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Associations of Electric Shock and Extremely Low-Frequency Magnetic Field Exposure With the Risk of Amyotrophic Lateral Sclerosis

The Euro-MOTOR Project

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We explored the associations of occupational exposure to extremely low-frequency magnetic fields (ELF-MF) and electric shocks with the risk of amyotrophic lateral sclerosis (ALS) in a pooled case-control study (European Multidisciplinary ALS Network Identification to Cure Motor Neurone Degeneration (Euro-MOTOR)) of data from 3 European countries. ALS patients and population-based controls were recruited in Ireland, Italy, and the Netherlands between 2010 and 2015. Lifetime occupational and lifestyle histories were obtained using structured questionnaires. We applied previously developed job exposure matrices assigning exposure levels to ELF-MF and potential for electric shocks. Odds ratios and 95% confidence intervals were estimated by means of logistic regression for exposure to either ELF-MF or electric shocks, adjusted for age, sex, study center, education, smoking, and alcohol consumption and for the respective other exposure. Complete occupational histories and information on confounding variables were available for 1,323 clinically confirmed ALS cases and 2,704 controls. Both ever having had exposure to ELF-MF above the background level (odds ratio = 1.16, 95% confidence interval: 1.01, 1.33) and ever having had potential exposure above background for electric shocks (odds ratio = 1.23, 95% confidence interval: 1.05, 1.43) were associated with ALS. Adjustment for the respective other exposure resulted in similar risk estimates. Heterogeneity in risks across study centers was significant for both exposures. Our findings support possible independent associations of occupational exposure to ELF-MF and electric shocks with the risk of ALS.

amyotrophic lateral sclerosis; electric shock; extremely low-frequency magnetic fields; occupational exposure; pooled case-control studies

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; *C9orf72*, chromosome 9 open reading frame 72 gene; ELF-MF, extremely low-frequency magnetic fields; Euro-MOTOR, European Multidisciplinary ALS Network Identification to Cure Motor Neurone Degeneration; ISCO-88, International Standard Classification of Occupations 1988; JEM, job exposure matrix; OR, odds ratio; PAN, Prospective ALS Study in the Netherlands.

Occupations which involve working with electricity (electrical occupations) have been associated consistently with an increased risk of amyotrophic lateral sclerosis (ALS) (1). Exposure to extremely low-frequency magnetic fields (ELF-MF) and exposure to electric shocks have been suggested as possible causes (1). Several reviews have found a modest but significantly increased risk of ALS for persons working in occupations with relatively high ELF-MF exposures (1–6). A recent meta-analysis, however, showed that heterogeneity between studies was considerable; this appeared to be the result of differences in exposure assessment methods (6).

Only a few studies have evaluated both ELF-MF and electric shocks. Findings from cohort studies conducted in the Netherlands and Switzerland suggested that the observed increased risk of ALS among persons in electrical occupations is driven by exposure to ELF-MF rather than exposure to electric shocks (7, 8). Increased ALS mortality was also associated with medium or high exposure to ELF-MF (compared with low exposure) in a US case-control study, while an inverse association between electrical shock exposure and ALS mortality was observed (9). No association was found for ELF-MF exposure in a third cohort study carried out in Sweden. In that study, only an association between ALS and electric shock in people under age 65 years was reported (10).

In the US case-control study, the occupations of the cases and controls were identified from mortality records (9), whereas investigators in the Swedish and Swiss cohort studies used census occupational titles from 1 and 2 time points, respectively (7, 10). However, using a full occupational history—information on all occupations held by the participants up to baseline—is generally considered the best approach (6). Such information was collected in the Dutch cohort study (8). The recent meta-analysis of occupational ELF-MF exposure and ALS risk showed that increased risks emerged only from studies that were able to evaluate full occupational histories (6).

In addition to exposure assessment, case ascertainment is one of the other major challenges involved when studying neurodegenerative disorders (11). All of the above studies used mortality records for case identification. Although mortality records give a relatively complete picture of the incidence of a fatal disease like ALS (12), information on such records is limited. Moreover, disease coding for "motor neuron disease" is often used when studying ALS, while this code may also refer to other motor neuron diseases. A case-control design offers the opportunity to study clinically confirmed ALS cases, as well as a collection of additional disease-related information, such as the site of disease onset and genetic variants (e.g., chromosome 9 open reading frame 72 gene (*C9orf72*) repeat expansion).

We used job exposure matrices (JEMs) similar to those applied in the cited cohort studies (7, 8, 10) to explore the associations of ALS with lifetime occupational exposure to ELF-MF and electric shocks in pooled analyses of population-based case-control studies from 3 European countries.

