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Occupational Exposure to Extremely Low-Frequency Magnetic Fields and the Risk of ALS: A Systematic Review and Meta-Analysis

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We performed a meta-analysis to examine associations of occupational exposure to extremely-low frequency magnetic fields (ELF-MF) with amyotrophic lateral sclerosis (ALS). Epidemiologic studies were identified in EMBASE and MEDLINE, in reference lists and a specialist database. We included studies that reported risk estimates of ALS in association with occupational ELF-MF exposure. Summary relative risks (RR) or odds ratios (OR) were obtained with random effect meta-analysis, and analyses were stratified by type of exposure assessment. This was done to evaluate whether observed heterogeneity between studies could be explained with differences in the way the exposure had been determined. We included 20 studies in our meta-analysis. Overall, studies reported a slightly increased risk of ALS in those exposed to higher levels of ELF-MF compared to lower levels with a summary RR (sRR) of 1.14 (95% Confidence Interval [CI] 1.00–1.30) and for workers in electrical occupations (sRR 1.41, CI 1.05–1.92), but with large heterogeneity between studies ($I^2 > 70\%$). Self-reported exposure or occupations determined from death certificates did not show increased risks. Highest-longest types of exposure translated into increased risks of ALS if the studies had evaluated the whole occupational history, in contrast to evaluating only few points in time (e.g., from census records); sRR were 1.89 (CI 1.31–2.73, I^2 0%) and 1.06 (CI 0.75–1.57, I^2 76%), respectively. In this meta-analysis, we observed an increased risk of ALS in workers occupationally exposed to ELF-MF. Results of studies depended on the quality of the exposure assessment. Bioelectromagnetics. 39:156–163, 2018. © 2018 Wiley Periodicals, Inc.

Keywords: amyotrophic lateral sclerosis; motor neuron disease; exposure assessment; electrical occupations; magnetic fields

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive motor neuron disease without cure. It has been estimated that the majority of cases (~90%) are sporadic, which implies that environmental factors might play an important role in the development of the disease. Understanding these risk factors could therefore provide opportunities for prevention.

ALS has been associated with occupational exposure to extremely-low frequency magnetic fields (ELF-MF) at work, as well as with work in "electrical occupations." The latter has been assumed to possibly represent risk of electrical shocks rather than magnetic field exposure. Previous reviews on the topic have concluded a slight but significant increased risk among jobs with relatively high ELF-MF exposure [Li and Sung, 2003; Hug et al., 2006; Kheifets et al., 2009; Zhou et al., 2012; Vergara et al., 2013]. Although an association with electrical work was observed, the reviews could not provide a conclusive answer as to whether ELF-MF increased the risk of ALS. All reviews highlighted the heterogeneity between the original studies and hypothesized methodologic differences between studies to cause this heterogeneity. Since the most recent systematic review, results from several new large studies from

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Sweden, Denmark, Switzerland, the United States, and the Netherlands have been published [Fischer et al., 2015; Huss et al., 2015; Vergara et al., 2015; Koeman et al., 2017; Pedersen et al., 2017].

We conducted a meta-analysis on the association between occupational exposure to ELF-MF and the risk of ALS, for which we updated the study base with the most recent studies. We explored if differences in encountered ELF-MF exposure levels or differing exposure assessment methods could explain the previously noted heterogeneity in study results.

METHODS

We searched publications in EMBASE and MEDLINE using the search words "neurodegenerative," "motor neuron disease," "amyotrophic lateral sclerosis" in combination with "electromagnetic," "electric," "magnetic," "EMF," "electrical," and "occupational," "occupation," "job," "work," "workplace," "worker," as well as "exposure" or "exposed." We additionally checked EMF-portal (www.emf-portal.org) using the outcome-related search terms listed above, and reference lists of previous reviews. We included peer-reviewed papers published in the English language until May 10, 2017 if they reported risk estimates of ALS in association with occupational exposure to ELF-MF or occupational titles grouped as "electrical workers."

