did not change between the 1995-1999 and the 2000-2004 cohorts, with the notable exception of the mean time delay from onset to diagnosis, which was significantly decreased in the last 5-year period.

Conclusions: In the examined decade, the incidence of amyotrophic lateral sclerosis in Italy has been stable, and the clinical and demographic characteristics of the patients have shown no relevant modifications. *Neurology*® 2009;72:725-731

GLOSSARY

ALS = amyotrophic lateral sclerosis; **CI** = confidence interval; **EEC** = El Escorial diagnostic criteria; **EEC-R** = El Escorial revised criteria; **MND** = motor neuron disease; **PARALS** = Piemonte and Valle d'Aosta Register for ALS; **PCRA** = Piemonte Central Regional Archive; **VACRA** = Valle d'Aosta Central Regional Archive.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by a progressive impairment of motor function at bulbar and spinal level. Its cause is unknown. The disorder is generally sporadic, although approximately 5% of cases have a positive family history for ALS.¹ Recent European and American studies reported similar incidence rates, ranging from 1.5 to 2.5 cases/100,000 population/year, using a prospective cohort design and the same case definition.²⁻⁷ However, it remains unclear whether in the last decades there has been an increase of ALS frequency or a modification of its demographic characteristics, since mortality studies indicate an increase,⁸⁻¹⁰ whereas incidence studies report a relative steadiness.^{5,6}

Supplemental data at
www.neurology.org

*See the appendix for a list of participating centers.

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The aim of this study was to describe the temporal patterns of incidence and the demographic characteristics of ALS in Piemonte and Valle d'Aosta, Italy, in the 10-year period January 1, 1995, to December 31, 2004, and to evaluate the lifetime risk for ALS in this population.

METHODS The Piemonte and Valle d'Aosta Register for ALS (PARALS) is a prospective register collecting all cases of ALS incident in Piemonte and Valle d'Aosta, Italy (total population at the 2001 national census, 4,332,842; total area 28,692 km²). The register was established in 1995 and is still operating. Epidemiologic data about the 1995–1996 period have been previously published.³

Case collection. The main sources of cases are the neurologic departments of the two regions. In each department, one or more investigators were identified as study referents. Investigators used an ad hoc questionnaire to collect patients' demographic information, clinical history, neurologic and laboratory findings, and treatments. Diagnostic EMG examination was performed in all cases according to standard procedures. The questionnaires were revised by the investigators of the coordinating center and checked for accuracy and completeness. Discrepancies were solved by discussing each case with the local investigators. From 2000, information about family history of ALS was systematically collected.

The secondary sources of cases were 1) the Piemonte Central Regional Archive (PCRA) and the Valle d'Aosta Central Regional Archive (VACRA), which include all discharges from all Italian private and public hospitals of individuals resident in the two regions, coded according to the International Classification of Diseases, 9th revision, Clinical Modification (codes 335.20, 335.21, and 335.22); and 2) the mortality coding from the Italian Statistical Bureau. Rehabilitation and geriatrics departments as well as ALS experts practicing in regions adjacent to the study area were also contacted and asked to report all possible cases of ALS patients resident in Piemonte seen in consultation. Clinical records of cases found through secondary sources were obtained, and relevant clinical information for each case was analyzed in order to verify if the patient met the eligibility criteria; all living patients were contacted by phone and visited by one of the neurologists involved in the study.

According to the data of the Italian National Health System,¹¹ few patients seek medical care exclusively outside their region of residence, since the provision of benefits from the Italian National Health System and Social Security is based on prescription by a specialist practicing in the area where the patient is resident.

Diagnostic criteria. The diagnosis of ALS was based on the original El Escorial diagnostic criteria (EEC),¹² although from 2000 cases were also classified according to El Escorial revised criteria (EEC-R).¹³ EEC require the presence of upper and lower motor neuron signs and symptoms and the progressive diffusion of signs and symptoms from one region to another, in the absence of neuroimaging and electrophysiologic evidence of other diseases that might explain the clinical features. EEC distinguish four levels of diagnostic certainty: definite, probable, possible, and suspected ALS. EEC-R has abolished the suspected level and introduced two other categories: probable ALS laboratory supported and definite familial ALS laboratory supported. In our

registry, patients with all forms of motor neuron disease (MND) are enrolled, but only subjects with definite or probable ALS have been included in the present study. According to EEC-R, upper motor neuron signs were defined on clinical basis only, not considering neurophysiologic evidence.¹³

