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ORIGINAL ARTICLE

Incidence of amyotrophic lateral sclerosis in the province of Novara, Italy, and possible role of environmental pollution

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Abstract

Objective and methods: Based on nationwide death certificates, a cluster of amyotrophic lateral sclerosis (ALS) has been reported in the area of Briga (Novara province, northern Italy), known for its severe environmental contamination. We further investigated this finding, by following up with the collection of recent incidence ALS data in 2002–2012 of Novara province, also to assess the possible long-term effects of environmental pollution in that area. *Results*: In the whole Novara province we identified 106 ALS cases, of which 35 were from the Briga area. Incidence rates of Novara province were 3.98, 5.14 and 2.97 for the total population, males and females, respectively, compared with the Briga area where they were 4.65, 4.27 and 4.98, respectively. The ratio of observed-to-expected ALS cases in the Briga area, using incidence of the rest of Novara province as a reference, was 1.17 (95% CI 0.81–1.62), with a value of 0.83 (95% CI 0.47–1.37) in males and 1.68 (95% CI 1.03–2.60) in females. *Conclusions*: Overall, our study did not confirm previous findings of an excess ALS incidence in an area characterised by severe environmental heavy metal pollution, and it suggests the need to interpret with caution clusters identified through mortality data.

KEYWORDS: *Amyotrophic lateral sclerosis*, *incidence study*, *environmental pollution*, *heavy metals*

Introduction

Amyotrophic lateral sclerosis (ALS) is an adult-onset, fatal disorder, characterised by degeneration of both upper and lower motor neurons. Clinical presentation of ALS includes muscle atrophy and weakness. Subsequently, spreading paralysis of the voluntary muscles often develops, and eventually of the respiratory muscles. Approximately half of patients with ALS die within 30 months from symptoms onset, usually from respiratory insufficiency, whereas about 10% of patients may survive for more than a decade (1–5). About 5–10% of ALS patients have a familial form (6). If no family history is identified, the disease is assumed to be sporadic.

Worldwide, ALS incidence ranges from 2 to 4/100,000 people per year with the exception of some high-risk areas around the Pacific Rim such as Guam or parts of Western New Guinea (7). In Europe, the median annual incidence rate is around 2 cases/100,000/year, while the median prevalence is over 5 cases/100,000 population (8).

The aetiology of ALS is still unknown. Genetic factors play a major role in the familial form (9), while for the aetiology of the sporadic form several environmental and life-style factors might be involved, such as heavy metals (particularly lead and mercury) and the metalloid selenium, solvents, pesticides, electric shocks and electromagnetic

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fields, smoking, severe head trauma and intense sport activity (10–12).

Generally, ALS is rare before the age of 40 years; thereafter it increases with age with a peak incidence in those aged 70–79 years; male:female ratio ranges from 1.2 to 1.5 (13). Mean age at onset ranges from 58 to 63 years for the sporadic form and 40 to 60 years for the familial form (14–20).

During recent decades, an increasing mortality or incidence of ALS has been reported in some countries, although this has not been observed elsewhere (21–33). In addition, there is evidence for an uneven distribution of the disease in several countries, suggesting a potential role of environmental factors. In Italy, a study describing the distribution of ALS mortality in the period 1980–2001 has detected 16 single clusters scattered throughout the country, i.e. municipalities with higher mortality rates for motor neuron disease, a disease almost entirely represented by ALS. One of these clusters, based on 54 ALS deaths, was detected in the province of Novara (Piedmont, northern Italy), and Briga Novarese municipality was the centroid of this area of 10 km radius (Figure 1) (34).

The Briga area is known for its heavy level of metal contamination due to metal production plants in the area, particularly for domestic tap production. Heavy metals originating from discharge water of metal production activities had great impact on soil, surface water and groundwater quality in the Briga area (35).

We here report a further investigation of these findings, through the collection of incidence ALS data in the period 2002–2012 from the Briga area, and also assess the possible involvement of environmental pollution in ALS aetiology in that area.

