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This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/122097 since 2017-05-21T22:17:14Z

Published version:

DOI:10.1093/aje/kwr229

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24 April 2024

AMJEPID	kwr229	MG
Journal Name	Art. No.	PE Code

NOT FOR PUBLIC RELEASE

American Journal of Epidemiology
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DOI: 10.1093/aje/kwr229

Original Contribution

Coffee and Amyotrophic Lateral Sclerosis: A Possible Preventive Role

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Initially submitted November 19, 2010; accepted for publication June 3, 2011.

The relation between coffee intake and risk of amyotrophic lateral sclerosis (ALS) was investigated in 377 newly diagnosed ALS patients from 4 Italian population-based registries in the European ALS Consortium (EURALS Group) (2007–2010). For each patient, 2 age- and sex-matched hospital controls were selected, one from a neurology department and one from a nonneurologic department. Two additional healthy control groups were identified from local general practitioners' (GPs') lists ($n = 99$) and residents of the same area as a cancer cohort ($n = 7{,}057$). Coffee intake was defined in terms of status (ever consuming coffee daily for $\geq$6 months vs. never), duration, and history (never, former, or current). Ever coffee drinkers comprised 74.7% of ALS patients, 80.4% of neurologic controls, 85.6% of nonneurologic controls ($P = 0.0004$), 88.9% of GP controls ($P = 0.0038$), and 86.0% of cancer cohort controls ($P < 0.0001$). Current coffee drinkers comprised 60.2% of ALS patients, 70.2% of neurologic controls ($P = 0.0294$), 76.4% of nonneurologic controls ($P < 0.0001$), and 82.3% of GP controls ($P = 0.0002$); duration of intake was $\geq$30 years for 62.3%, 67.7%, 74.7%, and 72.6%. ALS patients had lower lifetime coffee exposure: Odds ratios were 0.7 (95% confidence interval (CI): 0.5, 1.1), 0.6 (95% CI: 0.4, 0.8), and 0.4 (95% CI: 0.2, 0.9) in comparison with neurologic, nonneurologic, and GP controls, respectively. In current (vs. never) coffee drinkers, odds ratios were 0.7 (95% CI: 0.5, 1.0), 0.5 (95% CI: 0.3, 0.7), and 0.4 (95% CI: 0.2, 0.8), respectively. These findings provide epidemiologic evidence of an inverse correlation between coffee intake and ALS risk.

amyotrophic lateral sclerosis; coffee; motor neuron disease

Abbreviations: ALS, amyotrophic lateral sclerosis; EURALS Group, European ALS Consortium; GP, general practitioner.

Amyotrophic lateral sclerosis (ALS) is a rare, severe neurologic disorder causing motor neuron degeneration and death within 3–5 years of symptom onset in approximately 80% of patients (1). Although results of several epidemiologic studies have been reported, no environmental factors or specific occupations have been consistently found to be associated with motor neuron loss, with the exception of exposure to pesticides (2–4). Small sample sizes and differences in study design may explain the contrasting and mostly negative findings. Therefore, we designed a case-control study of newly diagnosed ALS patients from 4 Italian population-based registries participating in the European ALS Consortium (EURALS Group) (5). The aim was to assess the role of traumatic events and other environmental agents as risk factors for ALS. While assessing the independent role of trauma and adjusting for possible confounders, including age, sex, physical activity, alcohol drinking, smoking, and coffee intake, we detected an inverse association between coffee consumption and risk of ALS.

MATERIALS AND METHODS

The study population included patients with newly diagnosed ALS enrolled in population-based registries in 4 administrative regions of Italy (Lombardia, Piemonte and Valle D'Aosta, Puglia, and Liguria; total population = 19,997,078 in the 2009 Italian census) from September 2007 through

April 2010. Patients were aged 18 years or older and had to fit one of the categories of the El Escorial diagnostic classification (''definite,'' ''probable,'' or ''possible'' ALS) (6). Every patient had to be a resident of the study area. For each patient, 2 age- ($\pm$5 years) and sex-matched hospital controls were selected. The first control was chosen from a neurology department and the second from a nonneurologic department. Patients with neurodegenerative disorders or clinical conditions related to trauma or orthopedic illnesses were excluded. We also tried to match cases and controls by source of interview (patient or surrogate). Informed surrogates were chosen for patients who were unable to answer or unaware of their clinical condition and for their matched controls.