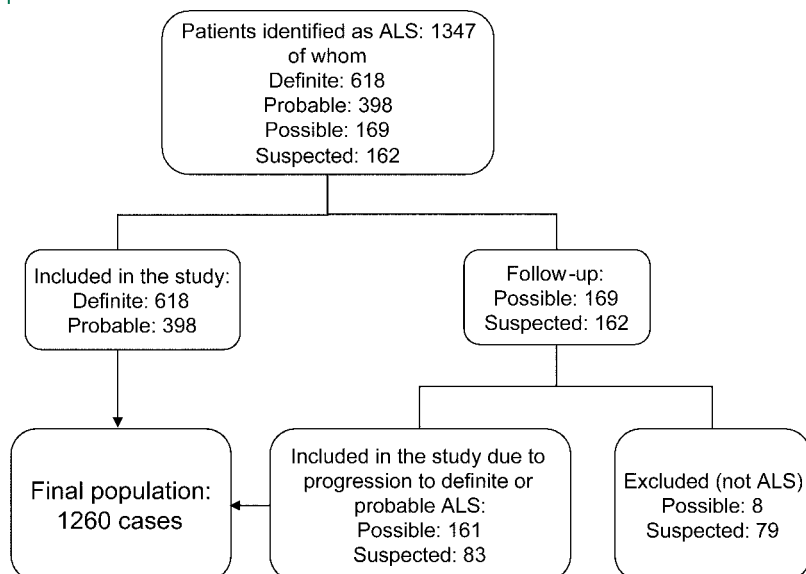
Follow-up. A clinical follow-up of each patient has been performed at regular intervals (2 to 4 months). A standard form was used for collecting clinical information at each follow-up visit, including therapeutic interventions. At each follow-up visit, EEC diagnosis has been verified and if necessary modified.

Statistical methods. The prevalence rate was estimated on December 31, 2004. Incidence rates have been age- and sex-adjusted to the 2001 Italian census population. Ninety-five percent confidence intervals (CIs) have been calculated assuming a Poisson distribution.¹⁴ The cumulative lifetime risk of ALS has been estimated using the cumulative distribution function of an exponential distribution, and expressed as a percentage. The number of unobserved cases has been estimated according to the two-source capture-recapture method¹⁵; the two sources were the neurologic departments and the PCRA/VACRA, which may be considered largely independent, since neurologists only partially cover the data of the regional registries. Comparison with other studies has been done through data on ages between 45 and 74 years. In this comparison, standardized rates were calculated using the direct method with the 1990 US population as standard, because this was the standard used to make comparisons in previous studies. Comparisons between means were made with Student *t* test; comparison between categorical variables was made with χ^2 test; temporal trend of incidence rates was assessed with χ^2 for trend. All tests were two-sided. A *p* value <0.05 was considered significant. Data were processed using SAS statistical package (Cary, NC; version 8.2).

The study was approved by the ethical committee of the coordinating center.

RESULTS Patients' clinical characteristics. During the 10-year period of observation, 1,347 Piemonte and Valle d'Aosta residents were diagnosed with ALS. In 1,260 of these cases, a diagnosis of definite or probable ALS was made at diagnosis or during the follow-up; these patients are included in the present study. A flow chart of the diagnostic process is reported in figure 1. Of the remaining 87 cases (8 possible and 79 as suspected ALS), 23 had final diagnoses of non-ALS MNDs (i.e., progressive muscular atrophy, primary lateral sclerosis, monomelic MND, adult spinal muscular atrophy, Kennedy disease) and 64 were reclassified as having other ALS-mimicking disorders (the most common being cervical myelopathy, motor neuropathy, and multifocal motor neuropathy). The complete list of final diagnoses is reported in table e-1 on the *Neurology*[®] Web site at www.neurology.org. In particular, 9 cases presented with progressive muscular atrophy (7 men, mean age at onset 42.3 years, range 19 to 53), with weakness and wasting of hand muscles and no signs of UMN involvement. They had only a mild progression of symptoms during the follow-up.