Methods

Study area

The study area is the province of Novara, located in Piedmont Region (northern Italy) with an extension area of 1300 km^2. During the study period, the population increased and varied from 340,000 persons in 2002 to up to 360,000 persons in 2012 with a population density of approximately 270 inhabitants/km^2. In the Novara province there are five main municipalities: Novara, the largest, with 100,000 inhabitants (inh), Trecate (20,000 inh), Galliate (16,000 inh) in the south, Borgomanero (22,000 inh) and Arona (14,000 inh) in the north, and other small towns with less than 3,000

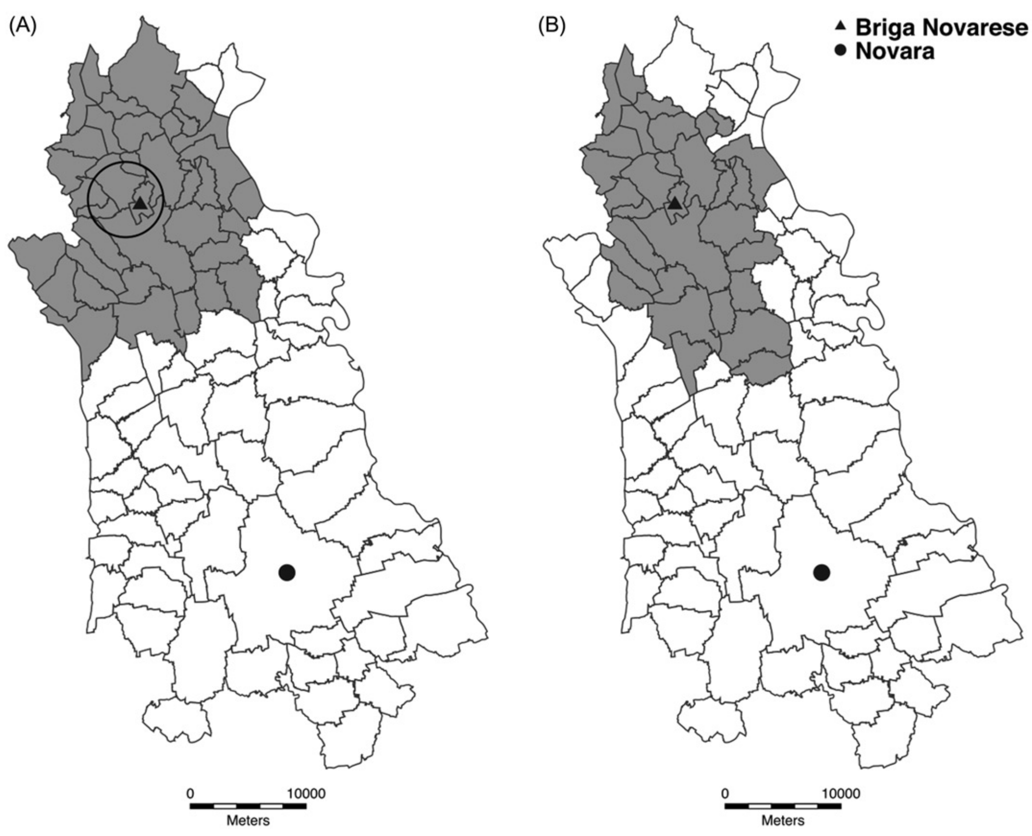

Figure 1. (A) Province of Novara and municipalities of the Briga area (gray area): Agrate Conturbia, Ameno, Armeno, Arona, Boca, Bogogno, Bolzano Novarese, Borgomanero, Briga Novarese, Cavallirio, Colazza, Comignago, Cressa, Cureggio, Dormelletto, Fontaneto d'Agogna, Gargallo, Gattico, Gozzano, Grignasco, Invorio, Maggiora, Meina, Miasino, Nebbiuno, Oleggio Castello, Orta San Giulio, Paruzzaro, Pella, Pettenasco, Pisano, Pogno, Prato Sesia, Romagnano Sesia, San Maurizio d'Opaglio, Veruno, Soriso. Area of Briga and Borgomanero (black circle) interested by the study on soil, groundwater quality of ARPA Piemonte 2010 (35) B) District of taps of the province of Novara (gray area), adapted from Rogatti et al. 2013 (63).

inhabitants. Generally, the land is flat in the south, mainly devoted to rice and maize production; other prominent activities are industrial manufacture and service industries. Furthermore, in Trecate, surrounding the suburbs of Milan province, there is significant oil refining. The north is hilly and characterised by forests and vineyards. Finally, in the southern area near Lakes Orta and Maggiore, there is intensive cultivation of flowers in greenhouses and a great number of metal production plants, particularly specialising in the manufacture of water valves and household taps (Figure 1). In this latter area, henceforth named as the 'Briga area', the number of tap production units increased from 69 in 1961 to 300 in 1991, with, respectively, 110 and 3083 workers and exports of more than 600 billion lire in 1994. Furthermore from 1991 to 1998 a 22% of workers increase was registered, although the production units did not significantly increase. Overall, around 22% of the labour force was involved in tap production units, excluding domestic production involvement of family members (36). According to the Novara Chamber of Commerce, Industry, Craft and Agriculture , in the three main municipalities of Briga area, Gozzano, Briga Novarese and Borgomanero, there were still, respectively, 56 (4.66/km^2), 20 (4.2/km^2) and 29 (0.9/km^2) production units in the metalworking sector in 2010 (35). Furthermore, until the 1950s, in this area tap production was carried out typically within artisan enterprises thanks to an ancient tradition linked to the processing of ferrous materials and assigning to females the task of the preparation of casting molds at their own home (37).