After giving informed consent, each case and control (or surrogate) was interviewed by a trained investigator, and ad hoc semistructured forms were used to collect the following data: date of enrollment, sex, date of birth, marital status, education, occupation, physical exercise, family history of ALS and other neurodegenerative disorders, El Escorial diagnostic category, site of onset of symptoms (bulbar, limbs, respiratory, or generalized), disease duration at diagnosis, and functional impairment, measured with the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (7). A detailed history of traumatic events was collected as per study protocol. Tobacco, coffee, and alcohol were chosen as confounders. Overall coffee intake was assessed as daily consumption for at least 6 months during the participant's entire lifetime (ever vs. never), duration of exposure (in years), and history of consumption (never, former, or current). Tobacco and alcohol intake were assessed similarly and dichotomized as ever versus never.

The study was considered complete after enrollment of at least 410 cases and 819 controls under the assumption that 1% of controls would report at least 1 traumatic event requiring hospitalization as compared with 3.9% of ALS patients (odds ratio = 3.9), with a 5% significance level and 80% power. The study also had sufficient statistical power to detect a 5-fold increase in ALS risk due to trauma, through recruitment of at least 244 ALS cases and 488 matched controls.

Because the 2 control populations were not representative samples of the general population, 2 additional groups were identified for comparison. The first group (defined as the ''GP control group'') comprised persons recruited from general practitioners' (GPs') lists and chosen as population controls in a parallel case-control study, which is currently exploring the association between ALS, physical activity, trauma, and sports. The second group (defined as the ''cancer control group'') included healthy Italians residing in the same geographic area as a cohort of patients with cancer of the colon or rectum (8).

The recorded information was transferred from the forms into a World Wide Web database and centralized for analysis. We conducted univariate and multivariate analyses using conventional parametric tests, as appropriate. Data are presented as percentages and as odds ratios with 95% confidence intervals. Multivariate analysis was conducted using 3 different logistic regression models to assess the effects of the 3 separate aspects of coffee consumption: 1) status (daily consumption for $\geq$6 months; ever vs. never); 2) duration of coffee consumption (0, 0.5–30, 31–50, or >50 years); and 3) history (never, former, or current consumption). We conducted separate analyses for each control group: univariate analysis (comparing ALS cases with neurologic controls, nonneurologic controls, GP controls, and cancer controls) and multivariate analysis (comparing ALS cases with neurologic controls, nonneurologic controls, and GP controls) using logistic regression models. In each model, data were adjusted for age, sex, education, physical activity, smoking, alcohol intake, and interviewee (patient/control or surrogate).

Data were analyzed using the SAS software package for personal computers, version 9.1 (SAS Institute, Inc., Cary, North Carolina). The study was approved by the institutional review board of each center.

RESULTS

A total of 458 ALS patients and 820 controls (413 neurologic, 407 nonneurologic) were recruited. Eighty-one cases and 66 controls were later excluded, for the following reasons: 1) empty questionnaires (52 cases, 28 controls); 2) duplicate input (14 cases, 28 controls); 3) suspected ALS as an El Escorial diagnostic category (8 cases, 8 controls); 4) residency outside of the study area (3 cases, 2 controls); and 5) unavailable matched controls (4 cases).

Table 1 shows the main characteristics of the study sample. The ALS patients included 146 women and 231 men aged 27–89 years. The age range of the controls was 29–94 years for neurologic controls and 26–90 years for nonneurologic controls. The median age of the cases was 67 years, that of neurologic controls was 68 years, and that of nonneurologic controls was 67 years. The median numbers of years of education were 8 (range, 0–28), 8 (range, 0–26), and 8 (range, 0–25), respectively. The GP control group comprised 99 people aged 32–85 years (median, 64 years) with 3–22 years of education (median, 10). Subjects in the cancer control group were aged 19–79 years (median, 57 years).

The proportion of smokers was significantly lower in the ALS group than in neurologic controls, nonneurologic controls ($P = 0.0492$), the GP control group, and the cancer control group ($P = 0.0003$) (Table 1). Physical exercise was also less frequent among ALS cases. Alcohol consumption levels were similar for patients with ALS and neurologic controls but lower for ALS cases than for nonneurologic controls ($P = 0.0056$). An informed surrogate was interviewed on behalf of one-quarter of ALS patients but fewer neurologic controls ($P = 0.0217$) and nonneurologic controls ($P < 0.0100$). Proxies were almost exclusively spouses and offspring.