Figure 1 Piemonte and Valle d'Aosta Register for amyotrophic lateral sclerosis: Diagnostic flow chart



The reassessment of 2000–2004 cases with EEC-R allowed us to reclassify 39 out of the 74 possible ALS cases to probable laboratory-supported ALS.

The 1,260 patients meeting the eligibility criteria included 687 men and 573 women. Their mean age at onset was 64.8 years (SD 11.2; range 20–90) (men, 64.4 [SD 10.4]; women, 65.3 [SD 10.7]; $p = \text{NS}$); their mean age at diagnosis was 65.6 years (SD 11.2) (men, 65.2 [SD 10.9]; women, 66.2 [SD 11.3], $p = \text{NS}$). The age at onset was <45 years in 69 cases (5.5%) and ≥ 75 years in 263 cases (20.9%). The presentation was spinal (including respiratory onset) in 787 cases (62.5%) and bulbar in 473 (37.5%). Bulbar onset was more common among women (women, 260 [45.5%]; men, 213 [31.0%]; $p = 0.00001$).

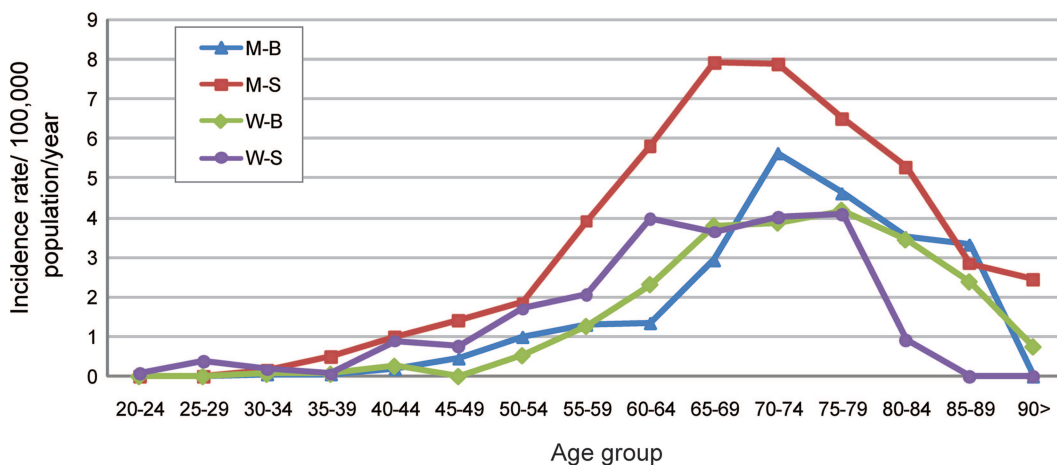
The mean time delay from onset to diagnosis was 10.4 months (SD 10.1); it showed no difference between genders (men, 10.0 [SD 11.1]; women, 10.8 [SD 8.5]), but was shorter in bulbar onset (9.8 [SD 11.4]) than in spinal onset patients (10.9 [SD 9.6]) ($p = 0.0006$).

According to EEC, at diagnosis definite ALS was diagnosed in 618 cases (49%), probable ALS in 398 (31.6%), possible ALS in 161 (12.8%), and suspected ALS in 83 (6.6%). Patients with bulbar onset were more likely to have been classified as suspected or possible ALS at diagnosis ($p = 0.002$) (table e-2). No correlation was found between diagnostic categories and age, gender, and disease duration at diagnosis.

Incidence. The mean annual crude incidence rate in the 1995–2004 period was 2.90/100,000 population (95% CI, 2.72 to 3.09). When standardized to the Italian 2001 census population, the incidence rate was 2.64/100,000 (men, 2.97/100,000; women, 2.32/100,000), with a men to women rate ratio of 1.28:1. The crude incidence rate was higher in men than in women (table e-3) ($p = 0.001$), and increase up to a peak in the 70–74 age class in men and in the 75–79 age class in women, with a subsequent decrease in older ages. The age-specific incidence rates by gender and site of onset (spinal vs bulbar) are shown in figure 2. Among women, the incidence rates of bulbar onset and spinal onset tended to overlap, and the difference between men and women was mainly due to the higher incidence of spinal onset among men.