Environmental pollution

There is clear evidence of the occurrence of severe environmental pollution in the Briga area. The Regional Agency for the Protection of the Environment of Piedmont (ARPA) showed severe environmental pollution from heavy metals, especially for As, Sn, Pb and Zn, in soils of the Briga area compared to Novara province and, more generally, the overall Piedmont region, due to a common antropic origin (35). In the same area, there are 15 contaminated sites ascribed to the Regional Register resulting from uncontrolled discharges (e.g. metals and heavy metals) from the production units until the mid-1990s (38). Specific studies on the water of upper aquifers of the contaminated sites showed concentrations of Al, Mn, Ni, Pb, total Cr beyond the limits of the D.Lgs. 152/2006 (39), the Italian standards relating to the environment. Deeper groundwater intended for human consumption was under the mandatory limits of D.Lgs.31/2001, the Italian standards on drinking water quality, and D.Lgs.152/2006 always distributed to the population (39,40). Surface waters showed poor condition, always due to discharges from earlier metal industries.

Data collection and analysis

In order to collect data of all incident ALS cases in the province of Novara in the period 2002–2012, different databases have been examined. Data from the registries of hospital discharge records (using the 335.20 code of International Classification of Diseases 9 Clinical Modification - ICD-9-CM) have been collected from the Regional Expert Centre for ALS (CRESLA) at the Hospital of Novara and the Neurology Department of Veruno. Hospital discharge records are mandatory nationwide, and are a reliable source of data. Moreover, they are continuous over the study period and allowed to collect cases that had been treated in the two hospitals considered as reference centres for ALS health care services in the study area. We also consulted the Piemonte and Valle d'Aosta registry for ALS (PARALS) at the University of Turin (41) and data from death certificates of the archives of Novara, Vercelli and Omegna Local Health Districts in order to avoid loss of cases identification outside their province or region of residence.

Only 'clinically definite', 'clinically probable' and 'clinically probable-laboratory-supported' ALS cases according to the El Escorial-revised classification (rEEC) have been included, along with the date of diagnosis (42). Each diagnosed case has been validated by evaluation of medical history and any possible duplication has been correctly identified. Moreover, a clinical follow-up (2–4 months) of each patient has been performed by PARALS and Neurology units, thus rEEC diagnosis of 'clinically possible' ASL cases has been verified and, if necessary, switched in the categories considered above, or discharged as other neurological diseases (41).

Indirect standardisation was carried out considering the resident population from 2002 to 2012 and dividing it into five age classes (35–44, 45–54, 55–64, 65–74 and >75 years). We used age-specific rates in the Novara province population after excluding residents in the Briga area, to compute the expected number of cases in the Briga area, and we calculated the incidence ratio between the total number of observed cases versus the number of expected ones. Finally, for the total population, males and females, the standardised incidence ratio (SIR) was calculated.

This research was approved by the Ethics Committee of the University of Milan, and of the Ospedale Maggiore della Carità of Novara and the ICS Maugeri of Veruno. All data are presented in an anonymised form and only pooled data are reported. Finally, data analyses were performed using software Excel (Office package 2010) and Stata (Version 14.2, Stata Corp. College Station, TX 2015).

Results

In the period from 2002 to 2012 in the province of Novara we identified 106 ALS cases from hospital discharge registers, cross-checked with data from death certificates and PARALS (Figure 2). In the whole province, we observed from six new cases of ALS in 2003 to 15 new cases in 2012, with a median value of nine new cases per year and crude incidence rate of 2.5 cases/100,000 persons. Table 1 shows median age and sex distribution of selected cases according to study area. Thirty-five subjects out of 106 cases were residents in the investigated area of Briga Novarese, with 15 males and 20 females (43% vs. 57%, respectively), leading to a male:female ratio of 0.75, while 71 lived in the remainder of the province of Novara, with 43 males and 28 females (61% vs. 39%, respectively), with a male:female ratio of 1.54. According to age groups, we identified an increasing number of cases with increasing age. This trend is still evident for both sexes in the two areas, except for the age class over 75 years in the Briga area. The lowest number of cases was found in the age class 35–44 years, both in the Briga area and in the rest of the province (Table 2).

