Physical Activity and Amyotrophic Lateral Sclerosis: A European Population-Based Case–Control Study

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Objective: To assess whether physical activity is a risk factor for amyotrophic lateral sclerosis (ALS).
Methods: From February 2008 to April 2012, 652 patients with ALS from European population-based registries (France, Ireland, Italy, United Kingdom, Serbia) and 1,166 population controls (matched for age, sex, and residency) were assessed. Upon direct interview, data were collected on occupation and history of sport and leisure activities, physical activity, and accidental injuries. Physical exercise was defined as having spent time doing activities that caused an individual to breath hard at least once per month and was coded as none, job-related, and/or sport-related. Sport-related and work-related physical exercise were quantified using metabolic equivalents (METs). Risks were calculated using conditional logistic regression models (adjusting for age, country, trauma, and job-related physical activity) and expressed as odds ratios (ORs) and adjusted ORs (Adj ORs) with 95% confidence intervals (CIs).
Results: Overall physical activity was associated with reduced odds of having ALS (Adj OR = 0.65, 95% CI = 0.48–0.89) as were work-related physical activity (Adj OR = 0.56, 95% CI = 0.36–0.87) and organized sports (Adj OR = 0.49, 95% CI = 0.32–0.75). An inverse correlation was observed between ALS, the duration of physical activity ($p = 0.0041$), and the cumulative MET scores, which became significant for the highest exposure (Adj OR = 0.34, 95% CI = 0.21–0.54). An inverse correlation between ALS and sport was found in women but not in men, and in subjects with repeated traumatic events.
Interpretation: Physical activity is not a risk factor for ALS and may eventually be protective against the disease.

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Members of the EURALS Consortium are listed in the Appendix on page 8.

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Amyotrophic lateral sclerosis (ALS) is a rare, neurodegenerative disease of multifactorial etiology. A number of environmental risk factors have been investigated, including exaggerated physical activity. This association is biologically plausible, because vigorous exercise may induce oxidative stress and glutamate excitotoxicity.[1] However, data are conflicting in experimental animals, as increased physical activity has been reported to be beneficial, null, or harmful in transgenic SOD1 ALS mice.[2–4] In humans, an association between physical activity and ALS was postulated by some studies[5–7] but not others.[8–11] Small sample size, selection bias, nonrepresentative control populations, and inadequate control of confounders are limiting factors in these studies. The conflicting results can also be explained by the difficulties inherent in the assessment of exposure to physical activity. Thus, we decided to carry out a large European case–control study using representative population samples and standardized modalities of data collection, to reveal whether physical activity is a risk factor for ALS.

Our aim was to investigate the association between lifestyle and the risk of subsequently developing ALS. More specifically, the study sought to verify whether, compared to the general population, patients with ALS have a greater exposure to physical activity.

Subjects and Methods

This is a population-based, case–control study. Starting on February 1, 2008 and ending on April 30, 2012, cases were recruited from patients with newly diagnosed ALS attending centers participating in the EURALS Consortium,[12] including Italy (Lombardy, Piedmont and Valle d'Aosta, Puglia, Liguria), Ireland, France (Limoges), Serbia (Belgrade), and England (Preston), for a total population of about 30 million. Case eligibility criteria included male and female sex; being 18 years or older; having definite, probable, or possible ALS (according to the original El-Escorial criteria[13]); and being resident in the area of the local registry. Patients were enrolled by neurologists in consecutive order during ambulatory visits or hospitalizations. Controls were enrolled by local general practitioners (GPs) during routine visits. Each GP received an anonymized list including the age and sex of each ALS patient who lived in his/her area and was included in the study. For each eligible case, the GPs were asked to identify 2 random controls matched for sex, age (±2.5 years), and residency. All contacted individuals (whether cases or controls) agreed to participate in the study.

After informed consent, patients, and controls were interviewed by a trained investigator at each center, who used an ad hoc structured questionnaire. At the beginning of the study, each interviewer received specific guidelines to perform the interview.