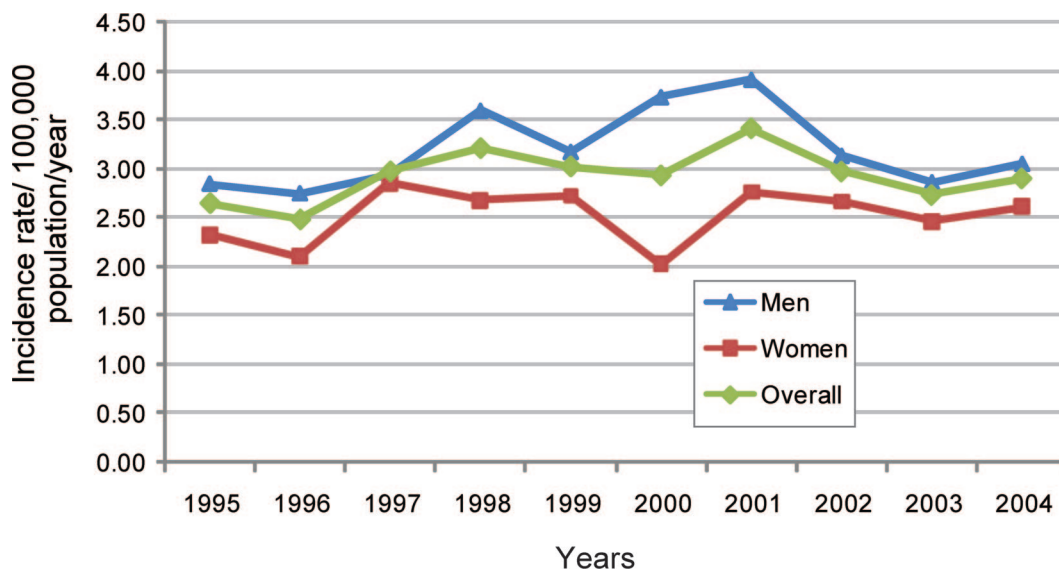
The incidence rate did not show any relevant variation during the 10-year period of the study (figure 3) and was constantly higher among men, with a men to women rate ratio ranging from 1.04 (in 1997) to 1.71 (in 2000). The cumulative lifetime

Figure 2 Incidence rates by age groups and site of onset (bulbar vs spinal) in men and women



F-B = women, bulbar; F-S = women, spinal; M-B = men, bulbar; M-S = men, spinal.

Figure 3 Incidence rates for amyotrophic lateral sclerosis in Piemonte and Valle d'Aosta, 1995 to 2004



Circles = overall cases; squares = men; triangles = women.

risk for ALS was 1/278 for men and 1/432 for women (table e-4).

Capture-recapture estimation. The results of the two-source capture-recapture method are reported in table e-5. The neurologic centers (main source) identified 1,138 cases (90.3% of all cases), and 211 were unique to that source; the Piemonte Central Regional Archive (secondary source) identified 1,048 cases (83.2% of all cases), and 121 were unique to that source. The capture-recapture model estimated that 27 patients were unobserved, thus increasing the annual observed crude incidence to 2.96/100,000 population. In no single year did the lower limit of adjusted incidence exceed the point estimate of unadjusted incidence, confirming the high level of ascertainment across the 10-year study.

Comparison of the 1995–1999 and the 2000–2004 periods. Demographics and clinical features did not change between the 1995–1999 and the 2000–2004 cohorts (table), with the exception of the mean time delay from onset to diagnosis, which significantly decreased in the last 5-year period (1995–1999, 11.0 months; 2000–2004, 9.6 months; $p = 0.0001$). The standardized incidence rate was substantially identical in the two periods (2.65 vs 2.64). A family history of ALS was found in 16 cases (2.6%) in the 1995–1999 period and in 37 (5.8%) in the 2000–2004 period. However, family history of ALS was accurately assessed only since 2000.

Prevalence. A total of 343 patients were alive at the prevalence day (December 31, 2004), corresponding to a crude prevalence rate of 7.89 (95% CI, 7.09 to 8.75)/100,000 population. The characteristics of the

prevalent cohort compared to those of the incident cohort are reported in the table. The prevalent cohort included fewer bulbar patients, had a lower age at onset, and had a slightly higher mean diagnostic delay.