For the period 2002–2012, the number of observed cases and incidence rates of the rest of the Novara province and Briga area, number of expected cases in Briga area, incidence ratio and SIR with 95% CI are reported for the total population, males and females and age groups in Table 2. Incidence rates of Novara province were 3.98, 5.14 and 2.97 for the total population, males and females, respectively. Overall incidence rates in the Briga area were 4.65, 4.27 and 4.98 for the total population, males and females, respectively.

Comparing the number of expected to observed cases in the total Briga population, we found an excess of five cases (30 expected vs. 35 observed cases), mainly due to an excess in females (12 vs. 20 cases) rather than males (18 vs. 15 cases). SIR analysis showed a value of 1.17 (95% CI 0.81–1.62) for the total population, with SIR respectively lower in males (0.83, 95% CI 0.47–1.37) and higher in females (1.68, 95% CI 1.03–2.60). When we stratified for age groups, we found incidence ratios of 9.92 (95% CI 2.70–25.40) for males in the 45–54 years age class and of 3.64 (95% CI 1.82–6.52) for females in the 65–74 years age class, which corresponds to two or three times, respectively, the observed than the expected cases in the Briga area.

Discussion

In this study, we investigated recent ALS incidence in an Italian province where severe environmental pollution from industrial chemicals has occurred. Previous studies in the same or neighbouring Italian regions reported an incidence of 3.46 (95% CI 2.83–4.20) in Novara province and 3.41 (95% CI

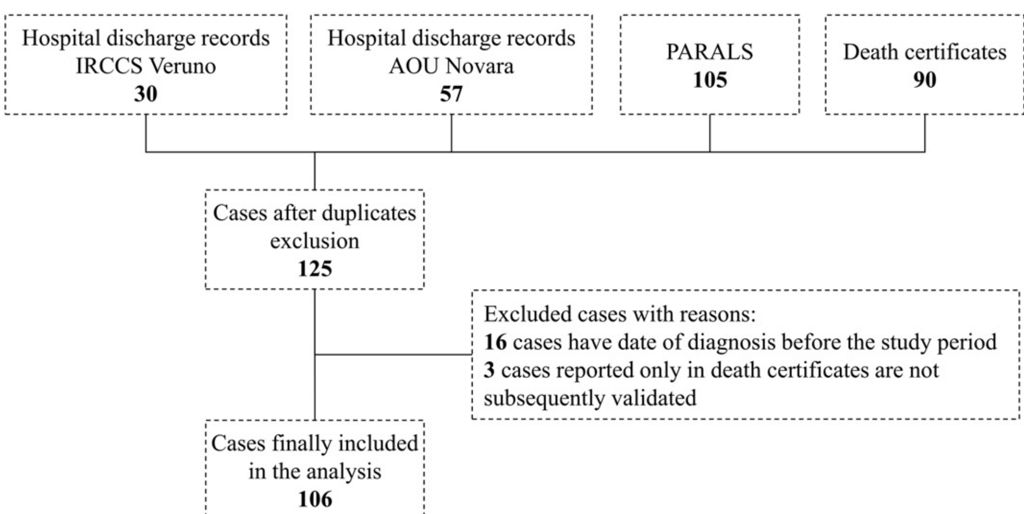

Figure 2. Flow diagram of identification of ALS cases from difference database sources.

Table 1. Median age and sex distribution of ALS cases in the study period (from 2002 to 2012) for total Novara province, Briga area and the rest of the Novara province.

	Total				Males			Females		
	n	Median Age	Range	M/F ratio	*n*	Median Age	Range	*n*	Median Age	Range
Briga area	35	67	44–87	0.75	15	63	44–87	20	68	50–87
Rest of Novara Province	71	72	35–88	1.54	43	71	35–88	28	73	45–82
Total	106	70	35–88	1.21	58	69	35–88	48	70	45–87

Table 2. Number of observed cases and incidence rates of the rest of Novara province and Briga area, number of expected cases in Briga area, incidence ratio and Standardised Incidence Ratio (SIR) with 95% confidence interval (CI) for the total population, males and females and age groups in the period 2002–2012.