There were significantly fewer coffee drinkers among ALS patients than among nonneurologic controls ($P = 0.0004$), GP controls ($P = 0.0038$), or cancer controls ($P < 0.0001$) (Table 2). The proportion of current coffee drinkers was 60.2% among ALS cases but somewhat higher among neurologic controls ($P = 0.0294$), nonneurologic controls ($P < 0.0001$), and GP controls ($P = 0.0002$) (Table 2). Duration of coffee intake was 30 years or longer in 62.3% of ALS cases, 67.7% of neurologic controls, 74.7% of nonneurologic controls, and 72.6% of GP controls. The differences between ALS cases and nonneurologic and GP controls were significant (Table 2).

Table 1. Characteristics of a Sample of Newly Diagnosed ALS Patients and Age- and Sex-Matched Controls, Italy, 2007–2010

	ALS Patients (n = 377)		Neurologic Controls (n = 377)		Nonneurologic Controls (n = 377)		General Practitioner Controls (n = 99)		Cancer Controls (n = 7,057)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Female sex	146	38.7	146	38.7	146	38.7	36	36.4	3,109	44.1
Age, years										
<65	158	41.9	174	46.2	167	44.3	53	53.5	NA[a]	NA
65–74	149	39.5	125	33.2	137	36.3	29	29.3	NA	NA
>74	70	18.6	78	20.7	73	19.4	17	17.2	NA	NA
Physical activity (ever)	233	61.8	241	63.9	271**	71.9	79***	79.8	NA	NA
Education, years										
<5	20	5.3	31	8.2	22	5.8	1	1.1	2,624[b]	37.2
5–7	127	33.7	124	32.9	134	35.5	19	20.4		
8–12	124	32.9	118	31.3	103	27.3	32	34.4	2,140	30.3
13–17	81	21.5	77	20.4	87	23.1	27	29.0	2,293	32.5
≥18	25	6.6	27	7.2	31	8.2	14	15.1		
Smoking (ever)	174	46.2	186	49.3	201*	53.3	53	53.5	3,929***	55.7
Alcohol drinking (ever)	166	44.0	172	45.6	204**	54.1	55*	55.5	NA	NA
Interviewee										
Patient	282	74.8	308*	81.7	311*	82.5	99***	100.0	NA	NA
Surrogate	95	25.2	69	18.3	66	17.5	0	0.0	NA	NA

Abbreviations: ALS, amyotrophic lateral sclerosis; NA, not available.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (compared with ALS patients).

[a] Among cancer cohort controls, 2,010 (28.5%) were under age 50 years, 2,122 (30.1%) were aged 50–59 years, 2,191 (31.1%) were aged 60–69 years, and 734 (10.4%) were aged 70 years or more.

[b] For cancer controls, years of education were categorized as <8, 8–12, and ≥13.

Table 2. Coffee Consumption Among Newly Diagnosed ALS Patients and Age- and Sex-Matched Controls, Italy, 2007–2010

Coffee Consumption Variable	ALS Patients* (n = 324)		Neurologic Controls* (n = 362)		Nonneurologic Controls* (n = 368)		General Practitioner Controls (n = 99)		Cancer Controls (n = 7,057)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Status[a]										
Ever	242	74.7	291	80.4	315***	85.6	88**	88.9	6,068***	86.0
Never	82	25.3	71	19.6	53	14.4	11	11.1	989	14.0
Duration, years										
0	82	25.5	71	19.6	53	14.4	11	11.6	NA	NA
0.5–30	39	12.1	46	12.7	40	10.9	15*	15.8	NA	NA
31–50	124	38.5	151	41.7	160**	43.5	52***	54.7	NA	NA
>50	77	23.9	94	26.0	115***	31.2	17	17.9	NA	NA
Not specified	2						4			
History										
Never	82	25.3	71	19.6	53	14.4	11	11.5	NA	NA
Former	47	14.5	37	10.2	34	9.2	6	6.3	NA	NA
Current	195	60.2	254*	70.2	281***	76.4	79***	82.3	NA	NA
Not specified							3			

Abbreviations: ALS, amyotrophic lateral sclerosis; NA, not available.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (compared with ALS patients).

[a] Daily consumption for at least 6 months during the participant's entire lifetime. Information on coffee consumption status was missing for 53 ALS patients, 15 neurologic controls, and 9 nonneurologic controls.