DISCUSSION The incidence of ALS in Piemonte and Valle d'Aosta did not change over the 10-year period of the study. While most studies on ALS mortality have observed an increase of mortality rates,^{8–10} prospective incidence studies based on the registry methodology performed in Scotland (1989–1998) and Ireland (1995–2004) have found the absence of significant variations.^{5,6} Similarly, a previous small incidence study performed on the population of Rochester, MN, reported a steady incidence rate during a 75-year period.¹⁶ It is therefore likely that the reported increase of mortality rates is mostly related to an improvement of death certificate accuracy over time than to a real increase of ALS incidence.

Paralleling the absence of modification of the incidence of ALS, during the examined period we could not find any difference in the main demographic characteristics of patients (age at onset, gender distribution, site of onset), with the notable exception of a significant reduction of the mean diagnostic delay from 11.0 to 9.7 months. This reduction could be related to the increased awareness of ALS among the neurologists and other specialists in Piemonte after the implementation of the register.

The frequency of familial ALS in the 2000–2004 period is similar to that observed in other population registries,^{4,6} and lower than the 10% rate of familial ALS that is typically quoted for ALS.¹ In our opin-

Table Demographics and clinical features of patients diagnosed with ALS, 1995-1999 and 2000-2004 cohorts, and of the prevalent cohort

	1995-1999	2000-2004	Prevalent cohort
No. of cases	618	642	343
Mean age at onset, y (SD)	64.2 (11.2)	65.4 (11.1)	60.9 (11.9)
Mean age at diagnosis, y (SD)	65.1 (11.3)	66.1 (10.8)	61.9 (11.7)
Median age at onset, y (SD)	65.1	65.8	61.1
Median age at diagnosis, y (SD)	66.8	67.7	62.4
Men:women	329:289	358:284	193/150
Spinal:bulbar	395:223	392:250	261/82
Mean diagnostic delay, mo (SD)*	11.0 (11.5)	9.6 (7.6)	12.1 (14.3)
Incidence/100,000 (95% CI)*	2.65 (2.44-2.87)	2.64 (2.44-2.86)	—
Men, incidence/100,000 (95% CI)*	2.93 (2.67-3.26)	3.00 (2.70-3.34)	—
Women, incidence/100,000 (95% CI)*	2.39 (2.13-2.68)	2.30 (2.05-2.57)	—
Men (spinal onset), incidence/100,000 (95% CI)*	2.04 (1.80-2.31)	2.01 (1.77-2.27)	—
Men (bulbar onset), incidence/100,000 (95% CI)*	0.89 (0.73-1.09)	0.99 (0.83-1.19)	—
Women (spinal onset), incidence/100,000 (95% CI)*	1.45 (1.24-1.69)	1.29 (1.10-1.51)	—
Women (bulbar onset), incidence/100,000 (95% CI)*	0.94 (0.78-1.13)	1.01 (0.84-1.20)	—
Men to women rate ratio	1.2:1	1.3:1	1.3:1§
Men to women rate ratio, spinal onset	1.4:1	1.6:1	1.6:1
Men to women rate ratio, bulbar onset	0.9:1	1:1	1:1
Incidence/100,000, > 15 y (95% CI)*	3.09 (2.84-3.34)	3.05 (2.82-3.29)	—

*1995-1999 vs 2000-2004 cohorts, $p < 0.0001$.

*Age- and gender-adjusted to the 2001 Italian population census.

‡Age-adjusted to the 2001 Italian population census.

§Men to women ratio.

ALS = amyotrophic lateral sclerosis; CI = confidence interval.

ion, the latter figure is likely to be an overestimation of the frequency of familial ALS, since it is based on series from ALS referral centers, where patients are more likely to have a positive family history of ALS.¹

In our register, 87 cases who were initially referred as ALS (6.4% of all patients) were subsequently reclassified as having other disorders (i.e., false positive diagnoses). These figures compare to those of the Irish (7.3%)¹⁷ and Scottish registries (9.6%).¹⁸ Most cases diagnosed as possible ALS (161 out of 169) were reclassified to a higher level of diagnostic certainty during the follow-up; conversely, half of the cases who presented as suspected ALS had other MNDs or ALS mimicking syndromes. This is partly in contrast with the observation of another population-based register,⁷ in which the percentage of suspected ALS at diagnosis was higher (9.9% vs 6.6%). This discrepancy could be due to the lack of an active follow-up of most patients of the Lombardy register,⁸ which prevented the verification of the diagnosis of ALS in suspected patients over time. In our series, bulbar onset patients had a higher probability to be classified as possible or suspected ALS at the time of diagnosis, indicating that at presentation

bulbar patients have a lower diffusion of clinical signs.