	Rest of Novara province		Briga area				
Age classes	Observed cases	Incidence rates[a]	Observed cases	Incidence rates[a] (95% CI)	Expected cases	Incidence ratio (95% CI)	SIR (95% CI)
Total							
35–44	5	1.07	1	0.52 (0.00–3.01)	2.1	0.49 (0.01–2.72)	
45–54	7	1.74	6	3.67 (1.32–8.05)	2.9	2.11 (0.77–4.59)	
55–64	16	4.69	5	3.41 (1.08–8.03)	6.9	0.73 (0.24–1.70)	
65–74	19	6.31	14	10.73 (5.85–18.06)	8.2	1.70 (0.93–2.86)	
>75	24	8.78	9	7.39 (3.35–14.10)	10.7	0.84 (0.39–1.60)	
Overall	71	3.98	35	4.65 (3.24–6.47)	30.0		1.17 (0.81–1.62)
Males							
35–44	5	2.11	1	1.02 (0.00–5.84)	2.1	0.49 (0.01–2.69)	
45–54	1	0.49	4	4.90 (1.27–12.67)	0.4	9.92 (2.70–25.40)	
55–64	11	6.63	2	2.81 (0.27–10.34)	4.7	0.42 (0.05–1.53)	
65–74	12	8.84	3	5.08 (0.96–15.04)	5.2	0.58 (0.12–1.68)	
>75	14	14.62	5	12.10 (3.82–28.47)	6.0	0.83 (0.27–1.93)	
Overall	43	5.14	15	4.27 (2.38–7.06)	18.1		0.83 (0.47–1.37)
Females							
35–44	0	0	0	–	–	–	
45–54	6	3.01	2	2.45 (0.23–9 .00)	2.5	0.81 (0.10–2.94)	
55–64	5	2.85	3	3.98 (0.75–11.79)	2.2	1.40 (0.29–4.08)	
65–74	7	4.23	11	15.41 (7.65–27.67)	3.0	3.64 (1.82–6.52)	
>75	10	5.63	4	4.97 (1.29–12.86)	4.5	0.88 (0.24–2.26)	
Overall	28	2.97	20	4.98 (3.04–7.71)	11.9		1.68 (1.03–2.60)

[a]Cases per 100,000 persons.

3.22–3.60) in Piedmont Region in the period 1995–2004 (43), 3.22 (95% CI 2.66–3.90) in Liguria in 2009–2010 and male:female ratios were, respectively, 1.28 and 1.34 (44). In Emilia Romagna Region in the period 2009–2011, the incidence rate was 2.54 (95% CI 2.51–2.56), ranging from 2.01 in Parma and 3.34 in Modena, and male-to-female ratio was 1.17 (33,45). In Europe, the median incidence rate based on 21 studies encompassing the period 1990–2009 was 2.08 (interquartile range 1.47–2.43) (8). In the period 2002–2012 indirect standardised incidence was 4.65 in the Briga area and male:female ratio was 0.75, while in the rest of Novara province incidences were 3.98 and 1.54, respectively. Generally, males present higher incidence than females, ranging from 2.97 vs. 2.32 in Piedmont (41), and 3.71 vs. 2.77 in Liguria (44). Overall, the epidemiology of the disease in the entire Novara province confirmed the widely observed age-related increase, and thus we could observe a peak in the 65–74-years age class both in the Briga area and the rest of the province (41,44), despite our estimates being based on a relatively small number of cases.

Our results did not appear to confirm the presence of the previously described cluster of ALS in the study area and specifically in the area of Briga, which was long-term characterised by a severe degree of environmental pollution (34). Therefore, they seemed to not confirm the hypothesis that heavy metal pollution plays an important role in the aetiology of the disease, as suggested by some studies (46–49) but not by other observations (50).

The Briga area we investigated was characterised by severe environmental pollution from heavy metals such as As, Zn, Sn, Pb and Cu compared to the Novara province and Piedmont Region, due to widespread antropic contamination. In addition, the high As and Zn concentrations suggest elevated presence of these two elements in the bedrock. Very high Pb levels have also been detected in groundwaters in the investigated area (35), and these heavy metals have been suggested by some studies to increase ALS risk (51). In addition, studies on surface waters, groundwaters and soil in that area have shown high concentrations of other potentially neurotoxic elements such as Al, Mn, Cu, Zn, Ni, and total Cr (35,39).

The slightly higher incidence in females in the Briga area conflicts with previous findings. A possible explanation could be found in the high exposure of females to metals during processing of tap manufacture in their homes. The increasing urbanisation and economic boom since the 1950s allowed the consolidation and expansion of some companies and the creation of new businesses by a process of budding, especially small family businesses. Traditionally, females were involved in some particular aspects of tap manufacture that could be performed in their homes, leading to frequent dermal contact and inhalation of metal dust (36,37). A meta-analysis evaluating the association between ALS and occupational exposure to chemical agents indicated a stronger association in females than in males for such metals (especially chromium and lead) (52).