The odds for any coffee exposure were 20%–60% lower among cases than among controls, a significant difference (Table 3). An inverse correlation in the duration of coffee intake was also found between ALS patients and each control group, but no detectable trends. Current coffee drinkers were significantly fewer among ALS cases than among neurologic, nonneurologic, and GP controls. Former coffee drinkers did not differ from nondrinkers (Table 3). However, because 28 ALS patients (59.6%) stopped drinking coffee after onset of the disease, we repeated our analyses after excluding cases and controls who stopped consuming coffee after disease onset. In these cases, the odds for exposure among ALS patients decreased to 0.8 in comparison with neurologic controls, 0.7 for nonneurologic controls, and 0.5 for GP controls, approaching those of current drinkers (see Web Table 1, which appears on the *Journal*'s Web site (http://aje.oxfordjournals.org/)). The mean age at onset of ALS symptoms among current coffee drinkers was 63.4 years (standard deviation, 11.3), as compared with 62.6 years (standard deviation, 13.0) among nondrinkers, a nonsignificant difference.

The proportion of proxy responders was higher for ALS patients than for the control groups and may have introduced the potential for differential misclassification, with underestimates of coffee intake for some cases. Therefore, we repeated the multivariate analyses after excluding proxy respondents. The findings were virtually unchanged for overall coffee intake and history of consumption, but a trend was apparent for duration of exposure when comparing ALS patients with hospital controls (see Web Table 2).

The independent contributions of tobacco and alcohol (the most important confounders of coffee intake) and of all of the other variables included in the logistic regression models are depicted in Web Table 3. The direction of the effect of coffee exposure among ALS patients was confirmed when current coffee drinkers and nondrinkers were compared across different demographic and clinical variables (see Web Table 4).

DISCUSSION

In this case-control study, we found that coffee intake was less frequent and prolonged among patients with ALS than in different groups of patients with other clinical conditions (not associated with ALS or coffee exposure) or healthy persons. The robustness of the association was confirmed by the consistency of the findings and, to some extent, by the duration of exposure.

The data cannot be explained by the use of hospital controls (who might have reported higher-than-expected exposure to caffeine) because the proportions of coffee drinkers were similar among hospital controls and healthy controls. In addition, differences reflecting sociocultural habits in cases and controls are unlikely, because coffee consumption is fairly uniform in Italy. The possibility of reverse causation can also be excluded because, as indicated in Table 2, duration of coffee consumption was 30 years or longer in a lower proportion of ALS cases than in the control groups. This is normally a long period in a person's life, almost inevitably preceding the biologic onset of the disease. The inverse association between coffee intake and ALS could even be explained by smoking or alcohol consumption.

The absence of a true gradient is notable, as only current coffee drinkers seemed to have a lower risk of ALS, while the risk in former drinkers overlapped that of the general population. However, this risk decreased when we excluded

Table 3. Odds Ratios for ALS According to Category of Coffee Consumption in Multivariate Analysis, Italy, 2007–2010[a]

Coffee Consumption Model	ALS Patients vs. Neurologic Controls		ALS Patients vs. Nonneurologic Controls		ALS Patients vs. General Practitioner Controls	
	OR	95% CI	OR	95% CI	OR	95% CI
Model 1: status[b]						
Never	1		1		1	
Ever	0.7	0.5, 1.1	0.6	0.4, 0.8	0.4	0.2, 0.9
Model 2: duration, years						
0	1		1		1	
0.5–30	0.7	0.4, 1.3	0.7	0.4, 1.4	0.4	0.1, 1.0
31–50	0.7	0.5, 1.1	0.6	0.4, 0.9	0.4	0.2, 0.7
>50	0.8	0.5, 1.3	0.5	0.3, 0.8	0.8	0.3, 2.0
Model 3: history						
Never	1		1		1	
Former	1.1	0.7, 2.0	1.0	0.6, 1.7	1.2	0.4, 3.5
Current	0.7	0.5, 1.0	0.5	0.3, 0.7	0.4	0.2, 0.8

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; OR, odds ratio.
[a] Odds ratios were adjusted for age, sex, exercise, smoking, alcohol drinking, education, and interviewee.
[b] Daily consumption for at least 6 months during the participant's entire lifetime.

cases and controls who stopped drinking coffee after onset of the disease and approached the level in current drinkers (see Web Table 1).