In contrast to previous reviews, we excluded studies that reported risks by single, specific occupations, rather than groups of workers. We excluded such studies because single occupations might be associated with other occupational exposures, thus possible effects could not be disentangled from those of ELF-MF exposure. We also excluded studies that reported workers with specific occupational tasks (e.g., electrical plating) or where the level of ELF-MF exposure was unclear (e.g., when exposure to welding fumes was used as an indication for ELF-MF exposure). If several reports were published on the same study, we included the most recent one.

Data were extracted from the individual studies, and in case of doubt, discussed and questions resolved. If risk estimates were presented for more than two ELF-MF exposure levels (e.g., high vs. low and medium vs. low), we pooled risk estimates across all presented exposure categories (except the reference group), using a fixed-effects-within-study meta-analysis. In this way, we obtained a risk estimate for "any" exposure, named here "higher vs. lowest" exposure. In addition, we extracted risk estimates of the highest reported ELF-MF exposure category and the longest exposure duration ("highest-longest vs. lowest").

We preferred adjusted risk estimates over unadjusted ones. If authors reported results for both ELF-MF exposure and groups of electrical workers, we extracted both risk estimates and presented them separately. We used ELF-MF exposure that workers were reported to be exposed to, or we calculated exposure levels from other summary measures that were reported (usually from the cumulative exposure in microtesla [μT]-years divided by average number of years worked). Summary risk estimates were obtained with a random effects meta-analysis, and an I^2 value was calculated, which gives an indication of heterogeneity between the studies.

We conducted meta-analyses stratified by groups: (1) studies that provided quantitative estimates of ELF-MF exposure, and (2) results of "electrical workers." There is general consensus that reported occupation on death certificates is not sufficiently accurate to correctly assign exposure to ELF-MF. We therefore treated such studies as another separate group. Studies that relied on self-reported exposure were also separately analyzed, since it would be difficult for persons to know whether they had been exposed or not and to exclude possible reporting bias in case-control studies. We additionally explored whether higher ELF-MF exposure levels translated into higher risks, by presenting study results stratified by whether exposure levels were assigned based on a full occupational history (i.e., all occupations a person had) or on just a few points in time (e.g., from census data). We used meta-regression to assess whether higher ELF-MF exposure levels also translated into higher risks (as a linear effect), and tested if study results differed when exposure levels were assigned based on a full occupational history (i.e., all occupations a person had had) or on one to three points in time (e.g., at baseline) and whether the authors had evaluated mortality or incidence. Funnel plots were used to evaluate possible publication bias.

Analyses were performed in Stata (version 12; StataCorp, College Station, TX), using the "metan," "metareg," "metafunnel," and "metabias" commands.

RESULTS

We included 20 studies into our meta-analysis (Fig. 1). ALS patients were identified based on a physician's diagnosis in six studies (Table 1). The other 14 studies made use of the reported cause of death (International Classification of Disease (ICD): ICD-8 348, ICD-9 335.2, and ICD-10 G12.2).

A small increased risk emerged from studies evaluating ELF-MF exposure with a summary relative risk (sRR) of 1.14 (95% confidence interval [CI]

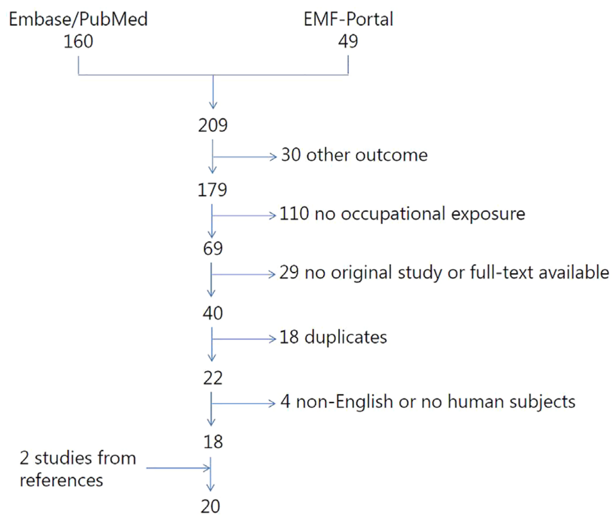

Fig. 1. Identification and selection of studies for the meta-analysis.