This study has some limitations. First, incidence estimates were generally imprecise due to small number of cases, as indicated by the wide confidence intervals of the estimates. However, the sample size was adequate to allow the detection of a strongly increased risk, should it have been as high as previously documented: a former mortality study was based on 54 deaths in the period 1980–2001, while our incidence data detected 106 newly-diagnosed cases in the period 2002–2012. Furthermore, the study design did not include collection of occupational and environmental exposure to chemicals for each subject, in order to assess specific ALS risk factors. Therefore, we are planning to conduct an *ad hoc* case-control study evaluating specific and personal exposure to environmental pollutants, including occupational exposure especially in subjects directly involved in the metal industry.

A plausible interpretation of the lack of consistency between our results and the previously described cluster of ALS in the polluted area can be due to a more reliable and comprehensive methodology in case retrieval and ascertainment compared with the previous investigation based on ALS mortality only (34). Furthermore, the mortality data could be influenced by a higher notification rate by the Department of Neurologic Rehabilitation of Veruno hospital which was one of the first reference centres for ALS diagnosis and treatment in the study area.

Strengths of our study included the use of incidence rather than mortality data, the use of reliable databases including hospital discharges records and Piemonte and Valle d'Aosta registry for ALS (PARALS) and the specific validation of included cases using medical history data. Finally, the indirect standardisation methods allowed a better ALS incidence estimation, considering the rarity of the disease, while the previous study was based on direct standardisation or only on mortality data.

In conclusion, our study does not confirm previous findings carried out in the same area, also suggesting that studies of ALS clusters based on mortality data are potentially biased for methodological weaknesses and should be considered with strong caution when addressing the hypothesis of the environmental aetiology of ALS. However, also taking into account some evidence from the epidemiological literature (2,11,12,49), the relation between environmental pollution and ALS risk is clearly worth further investigation.

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Declaration of interest

The authors report no conflict of interest.

References

1. Wijesekera LC, Leigh PN. Amyotrophic lateral sclerosis. Orphanet J Rare Dis. 2009;4:3.
2. Ingre C, Roos PM, Piehl F, Kamel F, Fang F. Risk factors for amyotrophic lateral sclerosis. Clin Epidemiol. 2015;7:181–93.
3. Talbot K. Motor neuron disease: the bare essentials. Practical Neurol. 2009;9:303–9.
4. del Aguila MA, Longstreth WT, , McGuire V, Koepsell TD, van Belle G. Prognosis in amyotrophic lateral sclerosis: a population-based study. Neurology. 2003;60:813–19.
5. Forsgren L, Almay BG, Holmgren G, Wall S. Epidemiology of motor neuron disease in northern Sweden. Acta Neurol Scand. 1983;68:20–9.
6. Byrne S, Bede P, Elamin M, Kenna K, Lynch C, McLaughlin R, et al. Proposed criteria for familial amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2011;12:157–9.
7. Ince PG, Codd GA. Return of the cycad hypothesis - does the amyotrophic lateral sclerosis/parkinsonism dementia complex (ALS/PDC) of Guam have new implications for global health? Neuropathol Appl Neurobiol. 2005;31:345–53.
8. Chio A, Logroscino G, Traynor BJ, Collins J, Simeone JC, Goldstein LA, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology. 2013;41:118–30.
9. Therrien M, Dion PA, Rouleau GA. ALS: recent developments from genetics studies. Curr Neurol Neurosci Rep. 2016;16:59.
10. Huisman MH, Seelen M, de Jong SW, Dorresteijn KR, van Doormaal PT, van der Kooi AJ, et al. Lifetime physical activity and the risk of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2013;84:976–81.
11. Bozzoni V, Pansarasa O, Diamanti L, Nosari G, Cereda C, Ceroni M. Amyotrophic lateral sclerosis and environmental factors. Funct Neurol. 2016;31:7–19.
12. Zufiria M, Gil-Bea FJ, Fernandez-Torron R, Poza JJ, Munoz-Blanco JL, Rojas-Garcia R, et al. ALS: a bucket of genes, environment, metabolism and unknown ingredients. Prog Neurobiol. 2016;142:104–29.
13. Manjaly ZR, Scott KM, Abhinav K, Wijesekera L, Ganesalingam J, Goldstein LH, et al. The sex ratio in amyotrophic lateral sclerosis: a population based study. Amyotroph Lateral Scler. 2010;11:439–42.
14. Testa D, Lovati R, Ferrarini M, Salmoiraghi F, Filippini G. Survival of 793 patients with amyotrophic lateral sclerosis diagnosed over a 28-year period. Amyotroph Lateral Scler Other Motor Neuron Disord. 2004;5:208–12.
15. Logroscino G, Traynor BJ, Hardiman O, Chio A, Mitchell D, Swingler RJ, et al. Incidence of amyotrophic lateral sclerosis in Europe. J Neurol Neurosurg Psychiatry. 2010;81:385–90.
16. Cudkowicz ME, McKenna-Yasek D, Sapp PE, Chin W, Geller B, Hayden DL, et al. Epidemiology of mutations in superoxide dismutase in amyotrophic lateral sclerosis. Ann Neurol. 1997;41:210–21.
17. Juneja T, Pericak-Vance MA, Laing NG, Dave S, Siddique T. Prognosis in familial amyotrophic lateral sclerosis: progression and survival in patients with glu100gly and ala4val