Where possible, for patients unable to give appropriate answers (for cognitive impairment or inability to speak), an informed proxy (relative or caregiver) was interviewed. For these cases, the matched controls were also tentatively interviewed through their proxies.

Baseline demographic and clinical data (date of birth, sex, years of education, weight, height, body mass index [BMI], residency) were collected in cases and controls. For ALS patients, relevant disease characteristics were also collected (El-Escorial category, date of onset of symptoms, date of diagnosis, and site of onset [spinal, bulbar, generalized]).

A detailed history of each occupation was collected, including job description, date of start and cessation, degree of physical activity (coded as mild, moderate, or strenuous), and hours spent per month. A detailed lifetime history of each sport was also collected, including type, date of start and cessation, degree of physical activity, and hours spent per month. Sport-related and work-related physical exercise was quantified using metabolic equivalents (METs), units used to estimate the amount of oxygen consumed by the body during physical activity.[14] Previous exposure to traumatic events (yes/no, with number and details) was also investigated along with drug intake, coffee, alcohol, and tobacco. Each physical activity was assigned its corresponding MET with reference to the compendium of physical activity.[14] The resulting MET was then multiplied for the number of years and the number of hours per week spent in the corresponding activity. The METs referring to each activity (whether work-related or sport-related) were summed for the calculation of the cumulative MET scores.

Definition of Study Variables

EXPLANATORY VARIABLES. *Physical exercise* was defined as time spent doing physical activities that make an individual breath hard at least once per month; physical activity was related to work, sport, or both. For patients with different occupations, the definition referred to the most enduring activity. *Organized sport* was any sport practiced for at least 1 year by joining a given sport association and participation to official competitions. *Professional sport* was any sport practiced for at least 1 year, intended as the main occupation. *Amateur sport* was any sport other than organized or professional. *Leisure activities* included any recreational activity performed at least weekly; leisure activities were pooled with amateur sports.

ADJUSTMENT VARIABLES. A number of variables have been selected as possible confounders or risk modifiers, among those thought to be associated (smoking, alcohol, coffee, trauma)[15–18] with the risk of ALS, or potentially affecting recall bias (a proxy respondent).

Interviewee was the person addressed for data collection (patient or proxy, ie, family member or other caregiver). *Traumatic injury* was any antecedent traumatic event requiring medical care. Smoking, alcohol, and coffee were defined as currently in use for at least 6 months.

A centralized online password-protected database, located at the Mario Negri Institute for Pharmacological Research (IRFMN), Milan, was used for data collection. A data-manager

TABLE 1. General Characteristics of the Sample

Variable	ALS, No. (%)	Controls, No. (%)
Registry, country		
Lombardy, Italy	223 (34.2)	438 (37.6)
Piemonte, Valle D'Aosta, & Liguria, Italy	105 (16.1)	207 (17.9)
Puglia, Italy	99 (15.2)	198 (17.0)
Limoges, France	51 (7.8)	100 (8.6)
Preston, England	35 (5.4)	67 (5.8)
Ireland	122 (18.7)	133 (11.4)
Belgrade, Serbia	17 (2.6)	21 (1.8)
Sex		
Women	280 (42.9)	503 (43.1)
Men	372 (57.1)	663 (56.7)
Age, yr		
<55	128 (19.6)	195 (16.8)
55–64	181 (27.8)	324 (27.9)
65–74	228 (35.0)	383 (33.0)
≥75	115 (17.6)	260 (22.4)
NS	—	4
Education, yr		
<6	159 (24.4)	254 (22.0)
6–9	151 (23.2)	236 (20.4)
10–14	248 (38.0)	458 (39.7)
≥15	94 (14.4)	207 (17.9)
NS	—	11
BMI		
<18.5	47 (7.6)	14 (1.2)
18.5–24	339 (54.6)	492 (43.4)
≥25	235 (37.8)	627 (55.3)
NS	31	33
Interviewee		
Patient/control	533 (81.9)	984 (87.6)
Proxy	118 (18.1)	139 (12.4)
NS	1	43
Traumatic injury		
Yes	299 (45.9)	491 (42.2)
No	352 (54.1)	673 (57.8)
NS	1	2
Coffee		
Yes	456 (72.2)	871 (76.9)
No	176 (27.8)	268 (23.1)
NS	20	7
Alcohol		
Yes	257 (39.5)	434 (37.3)
No	393 (60.5)	729 (62.7)
NS	2	3
Smoking		
Yes	311 (47.7)	541 (46.5)
No	341 (52.3)	622 (53.5)
NS	—	3

ALS = amyotrophic lateral sclerosis; BMI = body mass index; NS = not specified.