METHODS

Study population

Patients diagnosed with definite, (laboratory-supported) probable, or possible ALS according to the revised El Escorial criteria (13) were recruited in Ireland (nationwide), Italy (Apulia, Lombardy, Piedmont, and Valle d'Aosta regions), and the Netherlands (nationwide). The Prospective ALS Study in the Netherlands (PAN) was started in January 2006 (14), and all participants enrolled between February 2010 and 2015 were included in the European Multidisciplinary ALS Network Identification to Cure Motor Neurone Degeneration (Euro-MOTOR) Project (15). The Irish and Italian participants were recruited from 2011 to 2015, following the same protocols as those used in the Dutch study. Medical records of all cases were scrutinized to confirm the diagnosis and to exclude ALS mimic syndromes. Previous comparisons have indicated that the case-control samples were representative of the ALS population in each country in terms of demographic and clinical characteristics, except for site of onset in Ireland (15). Controls were matched to the cases by sex, age (±5 years), and geographic location. Controls were individually matched in Ireland and Italy; in the Netherlands they were frequency-matched.

Data on the demographic characteristics of participants and on their highest attained educational level, smoking and alcohol drinking habits, and lifetime occupational history were collected using structured questionnaires. Job title, industry, employer, year of starting and stopping employment, and hours worked per week were reported for each job ever held. All jobs were coded using the International Standard Classification of Occupations 1988 (ISCO-88) (16). Ethical approval was provided by each individual institutional review board, and all participants gave written informed consent.

For a replication study, we used the ALS cases diagnosed between 2006 and 2009 and corresponding controls from the Dutch PAN study.

Exposure assessment

We applied 2 previously developed JEMs based on ISCO-88 (17, 18). The ELF-MF JEM reflects both the intensity and probability of exposure to magnetic flux density for each job held (at the 4-digit level of ISCO-88) on an ordinal scale: low (background), medium, or high exposure. The electric shock JEM reflects the potential for electrical injury in each job held at the 3-digit level of ISCO-88, categorized into low, medium, and high risk. In order to estimate cumulative exposures, the low level was considered background and assigned a value of 0, the medium level was assigned a value of 1, and the high level was assigned a value of 4 to better reflect the exposure distribution. In addition, we assigned ever occupational exposure to gases and fumes, metals, mineral dusts, pesticides, or solvents, as potentially confounding exposures (8), by applying a previously developed JEM (19). All exposures were estimated up to 3 years prior to the survey for both cases and controls to eliminate recording of any exposure that may have occurred after ALS diagnosis. We chose the survey date as the starting point to make the timing comparable between cases and controls.

Any subject who had ever held a job that was assessed as involving exposure above the background level was considered exposed. Never exposure above the background level served as the reference category. The exposure metrics we analyzed for both exposures were: ever exposure above the background level; level of exposure (medium exposure only or ever having high exposure); duration of exposure; and cumulative exposure (the product of duration and level of exposure). For duration of exposure and cumulative exposure, we created quartiles based on the exposure distribution among the controls. Exposure assessment was done exactly the same way for the replication study.

Statistical analyses

Associations of occupational exposure to ELF-MF and electric shocks with ALS were investigated using logistic regression models, adjusting for sex, age, highest completed educational level (International Standard Classification of Education 2011 (20): 0–4 for the lowest levels (through high school or technical school); 5–6 for the highest levels (university and graduate school)), smoking status (never, former, or current smoker), alcohol consumption (never, former, or current drinker), and study center (Ireland; Italy—Apulia; Italy—Lombardy; Italy—Piedmont and Valle d'Aosta; the Netherlands). For age, we used age at the time of the survey because this was comparable between cases and controls. The mean duration between disease onset and the date of the survey was 1.5 years. The exposure estimates were entered into the model either as categorical variables or as continuous variables (for trend analyses). Additionally, we adjusted for the respective other exposure (ELF-MF or electric shocks) in 2-exposure models, and we tested for possible confounding by other occupational exposures.

By applying a term for interaction between exposure and study center, we tested for heterogeneity in the association between exposure and disease across centers in the Euro-MOTOR population. We further examined our findings using several sensitivity analyses. Since exogenous factors possibly had a minor role in the development of ALS in patients with the highly penetrant *C9orf72* repeat expansion (21, 22), we performed separate analyses excluding these cases ($n = 81$). To compare our results with those of previous studies, we limited analyses to men and to subjects under the age of 65 years. We also fitted a multinomial logistic regression model for site of onset (i.e., spinal or bulbar) to see whether there was any difference in effect between these groups. Lastly, we stratified analyses by the respective other exposure level (background or ever above background).