mutations in Cu, Zn superoxide dismutase. Neurology. 1997;48:55–7.
18. Huisman MH, de Jong SW, van Doormaal PT, Weinreich SS, Schelhaas HJ, van der Kooi AJ, et al. Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. J Neurol Neurosurg Psychiatry. 2011;82:1165–70.
19. Uenal H, Rosenbohm A, Kufeldt J, Weydt P, Goder K, Ludolph A, et al. Incidence and geographical variation of amyotrophic lateral sclerosis (ALS) in Southern Germany–completeness of the ALS registry Swabia. PLoS One. 2014;9:e93932.
20. Piemonte, Valle d'Aosta Register for Amyotrophic Lateral S. Incidence of ALS in Italy: evidence for a uniform frequency in Western countries. Neurology. 2001;56:239–44.
21. Neilson S, Robinson I, Alperovitch A. Rising amyotrophic lateral sclerosis mortality in France 1968-1990: increased life expectancy and inter-disease competition as an explanation. J Neurol. 1994;241:448–55.
22. Neilson S, Robinson I, Nymoen EH. Longitudinal analysis of amyotrophic lateral sclerosis mortality in Norway, 1966-1989: evidence for a susceptible subpopulation. J Neurol Sci. 1994;122:148–54.
23. Neilson S, Gunnarsson LG, Robinson I. Rising mortality from motor neurone disease in Sweden 1961-1990: the relative role of increased population life expectancy and environmental factors. Acta Neurol Scand. 1994;90:150–9.
24. Veiga-Cabo J, Almazan-Isla J, Sendra-Gutierrez JM, de Pedro-Cuesta J. Differential features of motor neuron disease mortality in Spain. Int J Epidemiol. 1997;26:1024–32.
25. Seljeseth YM, Vollset SE, Tysnes OB. Increasing mortality from amyotrophic lateral sclerosis in Norway? Neurology. 2000;55:1262–6.
26. Maasilta P, Jokelainen M, Loytonen M, Sabel CE, Gatrell AC. Mortality from amyotrophic lateral sclerosis in Finland, 1986-1995. Acta Neurol Scand. 2001;104:232–5.
27. Govoni V, Granieri E, Fallica E, Casetta I. Amyotrophic lateral sclerosis, rural environment and agricultural work in the Local Health District of Ferrara, Italy, in the years 1964-1998. J Neurol. 2005;252:1322–7.
28. Sejvar JJ, Holman RC, Bresee JS, Kochanek KD, Schonberger LB. Amyotrophic lateral sclerosis mortality in the United States, 1979-2001. Neuroepidemiology. 2005;25:144–52.
29. Okamoto K, Kobashi G, Washio M, Sasaki S, Yokoyama T, Miyake Y, et al. Descriptive epidemiology of amyotrophic lateral sclerosis in Japan, 1995-2001. J Epidemiol. 2005;15:20–3.
30. Murphy M, Quinn S, Young J, Parkin P, Taylor B. Increasing incidence of ALS in Canterbury, New Zealand: a 22-year study. Neurology. 2008;71:1889–95.
31. Cima V, Logroscino G, D'Ascenzo C, Palmieri A, Volpe M, Briani C, et al. Epidemiology of ALS in Padova district, Italy, from 1992 to 2005. Eur J Neurol. 2009;16:920–4.
32. Fang F, Valdimarsdottir U, Bellocco R, Ronnevi LO, Sparen P, Fall K, et al. Amyotrophic lateral sclerosis in Sweden, 1991-2005. Arch Neurol. 2009;66:515–19.
33. Mandrioli J, Biguzzi S, Guidi C, Venturini E, Sette E, Terlizzi E, et al. Epidemiology of amyotrophic lateral sclerosis in Emilia Romagna Region (Italy): a population based study. Amyotroph Lateral Scler Frontotemp Degener. 2014;15:262–8.
34. Uccelli R, Binazzi A, Altavista P, Belli S, Comba P, Mastrantonio M, et al. Geographic distribution of amyotrophic lateral sclerosis through motor neuron disease mortality data. Eur J Epidemiol. 2007;22:781–90.