1.00–1.30) and electrical occupations with an sRR of 1.41 (95% CI 1.05–1.91), but heterogeneity between studies was high (75% and 70%, respectively; Fig. 2). Four studies evaluated both exposure to ELF-MF and electrical occupations, with inconsistent results. Two studies showed higher risks in electrical occupations compared with workers exposed to ELF-MF [Savitz et al., 1998b; Feychting et al., 2003], while in the other two studies it was the other way around [Fischer et al., 2015; Huss et al., 2015]. Neither studies with self-reported exposure nor studies that evaluated ELF-MF exposure assigned to occupations registered on death certificates provided evidence of increased risks. Within studies that evaluated ELF-MF exposure, slightly higher sRR estimates emerged among studies that evaluated the full occupational history compared to studies that evaluated exposure at one to three points in time: sRR of 1.19 (95% CI 1.03–1.37) and 1.08 (95% CI 0.90–1.29), respectively, shown in Supplementary Figure S1.

The funnel plot for all studies evaluating ELF-MF exposure was indicative of asymmetry (P-value from Egger test = 0.03). When limited to studies with full occupational histories, this was not the case (P-value from Egger test = 0.32) (Supplementary Fig. S2).

Observed risks were higher when evaluating the highest-longest ELF-MF exposure versus lowest, with an sRR of 1.38 (95% CI 1.01–1.89). Again, elevated risks were identified primarily among studies that evaluated the full occupational history, rather than studies that evaluated occupations at one to three points in time (e.g., from census information). The stratified analyses resulted in sRRs of 1.89 (95% CI 1.31–2.73) without heterogeneity between studies ($I^2 = 0\%$) among studies with full occupational histories, and 1.08 (95% CI 0.75–1.57, $I^2 = 76\%$) in studies with limited information (Fig. 3). Results were similar when stratifying by study population: studies performed in industrial cohorts (e.g., utility workers or train drivers) provided an sRR of 1.79 (95% CI 1.19–2.69, $I^2 = 0\%$) versus 1.20 (95% CI 0.81–1.77, $I^2 = 79\%$) in general population studies.

Meta-regression did not provide evidence for an increase of ALS risk with increasing exposure to ELF-MF ($P = 0.3$ for higher vs. lowest and 0.4 for highest-longest vs. lowest). P-values depending on whether the full occupational history was collected or not were 0.4 and 0.08, respectively. If the outcome was based on a physician's diagnosis compared with death certificates, then meta-regression resulted in P-values of 0.7 and 0.6, respectively. Three studies evaluated timing of exposure, with diverging results: two studies indicated higher risks of ALS for persons with exposures in the more distant past [Savitz et al., 1998b; Sorahan and Mohammed, 2014] and another study for more recent exposures [Roosli et al., 2007].

DISCUSSION

Our meta-analysis shows an elevated risk of ALS for persons occupationally exposed to ELF-MF, if studies evaluated the full occupational history.

A previous systematic review and meta-analysis by Vergara et al. [2013] concluded moderately increased risks for ALS in occupationally exposed workers, and noted considerable heterogeneity among studies that was at least partially attributed to methodologic differences. In our analysis, we were able to update this meta-analysis with five large studies. Interestingly, among studies that had been able to assess the full occupational history, no heterogeneity was observed, indicating that imprecision of exposure assessment may be driving previously noted differences among study results.