To explore the possible residual confounding effect of educational level on the associations of exposure to ELF-MF and electric shocks with ALS, we controlled the analyses by individually matching for educational level in addition to sex, age, and center. We were able to match 1,181 pairs. Conditional logistic regression models were applied to this (post hoc) matched sample, with adjustment for smoking and alcohol consumption. Furthermore, we performed analysis after multiple imputation of missing values (10 iterations) to explore the effect of omitting observations with missing data from the complete-case analyses. We used the fully conditional specification method (23) with PROC MI in SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), assuming that data were missing at random.

RESULTS

The Euro-MOTOR population comprised 1,323 ALS cases and 2,704 controls for whom complete data were available on occupational exposure to ELF-MF and electric shocks, as well as for confounders (Table 1). The average age was 64.4 years for cases and 64.0 years for controls; 60% of the population was male. Educational level was higher among controls than among cases, with 26% and 19% being in the highest category, respectively.

We estimated that 49% of cases had ever been occupationally exposed to ELF-MF above the background level and that 7% of all cases had ever been highly exposed (Table 2). Among controls, these percentages were 43% and 5%, respectively. The risk of ALS associated with ever having exposure to ELF-MF was 1.16 (95% confidence interval (CI): 1.01, 1.33). Duration of exposure or cumulative exposure to ELF-MF did not show any trend.

Potential for electric shocks in the workplace was estimated for 40% of cases and 33% of controls, and ever having high exposure for 20% and 17%, respectively (Table 2). Having an ever-electric-shock risk above the background level was associated with an increased risk of ALS (odds ratio (OR) = 1.23, 95% CI: 1.05, 1.43). A significant trend in duration of exposure (OR = 1.005, 95% CI: 1.000, 1.010) was observed, but the risk estimates for the quartiles indicated no monotonical increase. No trend was observed for cumulative exposure to electric shocks.

Cumulative exposure to ELF-MF and cumulative exposure to electric shocks were moderately correlated (Pearson correlation: $R_P = 0.38$). Similar risks of ALS, albeit slightly attenuated, were observed when the models were adjusted for the respective other exposure. Additional adjustment for other occupational exposures resulted in similar findings for electric shocks, but the risks for exposure to ELF-MF were further attenuated (see Web Table 1, available at https://academic.oup.com/aje).

Heterogeneity in risks across study centers was significant for both ELF-MF ($P = 0.0007$) and electric shocks ($P = 0.011$). The Lombardy region of Italy had the highest risk estimates for both ELF-MF and electric shocks; Ireland had the lowest risk estimates for both exposures (Web Tables 2 and 3). Post hoc matched analyses based on 1,181 case-control pairs (Web Table 4) showed a similar picture for exposure to ELF-MF and electric shocks above the background level; for ELF-MF, the odds ratio was 1.18 (95% CI: 0.99, 1.39), and for electric shocks it was 1.19 (95% CI: 0.98, 1.44).

Sixty-four percent of cases were tested for the *C9orf72* repeat expansion. Excluding cases with known *C9orf72* repeat expansion ($n = 81$; 6% of all cases) or restricting analyses to men produced practically the same results (Web Tables 5 and 6). The risk estimates for subjects younger than 65 years were higher than those for the group as a whole. Multinomial analyses for site of disease onset indicated no difference in associations with either exposure. The imputed data set comprised 1,552 cases and 2,921 controls (Web Table 7), and the effect estimates for ever exposure above the background level remained virtually the same for both exposures in comparison with the complete-case analyses.

For the replication study, data on occupational exposure to ELF-MF and electric shocks, as well as covariates, were available for 443 ALS cases and 1,547 controls from the PAN population (Table 3). The odds ratios were 1.08 (95% CI: 0.86, 1.35) for ever exposure to ELF-MF above the background level and 1.58 (95% CI: 0.98, 2.53) for ever having high exposure (Table 4). For electric shocks, the respective odds ratios were 0.99 (95% CI: 0.76, 1.29) and 0.92 (95% CI: 0.66, 1.28). No significant trends with duration of exposure or cumulative exposure were observed.

DISCUSSION

In this pooled analysis of ALS case-control studies from 3 European countries, we observed a modestly increased risk of ALS after both exposure to ELF-MF and exposure to electric shocks.