(E.P.) located at the IRFMN supervised the study during recruitment to verify the appropriateness of matching and the correctness of data input through generation of queries and discussion of any incurring problem. No patient nor control was paid. The study was approved by the institutional review board of each center.

Statistical Analysis

Descriptive statistics are presented as count and percentage, median and range, or mean and standard deviation as appropriate. The association between physical activity and ALS was assessed according to 10 different conditional logistic regression models. To prevent reverse causation, all exposure factors (explanatory and adjustment variables) were censored 5 years before the date of symptom onset (for controls the same date of their matched cases). The duration of physical activity (overall and work-related or sport-related) was the time from start to cessation or up to 5 years from symptom onset (whichever came first), represented in quartiles. MET cumulative scores are also represented in quartiles. The results are reported as odds ratios (ORs) and adjusted ORs (Adj ORs) with 95% confidence intervals (CIs). To identify potential confounders or effect modifiers, we represented the data in subgroups defined by registry, sex, age, interviewee, BMI, traumatic injuries, coffee, alcohol, and smoking. Strata-adjusted ORs were calculated with the Mantel–Haenszel method; between-strata heterogeneity was assessed using the Breslow–Day test.

To assess the influence of physical activity on the age of symptom onset in ALS patients, multivariable general linear models (GLMs) with the same independent predictors of the conditional logistic models were performed. To assess the normality of age of symptom onset, the Shapiro–Wilk test was

TABLE 2. Categories of Physical Activity in ALS Patients and Controls: Conditional Logistic Regression Models

Model	ALS	Controls	OR (95% CI)	Adj OR (95% CI)[a]
I: Physical activity				
Yes/no	449/203	867/297	0.76 (0.61–0.73)	0.65 (0.48–0.89)[b]
II: Type of physical activity				
None	203	297	1.00, Ref	1.00, Ref
Leisure	45	49	1.34 (0.86–2.09)	0.71 (0.44–1.89)
Work	88	184	0.70 (0.51–0.95)	0.56 (0.36–0.87)[b]
Sport	198	362	0.80 (0.62–1.03)	0.77 (0.54–1.11)
Work & sport	118	274	0.63 (0.48–0.83)	0.47 (0.31–0.72)[b]
III: Sport activity				
Yes/no	316/336	644/522	0.76 (0.63–0.92)	0.77 (0.58–1.03)
IV: Sport category				
None	336	522	1.00, Ref	1.00, Ref
Amateur	211	384	0.74 (0.58–0.94)	0.88 (0.64–1.20)
Organized	90	243	0.50 (0.37–0.67)	0.49 (0.32–0.75)[b]
Professional	15	17	1.41 (0.66–2.99)	1.59 (0.63–4.02)
V: Duration of physical activity, yr				
None	203	297	1.00, Ref	1.00, Ref
1st quartile	116	207	0.73 (0.54–0.99)	0.89 (0.60–1.33)
2nd quartile	129	203	0.76 (0.55–1.05)	0.57 (0.37–0.88)[b]
3rd quartile	115	211	0.68 (0.50–0.93)	0.90 (0.59–1.36)
4th quartile	89	245	0.38 (0.27–0.54)	0.33 (0.21–0.52)[b]
NS	—	1		
VI: Duration of sport activity, yr				
None	336	522	1.00, Ref	1.00, Ref
1st quartile	80	158	0.72 (0.52–0.99)	0.98 (0.65–1.49)
2nd quartile	86	153	0.76 (0.55–1.05)	0.72 (0.47–1.10)
3rd quartile	80	159	0.66 (0.47–0.93)	0.91 (0.58–1.42)
4th quartile	70	173	0.57 (0.41–0.80)	0.56 (0.36–0.86)[b]
NS	—	1		
VII: Age of sport activity onset				
None	307	515	1.00, Ref	1.00, Ref
<15	107	260	0.69 (0.53–0.90)	0.67 (0.46–0.77)[b]
15–34	119	251	0.80 (0.61–1.03)	0.79 (0.54–1.12)
≥35	42	114	0.62 (0.42–0.90)	0.79 (0.49–1.29)
NS	—	5		
VIII: Cumulative MET scores				
MET = 0	192	294	1.00, Ref	1.00, Ref
1st quartile	91	218	0.64 (0.47–0.87)	0.79 (0.52–1.18)