To our knowledge, there are no published reports on the association between consumption of caffeinated beverages or intake of prescription medications and ALS risk. The only article on diet in ALS that mentioned coffee intake focused on decaffeinated coffee, which was associated with a higher risk of ALS (9). However, in that same study, Ascherio et al. (9) found that high consumption of tea, which also contains caffeine, was associated with a lower risk of ALS.

Epidemiologic studies have shown a positive correlation between dietary caffeine intake and reduced risk of Parkinson's disease, another neurodegenerative disease with links to ALS (10–12). In keeping with these observations, the neurotoxic effect exerted by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on dopaminergic neurons was reduced by caffeine and its metabolites (13, 14). Pooled estimates have also shown that coffee consumption is inversely associated with the risk of Alzheimer's disease (15). In a study of aged mice with Alzheimer's disease, caffeine reversed cognitive impairment and lowered brain amyloid-β levels (16). Caffeine has antioxidant properties (17, 18), which may counteract the oxidative stress associated with aging and risk of developing neurodegenerative diseases.

Caffeine has multiple targets in the brain—for example, adenosine, ryanodine, and γ-aminobutyric acid a receptors, and cyclic nucleotide phosphodiesterase isoenzymes (19). Its action on adenosine A2a receptors may explain the psychomotor stimulant effect, mediated by dopaminergic mechanisms. In an animal model of ALS, coffee was found to increase antioxidant enzyme capacity in the brains of male G39A mice, improving motor performance (20).

High calcium ion concentrations are harmful to motor neurons in persons with ALS (21), and caffeine can improve the sensitivity of ryanodine channels to calcium ions. Ryanodine binding sites are also involved in intracellular calcium ion signaling in the Golgi complex in neurons (22). This could be relevant, because derangement of the Golgi complex is one probable cause of some forms of progressive neuronal degeneration, such as Alzheimer's disease and ALS. A caffeine derivative known as LM11A-24 seems to protect degenerating motor neurons (23). In electrophysiologic studies on healthy human muscle, caffeine had positive effects on muscle and lower and upper motor neuron excitability (24).

This study has some strengths and several limitations. The major strength is the representativeness and size of the ALS sample, which included a large cohort of patients with newly diagnosed disease residing in the areas where the population-based registries were located. A second strength is the consistency of our findings across different controls, including population-based controls who were fairly representative of the Italian general population. A third strength is the unexpected observation, which reduced the probability of interview or interviewer bias. A fourth strength is the biologic mechanisms in support of caffeine's action and the fairly robust epidemiologic evidence of a similar association in patients with Parkinson's disease and Alzheimer's disease, two neurodegenerative disorders sharing some pathologic features with ALS. A fifth strength is the confirmation of our results even among strata of several variables that could act as potential confounders.

The main limitation is the nonstandardized collection of data on coffee consumption, which was used here as a confounding variable. Although we defined coffee drinkers as those who had consumed coffee daily for at least 6 months in their lifetime, the crude classification of coffee intake (ever vs. never) was weak. A second limitation is the use of controls from different sources, which may have affected the reported rates, and the different definitions of exposure. This may explain the higher proportion of smokers among our controls, which seems to contrast with the results of other studies (25). This may also be true for the cancer cohort controls, in whom intake was calculated as number of cups per day. A third limitation is the higher proportion of proxy responders among ALS patients than in all of the control groups. However, information bias can be excluded, because the inverse association remained when the analyses were limited to index subjects' interviews. A fourth limitation is that hospital controls might have a number of clinical conditions that benefit from caffeine intake. Although this possibility cannot be entirely excluded, it is unlikely considering the range of diseases leading to hospitalization. In addition, several neurologic controls had had strokes, and several nonneurologic controls had cardiovascular disorders, which have been associated with coffee consumption. A fifth limitation is the unknown numbers of cases and controls using decaffeinated coffee. However, no important effect on our estimates is likely, because few people in Italy drink decaffeinated coffee (4% in the cancer control group) (8). A sixth limitation is that this is the first observation of an association between coffee intake and ALS and, as such, it needs confirmation. In addition, only caffeine was discussed as a possible neuroprotective agent. Other components of coffee need proper assessment for a full evaluation of the biologic plausibility of the purported association between caffeine intake and risk of ALS.

Further studies are now being planned to investigate the possible protective association of caffeine and/or other coffee ingredients with motor neuron diseases using an ad hoc design and a predefined model for data collection.