In a recent meta-analysis based on 11 studies, an increased risk of ALS was reported for occupational exposure to ELF-MF

Table 1. Characteristics of Participants in a Pooled Case-Control Study of Occupational Exposure to Electric Shocks and Extremely Low-Frequency Magnetic Fields and Risk of Amyotrophic Lateral Sclerosis, Euro-MOTOR Project, 2010–2015

Characteristic	Total Population				Ireland				Italy—Apulia			
	Controls (*n* = 2,704)		Cases (*n* = 1,323)		Controls (*n* = 331)		Cases (*n* = 160)		Controls (*n* = 162)		Cases (*n* = 98)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Male sex	1,616	60	794	60	200	60	95	59	106	65	62	63
Age at survey, years[a]	64.0 (10.1)		64.4 (10.7)		64.5 (11.0)		64.9 (11.4)		64.5 (11.2)		64.1 (10.8)	
Educational level (ISCED (20))												
ISCED 0–4	1,999	74	1,072	81	262	79	133	83	143	88	92	94
ISCED 5–6	705	26	251	19	69	21	27	17	19	12	6	6
Smoking status[b]												
Never smoker	1,034	38	503	38	160	48	70	44	74	46	38	39
Former smoker	1,274	47	542	41	132	40	59	37	49	30	34	35
Current smoker	396	15	278	21	39	12	31	19	39	24	26	27
Alcohol drinking[b]												
Never drinker	413	15	283	21	61	18	26	16	84	52	37	38
Former drinker	117	4	103	8	19	6	16	10	5	3	6	6
Current drinker	2,174	80	937	71	251	76	118	74	73	45	55	56
Site of disease onset												
Spinal			902	68			122	76			75	77
Bulbar			418	32			38	24			22	22
Generalized			3	0.2							1	1

Characteristic	Italy—Lombardy				Italy—Piedmont and Valle d'Aosta				The Netherlands			
	Controls (*n* = 137)		Cases (*n* = 149)		Controls (*n* = 271)		Cases (*n* = 241)		Controls (*n* = 1,803)		Cases (*n* = 675)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Male sex	70	51	86	58	146	54	133	55	1,094	61	418	62
Age at survey, years[a]	63.6 (11.1)		65.6 (10.3)		63.9 (11.5)		65.5 (10.9)		63.7 (9.5)		63.7 (10.5)	
Educational level (ISCED (20))												
ISCED 0–4	82	60	133	89	227	84	225	93	1,285	71	489	72
ISCED 5–6	55	40	16	11	44	16	16	7	518	29	186	28
Smoking status[b]												
Never smoker	70	51	59	40	132	49	124	51	598	33	212	31
Former smoker	50	37	62	42	95	35	71	29	948	53	316	47
Current smoker	17	12	28	19	44	16	46	19	257	14	147	22
Alcohol drinking[b]												
Never drinker	42	31	42	28	86	32	88	37	140	8	90	13
Former drinker	3	2	12	8	18	7	16	7	72	4	53	8
Current drinker	92	67	95	64	167	62	137	57	1,591	88	532	79
Site of disease onset												
Spinal			107	72			154	64			444	66
Bulbar			42	28			87	36			229	34
Generalized											2	0.3

Abbreviations: ALS, amyotrophic lateral sclerosis; Euro-MOTOR, European Multidisciplinary ALS Network Identification to Cure Motor Neurone Degeneration; ISCED, International Standard Classification of Education.

[a] Values are expressed as mean (standard deviation).

[b] Three years before survey.

Table 2. Risk of Amyotrophic Lateral Sclerosis Associated With Occupational Exposure to Electric Shocks and Extremely Low-Frequency Magnetic Fields in a Pooled Case-Control Study, Euro-MOTOR Project, 2010–2015[a]