TABLE 2: Continued

Model	ALS	Controls	OR (95% CI)	Adj OR (95% CI)[a]
2nd quartile	117	193	0.93 (0.69–1.24)	0.90 (0.59–1.36)
3rd quartile	100	210	0.73 (0.54–0.98)	0.68 (0.44–1.05)
4th quartile	75	235	0.49 (0.36–0.67)	0.34 (0.21–0.54)[b]

Missing data in the multivariate conditional logistic models ranged from 6.8 to 9.2%; thus, no imputation techniques were used. Cumulative duration of physical activity: 1st quartile, 0–14.6 years; 2nd quartile, 14.6–30.0 years; 3rd quartile, 30.0–49.0 years; 4th quartile, >49.0 years. Cumulative duration of sport activity: 1st quartile, 0–10.0 years; 2nd quartile, 10.0–20.5 years; 3rd quartile, 20.5–40.1 years; 4th quartile, >40.1 years. The trend tests for Models V–VIII were assessed using the CONTRAST option in the PROC LOGISTIC procedure of the multivariate logistic models. The probability values were 0.0041, 0.1392, 0.5193, and 0.0031, respectively.

[a]OR adjusted for age (continuous), education (continuous), body mass index at admission (continuous), register (categorical), interviewee (binary), traumatic events (binary), coffee (binary), alcohol (binary), and smoking (binary; Models I, II, III, V, and VIII), plus work-related physical activity (Models IV, VI, and VII).

[b]Significant Adj OR.

Adj = adjusted; ALS = amyotrophic lateral sclerosis; CI = confidence interval; MET = metabolic equivalents; NS = not specified; OR = odds ratio; Ref = reference.

performed. The results of the GLMs are presented as least squares means (LSMEANS), and subgroup comparisons were performed using the post hoc Tukey test. LSMEANS are the means estimated based on the model used (ie, adjusted for all factors of interest). To control for a potential birth-cohort effect on physical activity, GLMs were later adjusted by decade of birth (1925–1934, 1935–1944, 1945–1954, 1955–1964).

The listwise deletion method was applied to missing data. All tests are 2-tailed, with significance set at 0.05. Due to the exploratory nature of the study, adjustment for multiple comparison was not performed. Data were analyzed using the SAS package for PC (SAS Institute, Cary, NC; v9.2).

A sample size of 585 cases and 1,170 controls was calculated based on the results of an unpublished pilot investigation involving 44 cases and 82 matched controls under the assumption of an OR of 2 or higher for soccer-related physical exercise (3% of controls; alpha = 0.05; beta = 0.20).