Exposure misclassification is of concern in nearly all presented studies. A variety of methods was used to assign exposure levels to job titles: measurements, exposure matrices, expert assessment, or a combination of the aforementioned. Given that absolute reported levels of ELF-MF exposure were assessed with different methods, the assigned levels may not be directly comparable across studies. For example, some studies assigned average exposure levels derived with measurements to occupational titles [Parlett et al., 2011; Koeman et al., 2017]. Others classified workers as

TABLE 1. Characteristics of Studies Included in the Meta-Analysis

Study	Design	Total N; number of cases	Outcome: source of information	Population	Exposure	Occupation: source of information	Time point of exposure assessment
Buckley et al. [1983]	Cohort	Unclear; 866 (17 electrical and electronics workers)	Death certificate	All deceased from England and Wales, 1959–1979	Electrical and electronics workers	Death certificate	Unclear
Davanipour et al. [1997]	Case-control	60; 28 (19 with any exposure to ELF-MF)	Physician diagnosis	Clinic-based cases in California (USA), blood and non-blood relatives as controls	Occupational ELF-MF, assigned by occupational hygienist	Interview/ questionnaire	Occupational history
Deapen and Henderson [1986]	Case-control	1,036; 518 (19 with electrically-related occupation)	Physician diagnosis	Cases via ALS society (USA), controls were neighbours, workmates or acquaintances of cases	Electrically related occupation	Interview/ questionnaire	Occupation three years prior to diagnosis
Fang et al. [2009]	Case-control	362; 109 (53 cases working with electronic or electrical machinery)	Physician diagnosis	Cases were from 2 major referral centres in New England, USA, general population controls	Self-reported exposure to electrical or electronic machinery	Interview/ questionnaire	Ever 10 times or more exposed
Feychting et al. [2003]	Cohort	4.8 million; 1,965 (334 exposed to levels >0.3 μT)	Death certificate	Swedish population	Occupational ELF-MF, exposure assigned with JEM	Census	Occupation at census
Fischer et al. [2015]	Case-control	28,044; 4,709 (2,438 with any ELF-MF exposure)	Physician diagnosis	Swedish population	Occupational ELF-MF, electric occupation	Census	Occupation at census
Gunnarsson et al. [1991]	Case-control	4,206; 1,961 (32 electricity workers)	Death certificate	Swedish population	Electric occupation	Census	Occupation at census
Gunnarsson et al. [1992]	Case-control	464; 92 (4 electricity work, 4 with self-reported ELF-MF exposure)	Physician diagnosis	Cases from departments of neurology and internal medicine in central- and south-Sweden, general population controls	Electric occupation, self-reported ELF-MF exposure	Interview/ questionnaire	Occupational history
Hakansson et al. [2003]	Cohort	646,694; 97 (82 with at least low ELF-MF exposure)	Death certificate	Industry cohort of Swedish industrial branches where welding could take place	Occupational ELF-MF, assigned with JEM	Census	Occupation at census
Huss et al. [2015]	Cohort	2.2 million workers; 1,091 (245 ELF-MF exposed cases, 20 electrical workers)	Death certificate	Swiss population	Occupational ELF-MF assigned with JEM, electrical work;	Census	Occupation at census
Koeman et al. [2017]	Case-cohort	4,344; 134 (78 exposed)	Death certificate	Dutch general population cohort	Occupational ELF-MF, assigned with JEM	Interview/ questionnaire	Occupational history
Noonan et al. [2002]	Case-control	1,560, 312 (197 with ELF-MF exposure, 19 electrical workers)	Death certificate	Deceased aged at least 60 years from Colorado (USA)	Occupational ELF-MF assigned with JEM, electrical occupations	Death certificate	Primary occupation
Park et al. [2005]	Case-control	2.4 million; 5,965 (N exposed cases not reported)	Death certificate	Deceased from 22 USA states	Occupational ELF-MF assigned with JEM	Death certificate	Primary occupation
Parlett et al. [2011]	Cohort	307,012; 40 (28 exposed)	Death certificate	National longitudinal mortality study based on census information, USA	Occupational ELF-MF assigned with JEM	Census	Occupation at census
Pedersen et al. [2017]	Cohort	32,006; 44 (29 exposed)	Physician diagnosis	Danish electric utility workers	Occupational ELF-MF, assigned with JEM	Occupational records	Occupational history
Roosli et al. [2007]	Cohort	20,141; 15 (12 in highest exposed jobs)	Death certificate	Swiss railway employees	Occupational ELF-MF assigned with JEM	Occupational records	Occupational history
Savitz et al. [1998a]	Cohort	193,905; 61 (44 exposed)	Death certificate	Electric utility workers (USA)	Occupational ELF-MF assigned with JEM	Occupational records	Occupational history
Savitz et al. [1998b]	Case-control	456; 114 (N exposed cases not reported)	Death certificate	Deceased that had occupational information on death certificate from 25 USA states	Electrical workers	Death certificate	Primary occupation