Exposure	Controls (*n* = 2,704)		Cases (*n* = 1,323)		Unadjusted for Other Exposure		Adjusted for Other Exposure	
	No.	%	No.	%	OR	95% CI	OR	95% CI
Extremely Low-Frequency Magnetic Fields								
Background level	1,547	57	678	51	1.00	Referent	1.00	Referent
Ever exposed above background level	1,157	43	645	49	1.16	1.01, 1.33	1.10	0.95, 1.28
Exposure level								
Background level	1,547	57	678	51	1.00	Referent	1.00	Referent
Medium level only	1,015	38	552	42	1.15	0.99, 1.33	1.10	0.94, 1.28
Ever exposed at high level	142	5	93	7	1.23	0.92, 1.65	1.13	0.83, 1.53
Duration of exposure, years								
Background level	1,547	57	678	51	1.00	Referent	1.00	Referent
<5	307	11	158	12	1.18	0.95, 1.47	1.08	0.86, 1.37
5–11	255	9	148	11	1.25	1.00, 1.58	1.21	0.95, 1.54
12–30	295	11	171	13	1.15	0.92, 1.43	1.10	0.88, 1.38
>30	300	11	168	13	1.07	0.85, 1.34	0.99	0.78, 1.27
Continuous variable					1.001	0.997, 1.006	0.999	0.994, 1.005
Continuous variable (excluding the nonexposed)					0.998	0.992, 1.005	0.996	0.989, 1.004
Cumulative exposure, unit-years[b]								
Background level	1,547	57	678	51	1.00	Referent	1.00	Referent
<5	289	11	149	11	1.19	0.95, 1.49	1.13	0.90, 1.43
5–13	288	11	162	12	1.22	0.98, 1.52	1.17	0.93, 1.47
14–33	282	10	164	12	1.14	0.91, 1.42	1.09	0.87, 1.37
>33	298	11	170	13	1.09	0.87, 1.37	1.01	0.79, 1.28
Continuous variable					1.000	0.998, 1.003	0.999	0.997, 1.002
Continuous variable (excluding the nonexposed)					0.999	0.996, 1.002	0.999	0.996, 1.002
Time since last exposure, years								
Background level	1,547	57	678	51	1.00	Referent	1.00	Referent
3–4	283	10	146	11	1.10	0.88, 1.40	1.00	0.79, 1.28
5–17	295	11	167	13	1.17	0.94, 1.46	1.13	0.89, 1.42
18–38	298	11	163	12	1.12	0.90, 1.40	1.05	0.83, 1.34
>38	281	10	169	13	1.23	0.99, 1.54	1.25	0.99, 1.59
Continuous variable (excluding the nonexposed)					1.002	0.995, 1.008	1.003	0.993, 1.014
Electric Shocks								
Background level	1,799	67	792	60	1.00	Referent	1.00	Referent
Ever exposed above background level	905	33	531	40	1.23	1.05, 1.43	1.19	1.01, 1.40
Exposure level								
Background level	1,799	67	792	60	1.00	Referent	1.00	Referent
Medium level only	452	17	261	20	1.21	1.01, 1.46	1.17	0.97, 1.42
Ever exposed at high level	453	17	270	20	1.25	1.03, 1.53	1.20	0.97, 1.48
Duration of exposure, years								
Background level	1,799	67	792	60	1.00	Referent	1.00	Referent
<6	227	8	135	10	1.45	1.14, 1.83	1.38	1.08, 1.77
6–16	221	8	124	9	1.04	0.81, 1.34	0.98	0.75, 1.28
17–37	232	9	127	10	1.25	0.98, 1.60	1.22	0.95, 1.58
>37	225	8	145	11	1.17	0.90, 1.50	1.18	0.90, 1.55
Continuous variable					1.005[c]	1.000, 1.010	1.005[c]	1.000, 1.010
Continuous variable (excluding the nonexposed)					1.005	0.998, 1.011	1.006	0.999, 1.014

Table continues

Table 2. Continued

Exposure	Controls (n = 2,704)		Cases (n = 1,323)		Unadjusted for Other Exposure		Adjusted for Other Exposure	
	No.	%	No.	%	OR	95% CI	OR	95% CI
Cumulative exposure, unit-years[b]								
Background level	1,799	67	792	60	1.00	Referent	1.00	Referent
<9 unit-years	227	8	135	10	1.32	1.04, 1.67	1.25	0.97, 1.60
9–29	221	8	124	9	1.15	0.89, 1.47	1.10	0.85, 1.42
30–70	232	9	127	10	1.14	0.89, 1.47	1.12	0.86, 1.46
>70	225	8	145	11	1.30	1.01, 1.67	1.30	1.00, 1.70
Continuous variable					1.001	1.000, 1.003	1.001	1.000, 1.003
Continuous variable (excluding the nonexposed)					0.998	0.992, 1.005	0.996	0.989, 1.004
Time since last exposure, years								
Background level	1,799	67	792	60	1.00	Referent	1.00	Referent
3–4	208	8	141	11	1.46	1.13, 1.87	1.46	1.12, 1.90
5–16	227	8	132	10	1.23	0.96, 1.57	1.17	0.90, 1.53
17–34	221	8	134	10	1.25	0.97, 1.59	1.22	0.94, 1.60
>34	249	9	124	9	1.05	0.82, 1.34	0.97	0.75, 1.26
Continuous variable (excluding the nonexposed)					0.996	0.988, 1.003	0.997	0.987, 1.008

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; Euro-MOTOR, European Multidisciplinary ALS Network Identification to Cure Motor Neurone Degeneration; OR, odds ratio.

[a] Logistic regression analysis. All models were adjusted for sex, age, study center, education, smoking status, and alcohol drinking.

[b] Cumulative exposure is the product of duration and level of exposure.

[c] P for trend < 0.05.

(summary relative risk = 1.14, 95% CI: 1.00, 1.30) (6). This estimate was not adjusted for electric shocks and was similar to our finding for ELF-MF exposure (OR = 1.16, 95% CI: 1.01, 1.33).