The incidence of ALS in Piemonte in the 1995-2004 period is substantially similar to that reported by the Irish and Scottish registers,^{5,6} but higher than that observed in Lombardy and Puglia, Italy^{4,7} (table e-6). These differences may be mostly explained by different methods and accuracy of case ascertainment, in particular in younger and older cases.⁷ In fact, the comparison of the ALS population registers shows large differences in the percentage of early onset ALS (<45 years), ranging from 5 to 23% among men and from 5 to 12% among women, and even larger variations in late onset ALS (≥ 75 years), ranging from 11 to 21% among men and from 8 to 27% among women. These diversities cannot be completely explained by the dissimilar age structures of the examined populations and the relatively small number of subjects in the youngest and oldest age groups, and could be related to the different access of older persons (in particular women) to health facilities in the different areas,^{4,19} and to a higher frequency of misdiagnoses (either false negative or false positive) in the youngest and in the oldest patients.⁷

As in other studies, the incidence rates increased in both genders up to a peak in the eighth decade of life and declined rapidly afterwards.^{4,7} This pattern of decreasing incidence among the very elderly suggests that the pool of susceptible individuals in the general population is reduced after a certain age,⁶ differently from Alzheimer disease²⁰ and, less clearly, from Parkinson disease,²¹ in which the incidence increases exponentially with age. However, an underestimation of ALS in older age groups cannot be excluded as a cause of the apparent decline of incidence in older age classes.

Bulbar onset was identified in about one third of patients, and it was significantly more frequent among women. When looking at the age-specific incidence rates, men and women had substantially similar incidences of bulbar onset at all ages. Therefore, the higher incidence among men is almost totally due to spinal onset patients. Among women, the age-specific incidence of bulbar onset is identical to that of spinal onset for the 65–79 age groups and even higher in the oldest age groups. These findings, similar to those reported in Scotland,¹⁹ indicate that older persons have a greater risk of developing bulbar ALS. This phenomenon could be related to the involvement of different susceptibility genes in the pathogenesis of the various clinical presentations of ALS, or the different susceptibility of bulbar and spinal motor neurons at different ages.

The cumulative lifetime risk, i.e., the probability of an individual to have ALS during his or her lifespan, indicates that ALS is far more common than previously believed, since 1 out of 278 men and 1 out of 432 women in Piemonte will develop ALS during their life; our finding is similar to the risk calculated for the Irish population.²² Such a relatively high lifetime risk should be considered when evaluating small clusters of cases, such as conjugal ALS or the occurrence of two cases in the same family, which could represent a mere coincidence and not necessarily an instance of common environmental toxins or a Mendelian genetic transmission.

The crude prevalence rate of ALS in Piemonte was 7.9/100,000 population, slightly higher than the prevalence rate reported in Ireland.⁶ Prevalent patients were significantly younger than incident ones, and were less likely to have a bulbar presentation. These findings indicate that the prevalent population, which basically corresponds to the patients that are enrolled in clinical trials, is substantially different from the incident population, having more favorable prognostic factors (i.e., younger age, spinal onset). This observation questions both the possibility to extrapolate the results of clinical trials to the whole ALS

population and the use of prevalent population for DNA collection for genetic studies.^{6,23,24}

According to the two-source capture-recapture method, we estimated that only 2% of patients were unobserved, indicating that the prospective design and the involvement of multiple sources of ascertainment has given a nearly full coverage of ALS population in the Piemonte register, and confirming the findings of another ALS register.⁵

Our data, together with those of other prospective population-based registries, indicate that ALS incidence in Western countries is fairly homogeneous, with negligible differences mostly due to methodologic and demographic reasons. The stability of the incidence and of the clinical and demographic characteristics of patients with ALS in Piemonte over the last decade conforms with these observations.

APPENDIX

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Join your colleagues at the 2009 AAN Annual Meeting in Seattle for this exciting event benefiting neuroscience research. The (shoe) rubber meets the road on Tuesday, April 28, starting at 6:30 a.m. for a 5k run or mile long walk along the beautiful Seattle waterfront. Proceeds support Clinical Research Training Fellowships in neurology.

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