ACKNOWLEDGMENTS

Author affiliations: Laboratory of Neurological Disorders, ''Mario Negri'' Institute, Milano, Italy (Ettore Beghi, Elisabetta Pupillo, Paolo Messina, Giorgia Giussani); Centro Regionale Esperto per la SLA, Department of Neuroscience, Faculty of Medicine, University of Torino, and San Giovanni Battista Hospital, Torino, Italy (Adriano Chiò, Cristina Moglia); Clinic of Nervous System Diseases, Department of Medical and Neurological Sciences, Faculty of Medicine, University of Foggia, Foggia, Italy (Stefano Zoccolella); Fondazione Serena, Centro Clinico NEMO, Hospital Ca' Granda, Milano, Italy (Massimo Corbo); and Department of Neurology and Psychiatry, Faculty of Medicine, University of Bari, Bari, Italy (Giancarlo Logroscino).

The authors received financial support from the Istituto Superiore di Sanità (grant 526D/8) for collection of data on

the cases and hospital controls and from the ALS Association (grant 1524) for collection of data on the general practitioner controls.

The European ALS Consortium (EURALS Group)—*Coordinator*: Ettore Beghi (Milano, Italy); *Steering Committee*: Ammar Al-Chalabi (London, United Kingdom); Adriano Chiò (Torino, Italy); Orla Hardiman (Dublin, Ireland); Giancarlo Logroscino (Bari, Italy); Albert Ludolph (Ulm, Germany); Douglas Mitchell (Preston, United Kingdom); Pierre-Marie Preux (Limoges, France); Robert Swingler (Dundee, United Kingdom); Bryan J. Traynor (Bethesda, Maryland, United States); *Members*: Elena Alvisi (Pavia, Italy); Monica Bandettini di Poggio (Genova, Italy); Massimiliano Bissolati (Milano, Italy); Paolo Buzzi (Mantova, Italy); Claudia Caponnetto (Genova, Italy); Rosa Capozzo (Bari, Italy); Alberto Cat Berro (Torino, Italy); Cristina Cereda (Pavia, Italy); Mauro Ceroni (Pavia, Italy), Antonietta Citterio (Pavia, Italy); Irene Colombo (Milano, Italy); Massimo Corbo (Milano, Italy); Maria Sofia Cotelli (Brescia, Italy); Luisa De Lodovici (Varese, Italy); Stefania Cammarosano (Torino, Italy); Carlo Ferrarese (Monza, Italy); Vincenza Fetoni (Melegnano, Italy); Massimiliano Filosto (Brescia, Italy); Fabio Formaglio (Milano, Italy); Sara Giacone (Torino, Italy); Maria Cristina Guaita (Legnano, Italy); Antonio Ilardi (Torino, Italy); Lorenzo Lorusso (Chiari, Italy); Christian Lunetta (Milano, Italy); Eleonora Maestri (Milano, Italy); Anna Micheli (Brescia, Italy); Andrea Millul (Milano, Italy); Alessandro Padovani (Brescia, Italy); Elena Palazzini (Melegnano, Italy); Michele Perini (Gallarate, Italy); Patrizia Perrone (Legnano, Italy); Alessandro Prelle (Milano, Italy); Alessandra Protti (Milano, Italy); Andrea Rigamonti (Lecco, Italy); Nilo Riva (Milano, Italy); Domenico Santoro (Milano, Italy); Patrizia Secchi (Legnano, Italy); Vincenzo Sidoti (Chiari, Italy); Fiorella Tavernelli (Gallarate, Italy); Lucio Tremolizzo (Monza, Italy); Eugenio Vitelli (Lodi, Italy); Stefano Zoccolella (Bari, Italy).

The authors are indebted to Dr. Silvano Gallus for his constructive comments and suggestions and to J. D. Baggott for editing.

Conflict of interest: Dr. Ettore Beghi serves on the editorial advisory boards of *Amyotrophic Lateral Sclerosis*, *Clinical Neurology & Neurosurgery*, and *Neuroepidemiology*; has received funding for travel and speaker honoraria from UCB-Pharma, Sanofi-Aventis, and GSK; and has received funding for educational presentations from GSK. Dr. Giancarlo Logroscino has received funding for educational presentations from Novartis and Lundbeck. Drs. Elisabetta Pupillo, Paolo Messina, Giorgia Giussani, Adriano Chiò, Stefano Zoccolella, Cristina Moglia, and Massimo Corbo declare no conflicts of interest.

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