We used the same exposure assessment method as in the previous cohort studies that evaluated both ELF-MF exposure and electric shocks (7, 8, 10), enabling mutual adjustment. The prevalence of exposure to ELF-MF was somewhat lower in our Euro-MOTOR case-control study (43% of controls were ever exposed) than in the Dutch cohort study (51%) (8), and the prevalence of potential for electric shock was somewhat higher (33% vs. 23% of controls were ever exposed, respectively). The correlation between cumulative exposure to ELF-MF and electric shocks that we observed ($R_P = 0.38$) was somewhat higher than reported previously ($R_P = 0.28$) (8). In line with the Dutch and Swiss cohort studies, we found a higher risk of ALS for those workers who had ever been exposed to ELF-MF above the background level, although this was not statistically significant when results were adjusted for electric shocks (OR = 1.10, 95% CI: 0.95, 1.28). We did not, however, observe any trend in duration or level of exposure to ELF-MF, whereas a clear exposure-dependent association was described by Koeman et al. (8). Moreover, based on the Dutch cohort, it was concluded that exposure to ELF-MF rather than electric shocks in electrical occupations may drive the risk of ALS (8), while our results suggested that both exposures may play a role. In addition, when we limited our analyses to men (as in the study by Koeman et al. (8)), the associations with ALS risk appeared stronger for electric shocks than for ELF-MF.

The risk of ALS due to electric shocks remained significant in the 2-exposure models, and there was a suggestion of an exposure-response relationship with duration of exposure, although risks were not monotonically increased. Moreover, the relationship was not confirmed in the post hoc matched analyses, showing no trend for electric shocks and virtually the same risk estimates for both exposures. The associations for both ELF-MF and electric shocks remained when analyses were limited to subjects who only experienced background-level exposure to the respective other exposure (Web Tables 5 and 6), indicating an independent association.

Our pooled analyses comprised 1,323 clinically confirmed ALS cases, which is a much larger number than in previous studies focusing on the risk of occupational exposure to ELF-MF and electric shocks. We took the full occupational history of each subject into account, allowing us to determine the risk of ALS with different measures of exposure, and we were able to adjust our analyses for possibly confounding lifestyle factors. Identification of the best metric for exposure assessment is complicated by the absence of an established mechanism whereby the exposures could affect motor neurons (1). Only for ELF-MF are there suggestions that exposure may increase levels of reactive oxygen species in human cells, and reactive oxygen species have been described repeatedly as playing a role in neurodegeneration (24).

Despite the application of the same protocol at all study centers, there was still heterogeneity in results. The main difference between the centers appeared to be the educational level of the controls and subsequently the prevalence of exposure.

Table 3. Characteristics of Participants in the Replication Case-Control Sample (PAN 2006–2009) in a Pooled Case-Control Study of Occupational Exposure to Electric Shocks and Extremely Low-Frequency Magnetic Fields and Risk of Amyotrophic Lateral Sclerosis, Euro-MOTOR Project, 2010–2015

Characteristic	Controls (n = 1,547)		ALS Cases (n = 443)	
	No.	%	No.	%
Male sex	931	60	277	63
Age at survey, years[a]	62.7 (10.0)		62.3 (10.7)	
Educational level (ISCED (20))				
ISCED 0–4	988	64	299	67
ISCED 5–6	559	36	144	33
Smoking status[b]				
Never smoker	516	33	148	33
Former smoker	777	50	194	44
Current smoker	254	16	101	23
Alcohol drinking[b]				
Never drinker	149	10	64	14
Former drinker	88	6	89	20
Current drinker	1,310	85	290	65
Site of disease onset				
Spinal			289	65
Bulbar			153	35
Generalized/unknown			1	0.2

Abbreviations: ALS, amyotrophic lateral sclerosis; Euro-MOTOR, European Multidisciplinary ALS Network Identification to Cure Motor Neurone Degeneration; ISCED, International Standard Classification of Education; PAN, Prospective ALS Study in the Netherlands.

[a] Values are expressed as mean (standard deviation).

[b] 3 years before survey.

In Italy, ever exposure to ELF-MF above background level varied from 25% among controls in the Lombardy region to 54% among controls in the Piedmont and Valle d'Aosta regions (Web Table 2). The same pattern was observed for electric shocks (Web Table 3). The observed heterogeneity may have been due to residual confounding by educational level. Another variable that varied between centers was alcohol consumption (Table 1), which may also explain some of the heterogeneity across centers.

On the whole, controls in our population had a higher educational level than the cases. Post hoc matching for sex, age, center, and education was applied to overcome this issue, resulting in similar findings overall, albeit with somewhat wider confidence intervals. The latter was also due to the decreased power of the post hoc analyses, since fewer cases were included ($n = 1{,}181$ vs. $n = 1{,}323$). The distributions of demographic characteristics and smoking and alcohol drinking habits were the same in both the full Euro-MOTOR population and the post hoc matched sample.