Results

A total of 684 ALS patients participated in the study. Thirty-two were excluded for duplicate input (n = 14), residency outside the study area (n = 3), or suspected ALS (n = 15). The sample analyzed included 652 ALS patients and 1,166 controls. There were no eligible cases or controls who declined participation in the study. The general characteristics of the sample are illustrated in Table 1. Median age (range) was 66 (27–93) years among cases and 67 (30–96) years among controls. Median (range) BMI value was, respectively, 23.9 (11.8–45.9) and 25.7 (14.4–44.4). The questionnaire was filled by a proxy in 18.1% of cases and in only 12.4% of controls because surrogate informants for matched controls were unavailable. Definite ALS was recorded in 301 cases (46.2%), probable ALS in 276 (42.3%), and possible ALS in 75 (11.5%). The onset of symptoms was spinal in 415 patients (63.7%), bulbar in 215 (33.0%), and generalized in 22 (3.4%). Symptom duration at interview was <12 months in 242 patients (37.2%), 12 to 24 months in 247 (38.0%), and >24 months in 161 (24.8%). In 2 additional cases, disease duration was unknown. Traumatic injuries were reported by 45.9% of ALS patients and 42.2% of controls ($p = 0.1225$; see Table 1). Coffee, alcohol, and smoking were reported by similar proportions of cases and controls. Drug exposure was not further investigated, because it was reported in rare instances in both cases and controls.

Overall physical activity was associated with reduced odds of having ALS (Adj OR = 0.65, 95% CI = 0.48–0.87; Model I), as was work-related physical activity (Adj OR = 0.56, 95% CI = 0.36–0.87; Model II; Table 2). Organized sports were significantly associated with reduced odds of ALS (Adj OR = 0.49, 95%CI = 0.32–0.75; Model IV). A biological gradient was detected for duration of physical activity ($p = 0.0041$) . An inverse correlation was found between the cumulative MET scores and the risk of ALS, which became significant for the fourth quartile of exposure (Adj OR = 0.34; 95% CI = 0.21–0.54; Model VIII).

Register, sex, and in part traumatic injuries acted as effect modifiers (Table 3). The risks were highly heterogeneous across registries ($p = 0.0009$), but in no case was there a direct correlation between physical activity and ALS. An inverse correlation between ALS and sports was found in women but not in men, and in subjects with repeated traumatic events. As in a previous study,[18] repeated head trauma was the only type to be significantly associated with the risk of ALS; a separate analysis was performed here on ALS and head trauma. A history of ≥2 traumatic head injuries was associated with

TABLE 3. Sport-Related Physical Activity and ALS: Subgroup Analyses[a]

Strata	Sport	ALS	Controls	*p*	OR (95% CI)	OR_{AdjMH} (95% CI)	Heterogeneity of *p*, Breslow–Day
Total	No	336	522	0.0003	0.76 (0.63–0.92)		
	Yes	316	644				
Registry							
Limoges, France	No	14	23	0.5487	0.79 (0.37–1.71)	0.72 (0.59–0.87)	<0.0009[b]
	Yes	37	77				
Preston, England	No	16	30	0.9283	0.96 (0.42–2.19)		
	Yes	19	37				
Ireland	No	49	21	<0.0001	0.28 (0.15–0.50)		
	Yes	73	112				
Lombardy, Italy	No	145	211	<0.0001	0.50 (0.36–0.70)		
	Yes	78	227				
Piedmont, Valle d'Aosta, and Liguria, Italy	No	50	102	0.8431	1.05 (0.66–1.68)		
	Yes	55	107				
Puglia, Italy	No	55	131	0.0754	1.56 (0.95–2.56)		
	Yes	44	67				
Belgrade, Serbia	No	7	12	0.3341	1.90 (0.52–6.96)		
	Yes	10	9				
Sex							
Female	No	201	285	<0.0001	0.51 (0.38–0.70)	0.69 (0.56–0.85)	0.0021[b]
	Yes	79	218				
Male	No	135	237	0.8612	0.98 (0.75–1.27)		
	Yes	237	426				
Traumatic injury							
No	No	198	357	0.3167	0.88 (0.68–1.14)	0.76 (0.62–0.92)	0.0521
	Yes	154	317				
1	No	91	130	0.1082	0.74 (0.52–1.07)		
	Yes	100	192				
2+	No	47	42	0.0012	0.43 (0.26–0.72)		
	Yes	61	127				

This table reported only the subgroups that led to at least borderline significance by the heterogeneity test ($p < 0.1$). Age, BMI, interviewee, coffee, alcohol, and smoking subgroups did not modify the effect of the association between ALS and sport activity.
[a]Subgroup analyses for age, BMI, interviewee, coffee, alcohol, and smoking are not included because they were nonsignificant.
[b]Effect modifiers.
Adj = adjusted; ALS = amyotrophic lateral sclerosis; BMI = body mass index; CI = confidence interval; MH = Mantel–Haenszel; OR = odds ratio.

increased odds of having ALS (OR = 2.82, 95% CI = 1.22–6.56). When history of head trauma was included as a confounder in a separate analysis, the results were virtually unchanged (data not shown).