(*Continued*)

TABLE 1. (Continued)

Study	Design	Total N; number of cases	Outcome: source of information	Population	Exposure	Occupation: source of information	Time point of exposure assessment
Sorahan and Mohammed [2014]	Cohort	73,051; 86 (49 exposed)	Death certificate	Electricity generation and transmission workers (UK)	Occupational ELF-MF, assigned on job title and facility	Occupational records	Occupational history
Vergara et al. [2015]	Case-control	63,553; 5,886 (5,251 exposed)	Death certificate	Deceased between 1991 and 1999 in the USA	Occupational ELF-MF assigned with JEM	Death certificate	Primary occupation

ELF-MF, extremely low-frequency magnetic fields; JEM, job-exposure matrix.

"high" exposed if workers would likely experience average exposures above 1 μT or intermittent exposures above 10 μT [Davanipour et al., 1997]. Again another study assessed exposure levels based on occupation and location [Sorahan and Mohammed, 2014]. Our study base, however, was too small to explore the quality of the quantitative exposure assignment as a source of heterogeneity between studies.

Part of the studies had access to the full occupational history, while others investigated only one or a few jobs (e.g., the primary occupation on the death certificate or the occupation at the census). Within those studies that did not capture the full occupational history, the question arises in how far all relevant ELF-MF occupational exposures during the life course were evaluated. For example, a third of the population in a Swedish population-based study reported different occupations for their primary (the longest held job) and last occupation [Feychting et al., 1998]. A similar percentage of job changes was reported in a Swedish region between the censuses of 1960 and 1970 [Gunnarsson et al., 1991]. Exposure misclassification due to job changes would matter less if higher exposed workers were less likely to be changing jobs, which might be the case especially in those studies that restricted their population to specific industries or electrical occupations. For example, in the Swiss railway study, only 2–3% of train drivers and shunting yard engineers had changed their job during almost a decade [Roosli et al., 2007]. In the Danish utility worker study, only about 1% of workers had changed occupation over the assessed period [Pedersen et al., 2017]. This could be the underlying reason why studies performed in industry cohorts and studies that evaluated the full occupational history identified elevated risks of ALS among workers exposed to ELF-MF.

Initial interest in the association between ALS and exposure to ELF-MF developed from the question of whether people who experience electrical trauma are at increased risk of the disease. In line with this question, most previous reviews have stressed that the increased risk of ALS in "electrical occupations" could also be due to electric shocks and not necessarily to magnetic field exposure. Electric shocks, however, occur by accident. Recently, attempts were made to identify occupations where workers are at higher risk of electric shock, using registered occupational electrical injuries. One of these studies reported a high concordance (67%)