The observations in the PAN 2006–2009 sample support the findings for ELF-MF exposure in the Euro-MOTOR analyses. On the basis of the full pooled case-control analyses, however, the risk of ALS from electric shocks seemed to be more pronounced than the risk from ELF-MF, which was not replicated in the PAN 2006–2009 case-control study. The exposure profiles and population characteristics of the replication case-control sample (PAN 2006–2009) were similar to those of the Euro-MOTOR pooled case-control studies, except that the PAN 2006–2009 sample had a higher proportion of more highly educated subjects. Residual confounding by educational level may explain the observed differences is effect estimates, and the findings for electric shocks should therefore be interpreted with caution.

The higher risks in the younger age group (age <65 years) for both exposures may indicate that ELF-MF and electric shocks are more important in early-onset ALS than in late-onset ALS. Fischer at al. (10) also reported a higher risk for electric shocks among younger subjects, but not for ELF-MF. Another explanation might be that the higher risk estimates in the younger age group were due to residual confounding by age. More recent exposures may also be the more relevant exposures. The results for time since last exposure to either ELF-MF or electric shocks, however, did not support such an explanation (Tables 2 and 4).

We cannot rule out possible selection bias. Although the case-control samples appeared to be representative of the ALS populations in each country, patients with quickly progressing ALS may be less likely to participate in research studies than those with slower disease progression. Such bias, however, is not expected to have affected the directions of the observed associations of occupational exposure to ELF-MF and electric shocks with ALS.

Body mass index (weight (kg)/height (m)^2) has been associated with the risk of ALS (25), although the causal relationship remains unclear. Unfortunately, we were not able to test possible effects of premorbid body mass index on the observed associations, since this information was missing for a major part of the study population. We assume body mass index not to be strongly associated with exposures in our population because of the variety of occupations in which exposure to ELF-MF or electric shocks may occur, but we cannot rule out possible unmeasured confounding.

While we did see an increased risk of ALS for ever exposure to both ELF-MF and electric shocks in the Euro-MOTOR population, these observations might also be a proxy for another relevant exposure that is associated with the use of electricity—for example, imperceptible contact currents, nuisance shocks, or other chemical exposures. This might also explain why we did not see clear trends with duration of exposure or cumulative exposure. The observed association for electric shocks in our analyses persisted after additional adjustment for exposure to gases and fumes, metals, mineral dust, pesticides, and solvents, while the association for ELF-MF was attenuated. The possible role of other electricity-related exposures remains unclear.

A well-recognized limitation of case-control studies is possible recall bias. However, when using JEMs, exposure assessment is based on job titles, which are less prone to recall bias than self-reported exposures. By design, JEMs assign the same exposure estimate to all workers within a job category without taking into account variability between workplaces and individual workers. A JEM approach, however, has been shown to perform as well as case-by-case expert assessment, particularly in a multicenter study (26). Moreover, the misclassification of exposure will generally result in less precise risk estimates and is unlikely to have introduced false risks in our population.

Table 4. Risk of Amyotrophic Lateral Sclerosis Associated With Occupational Exposure to Electric Shocks and Extremely Low-Frequency Magnetic Fields Within the Replication Case-Control Sample (PAN 2006–2009), Euro-MOTOR Project, 2010–2015[a]