35. ARPA (Regional Agency for the Protection of the Environment). Approfondimento delle attività di analisi e di studio sulla contaminazione diffusa del suolo e delle acque sotterranee di alcune aree della Provincia di Novara; 2010.
36. Rabellotti R, Il distretto della Rubinetteria del Piemonte Nord Orientale. In: Baici E, ed. L'economia novarese Analisi delle caratteristiche e prospettive del sistema economico provinciale. Novara: Interlinea; 2003.
37. Rogatti C. Il distretto dei rubinetti: la strategia delle imprese del settore della rubinetteria. Il caso CARLO NOBILI S.p.A. Novara: Università degli Studi del Piemonte Orientale 'Amedeo Avogadro'; 2013.
38. DGR 22-12378 26 aprile 2004. Istituzione e modalita' di attivazione dell'anagrafe regionale dei siti da bonificare a seguito dei criteri generali definiti dalla L.R. 42/2000. Suppl BU n 21 del 27 maggio 2004; 2004.
39. DLgs 152/2006. Norme in materia ambientale. GU n 88 del 14 aprile 2006; 2006.
40. DLgs 31/2001. Attuazione della direttiva 98/83/CE relativa alla qualità delle acque destinate al consumo umano. GU n52 del 3-3-2001-Suppl Ordinario n 41; 2001.
41. Chio A, Mora G, Calvo A, Mazzini L, Bottacchi E, Mutani R. Epidemiology of ALS in Italy: a 10-year prospective population-based study. Neurology. 2009;72:725–31.
42. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1:293–9.
43. Migliaretti G, Berchialla P, Dalmasso P, Cavallo F, Chio A. Amyotrophic lateral sclerosis in Piedmont (Italy): a Bayesian spatial analysis of the incident cases. Amyotroph Lateral Scler Frontotemp Degener. 2013;14:58–65.
44. Bandettini di Poggio M, Sormani MP, Truffelli R, Mandich P, Origone P, Verdiani S, et al. Clinical epidemiology of ALS in Liguria, Italy. Amyotroph Lateral Scler Frontotemp Degener. 2013;14:52–7.
45. Bonvicini F, Vinceti M, Marcello N, Rodolfi R, Rinaldi M. The epidemiology of amyotrophic lateral sclerosis in Reggio Emilia, Italy. Amyotroph Lateral Scler. 2008; 9:350–3.
46. Bocca B, Forte G, Oggiano R, Clemente S, Asara Y, Peruzzu A, et al. Level of neurotoxic metals in amyotrophic lateral sclerosis: a population-based case-control study. J Neurol Sci. 2015;359:11–17.
47. Malek AM, Barchowsky A, Bowser R, Heiman-Patterson T, Lacomis D, Rana S, et al. Exposure to hazardous air pollutants and the risk of amyotrophic lateral sclerosis. Environ Pollut. 2015;197:181–6.
48. Su FC, Goutman SA, Chernyak S, Mukherjee B, Callaghan BC, Batterman S, et al. Association of environmental toxins with amyotrophic lateral sclerosis. JAMA Neurol. 2016;73:803–11.
49. Wang MD, Little J, Gomes J, Cashman NR, Krewski D. Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. Neurotoxicology. 2016. [Epub ahead of print]. doi: 10.1016/j.neuro.2016.06.015.
50. Rooney J, Vajda A, Heverin M, Crampsie A, Tobin K, McLaughlin R, et al. No association between soil constituents and amyotrophic lateral sclerosis relative risk in Ireland. Environ Res. 2016;147:102–7.
51. Vinceti M, Bottecchi I, Fan A, Finkelstein Y, Mandrioli J. Are environmental exposures to selenium, heavy metals, and pesticides risk factors for amyotrophic lateral sclerosis? Rev Environ Health. 2012;27:19–41.
52. Capozzella A, Sacco C, Chighine A, Loreti B, Scala B, Casale T, et al. Work related etiology of amyotrophic lateral sclerosis (ALS): a meta-analysis. Ann Ig. 2014;26: 456–72.