An increased risk of ALS was detected among those reporting ≥2 traumatic events and not practicing sports as compared to those with no trauma who were practicing sports (Table 4).

TABLE 4. Conditional Logistic Model of Sport–Trauma Interaction

Sport/Trauma	ALS	Controls	*p*	OR (95% CI)	Adj OR (95% CI)
S-0T	154	320	Ref	1.00, Ref	1.00, Ref
S-1T	100	194	0.7343	1.07 (0.79–1.46)	1.00 (0.67–1.50)
S-2+T	61	128	0.9876	0.99 (0.67–1.42)	1.04 (0.64–1.69)
No S-0T	198	353	0.2468	1.17 (0.90–1.51)	1.14 (0.79–1.64)
No S-1T	92	128	0.0168	1.49 (1.07–2.08)[a]	1.31 (0.82–2.10)
No S-2+T	46	41	0.0003	2.33 (1.47–3.70)[a]	2.16 (1.14–4.07)[a]

[a]Significant comparisons.
Adj = adjusted (see text); ALS = amyotrophic lateral sclerosis; CI = confidence interval; No S-0T = no sport–no trauma; No S-1T = no sport–1 traumatic injury; No S-2+T = no sport–2+ traumatic injuries; OR = odds ratio; Ref = reference; S-0T = sport–no trauma; S-1T = sport–1 traumatic injury; S-2+T = sport–2+ traumatic injuries.

The mean age at symptom onset was 67.1 years in physically inactive patients and 61.5 years in those performing work-related and sport-related physical activity ($p < 0.0001$). When adjusting data by birth cohort, overall and sport-related physical activity were still associated with an earlier age at onset, but the differences tended to disappear (64.0 and 63.2 years, respectively, for physically inactive patients and those performing work-related and sport-related physical activity).

Discussion

This multicenter population-based case–control study suggests that physical activity is not a risk factor for ALS, and may eventually be protective against the disease. An inverse correlation was found for physical activity (overall), work-related and sport-related physical activity, and organized sports. Possible mechanisms underlying the neuroprotective effects of exercise include changes in motor neuron morphology, muscle–nerve interactions, glial activation, and altered levels of gene expression of antiapoptotic proteins, scavengers of reactive oxygen species, and neurotrophic factors.[19]

Consistent with our findings in a population-based case–control study, Longstreth and coworkers[8] showed that physical activity, whether at work, during leisure time, or both, and whether during a person's lifetime or during specific decades before the reference date, was not a risk factor for developing ALS. No difference between cases and controls was also found by Valenti et al[9] for past athletic activities or hard physical work. Also, Veldink et al[10] found no association between physical activity and the risk of developing ALS when considering both occupational and leisure activities. Our findings only partly overlap the results of a recent population-based case–control study with a similar design, which showed an increased risk of ALS with a greater amount of physical activity during leisure time but no association between the disease and occupational physical activity, and the absence of a dose–response relationship.[11] However, a significant correlation was found between physical activity (overall, recreational, and occupational) and earlier age at onset of the disease. The authors concluded that physical activity per se does not increase the risk of ALS, but a genetic profile or lifestyle promoting physical fitness increases ALS susceptibility.

We did not confirm the results of a pilot case–control study by our group done with the same design.[7] In that study, blue collar occupation and duration of exposure to physical exercise during sport were associated with an increased ALS risk. The source of cases (which were from a selected number of registries, nonrepresentative of our final sample) and the small sample size may explain the differences.