Exposure	Controls (n = 1,547)		Cases (n = 443)		Unadjusted for Other Exposure		Adjusted for Other Exposure	
	No.	%	No.	%	OR	95% CI	OR	95% CI
Extremely Low-Frequency Magnetic Fields								
Background level	882	57	237	53	1.00	Referent	1.00	Referent
Ever exposed above background level	665	43	206	47	1.08	0.86, 1.35	1.09	0.86, 1.37
Exposure level								
Background level	882	57	237	53	1.00	Referent	1.00	Referent
Medium level only	596	39	175	40	1.02	0.81, 1.29	1.05	0.82, 1.34
Ever exposed at high level	69	4	31	7	1.58	0.98, 2.53	1.71	1.04, 2.82
Duration of exposure, years								
Background	882	57	237	53	1.00	Referent	1.00	Referent
<5	154	10	52	12	1.24	0.86, 1.79	1.19	0.82, 1.73
5–11	139	9	46	10	1.08	0.74, 1.59	1.06	0.71, 1.56
12–30	177	11	62	14	1.27	0.90, 1.78	1.30	0.91, 1.85
>30	195	13	46	10	0.77	0.53, 1.13	0.82	0.55, 1.23
Continuous variable					0.996	0.987, 1.004	0.997	0.989, 1.006
Continuous variable (excluding the nonexposed)					0.986	0.974, 0.998	0.986	0.974, 0.999
Cumulative exposure, unit-years[b]								
Background level	882	57	237	53	1.00	Referent	1.00	Referent
<5	142	9	52	12	1.28	0.89, 1.85	1.21	0.83, 1.76
5–13	164	11	50	11	1.00	0.69, 1.45	0.99	0.68, 1.44
14–33	153	10	50	11	1.18	0.82, 1.69	1.18	0.81, 1.72
>33	200	13	54	12	0.91	0.63, 1.31	0.98	0.67, 1.44
Continuous variable					1.000	0.995, 1.005	1.001	0.995, 1.006
Continuous variable (excluding the nonexposed)					0.998	0.992, 1.005	0.999	0.992, 1.006
Time since last exposure, years								
Background level	882	57	237	53	1.00	Referent	1.00	Referent
3–4	241	16	58	13	0.82	0.58, 1.15	0.92	0.65, 1.30
5–17	175	11	48	11	0.93	0.64, 1.34	0.83	0.56, 1.22
18–38	146	9	54	12	1.29	0.89, 1.85	1.26	0.85, 1.86
>38	103	7	46	10	1.71	1.14, 2.56	1.65	1.09, 2.50
Continuous variable (excluding the nonexposed)					1.022[c]	1.011, 1.033	1.018	1.000, 1.037
Electric Shocks								
Background level	1,074	69	296	67	1.00	Referent	1.00	Referent
Ever exposed above background level	473	31	147	33	0.99	0.76, 1.29	0.97	0.73, 1.27
Exposure level								
Background level	1,074	69	296	67	1.00	Referent	1.00	Referent
Medium level only	198	13	65	15	1.07	0.77, 1.49	1.03	0.74, 1.44
Ever exposed at high level	275	18	82	19	0.92	0.66, 1.28	0.83	0.58, 1.18
Duration of exposure, years								
Background level	1,074	69	296	67	1.00	Referent	1.00	Referent
<6	91	6	37	8	1.34	0.88, 2.06	1.27	0.82, 1.97
6–16	99	6	38	9	1.15	0.75, 1.76	1.09	0.70, 1.69
17–37	138	9	38	9	0.81	0.75, 1.76	0.77	0.50, 1.20
>37	145	9	34	8	0.77	0.50, 1.19	0.84	0.53, 1.33
Continuous variable					0.994	0.986, 1.002	0.995	0.986, 1.004
Continuous variable (excluding the nonexposed)					0.988	0.976, 1.001	0.995	0.986, 1.004

Table continues

Table 4. Continued

Exposure	Controls (*n* = 1,547)		Cases (*n* = 443)		Unadjusted for Other Exposure		Adjusted for Other Exposure	
	No.	%	No.	%	OR	95% CI	OR	95% CI
Cumulative exposure, unit-years[b]								
Background	1,074	69	296	67	1.00	Referent	1.00	Referent
<9	95	6	42	10	1.40	0.93, 2.11	1.34	0.89, 2.04
9–29	81	5	30	7	1.11	0.69, 1.78	1.08	0.67, 1.75
30–70	116	7	24	5	0.65	0.40, 1.07	0.66	0.40, 1.09
>70	181	12	51	12	0.86	0.58, 1.26	0.85	0.56, 1.28
Continuous variable					0.999	0.997, 1.002	0.999	0.997, 1.002
Continuous variable (excluding the nonexposed)					0.999	0.996, 1.003	0.999	0.996, 1.003
Time since last exposure, years								
Background level	1,074	69	296	67	1.00	Referent	1.00	Referent
3–4	186	12	36	8	0.60	0.39, 0.91	0.62	0.40, 0.95
5–16	99	6	42	9	1.35	0.89, 2.06	1.45	0.93, 2.25
17–34	98	6	35	8	1.11	0.71, 1.74	1.02	0.63, 1.63
>34	90	6	34	8	1.24	0.80, 1.94	1.12	0.71, 1.77
Continuous variable (excluding the nonexposed)					1.020[c]	1.006, 1.034	1.006	0.987, 1.024

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; Euro-MOTOR, European Multidisciplinary ALS Network Identification to Cure Motor Neurone Degeneration; OR, odds ratio; PAN, Prospective ALS Study in the Netherlands.

[a] Logistic regression analysis. All models were adjusted for sex, age, education, smoking status, and alcohol drinking.

[b] Cumulative exposure is the product of duration and level of exposure.

[c] *P* for trend < 0.05.

Possible improvement in future exposure assessment for ELF-MF and electric shocks may be achieved by taking into account specific tasks (27). For the latter, however, more detailed information is needed than is usually available in general-population studies. Actual levels of exposure may also vary across countries due to different work practices, but because the occupations were categorized into "background," "medium," or "high" exposure to ELF-MF or electric shocks, jobs will have been ranked appropriately (17).

In conclusion, these results are supportive of possible independent associations of occupational exposure to ELF-MF and electric shocks with the risk of ALS.

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