An inverse correlation between ALS and sport-related exercise was found in women but not in men. A possible neuroprotective effect of female sex hormones against ALS cannot be excluded.[2]

Interestingly, a history of injuries was a risk factor for ALS only in physically inactive patients. In a previous report by our group,[18] antecedent trauma, repeated trauma, and severe trauma occurred more frequently in patients with ALS than in matched controls. In the present study, the reduction of the ALS risk in physically active patients with a history of traumatic injury is in favor of the purported protective action of physical activity.

In our study, history of physical activity was associated with an earlier onset of the disease. However, the difference tended to disappear when adjusting for birth cohorts. This finding may simply reflect a change with age in the tendency of a person to be physically active.

The major strength of this study is the representativeness of the study population. The mean age at diagnosis and the sex of our ALS cases overlap those of patients enrolled in the European population-based registries.[20] Other important strengths include censoring of the exposure 5 years before symptom onset for cases and controls (to reduce the risk of assessing clinical features in the prediagnostic period as risk factors) and a detailed collection of confounders and adjustment variables.

The study also has limitations. First, recall bias cannot be excluded. However, as recall bias is likely to be in the direction of greater recall by the patient group, we may have missed an even greater preventive action of physical activity. Second, the interviewers were not blind as to whether the interviewee was a case or a control. However, a more neutral data collection through a blind interview was unfeasible, because the setting of the interview (a hospital visit for a case and an outpatient visit for a control) and the appearance of the interviewee (an ALS patient or a healthy control) prevented any type of blinding. Third, the methods used to assess the extent of physical exercise may be imprecise, as they were not validated. In addition, the calculation of the MET scores, even if based on a detailed investigation of all work-related and sport-related activities, has been obtained retrospectively. Fourth, for several cases and controls the questionnaire was completed by proxies. However, proxies were spouses, sons, or daughters, all of them sufficiently informed to provide accurate information. Fifth, selection bias cannot be entirely excluded, as the ALS patients enrolled in the study did not represent the entire population included in each population-based registry. However, consecutive patients were enrolled as long as our resources permitted, and the baseline characteristics of the ALS cases were comparable to the characteristics of the patients included in the incidence studies for each registry separately. The 2 samples were fairly similar in terms of mean age at diagnosis, sex, site of onset, and disease duration (data not shown). Sixth, we did not investigate the genetic profile of all our ALS patients, because genetic testing was a secondary objective of our study, and during the first years of enrollment C9orf72 and other important mutations were unknown. The effects of physical exercise in patients with and without these mutations cannot be assessed in the entire cohort.

In conclusion, despite its limitations, our study contrasts the belief that physical activity is a risk factor for ALS and does not exclude the possibility of a protective action. To better understand the biological plausibility of our findings, we collected blood samples in a subgroup of cases and controls from different registries to perform focused genetic analyses and confirm our research hypothesis.

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Authorship

E.P. helped with data collection and study monitoring. P.M. did the statistical analysis. G.L., A.Ch., B.M., D.M., O.H., and Z.S. organized the study conduction at each registry's site. E.B. contributed with the study design, data interpretation, and writing of the first draft of the manuscript. All the other authors have been actively involved in the discussion on study conduct, data collection, and analysis and in the revisions of the manuscript. The members of the EURALS Consortium helped with patient recruitment and data collection.

Potential Conflicts of Interest

E.P.: grants/grants pending, Italian Drug Agency, Italian Ministry of Health, UE. P.M.: grants/grants pending, Italian Drug Agency, Italian Ministry of Health, EISAI, Lombardy Region, Sanofi-Aventis. A.Ch.: grants/grants pending: European Union, Italian Ministry of Health; scientific advisory boards, Biogen Idec, Cytokinetics. O.H.: grants/grants pending, Health Research Board, Merck Serono; consultancy, Biogen Idec, Novartis. E.B.: board membership, Viropharma, EISAI; travel expenses, UCB-Pharma, GSK; speaking fees, UCB-Pharma, GSK, Viropharma; paid educational presentations, GSK; grants/grants pending, Italian Drug Agency, Italian Ministry of Health, American ALS Association; consulting, GSK.

Appendix

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