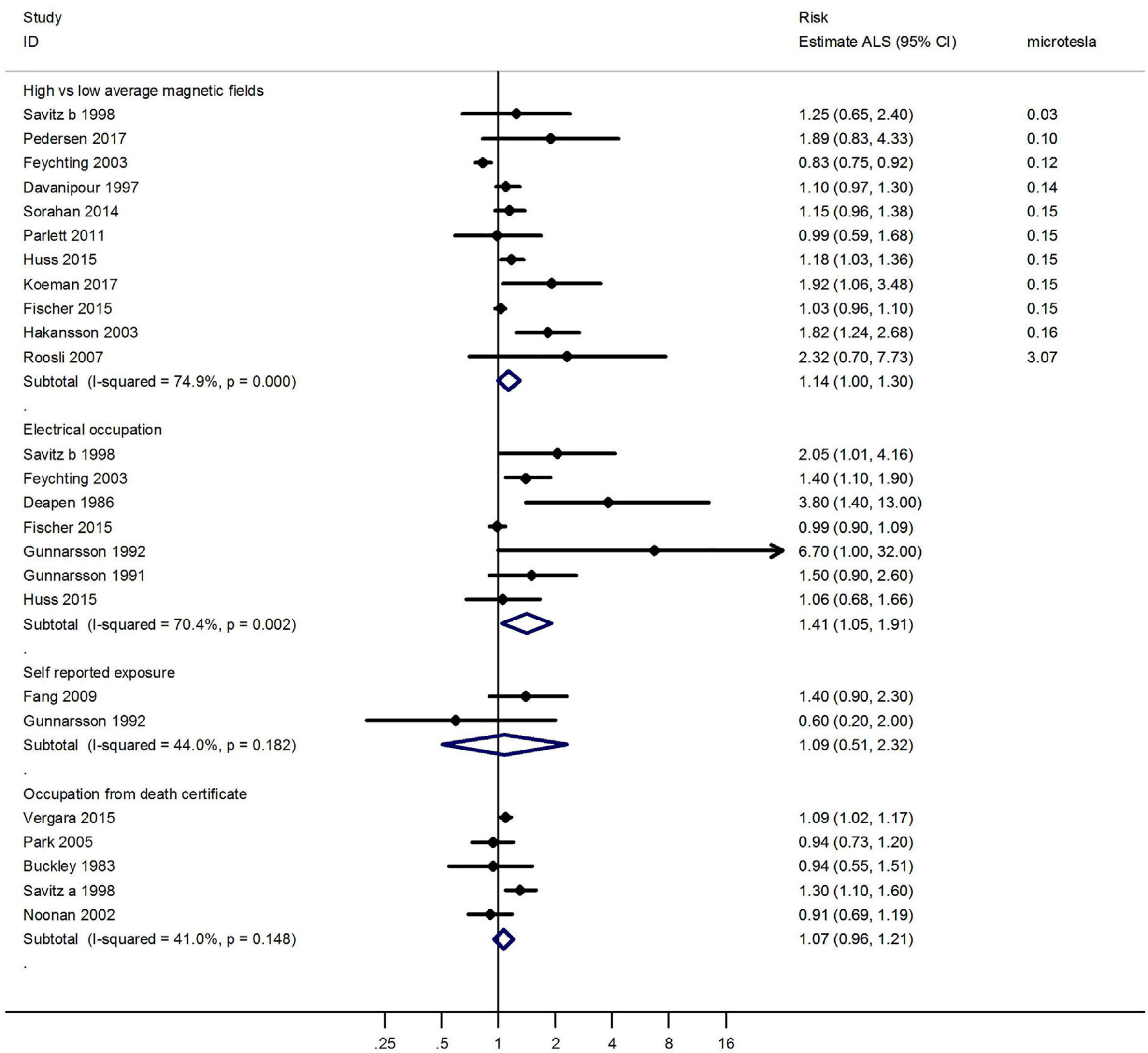

Fig. 2. Occupational exposure to ELF-MF or electrical occupation and the risk of ALS (microtesla indicates the minimum level that was considered exposed).

for occupations at high risk of electrical injury and exposure to ELF-MF, indicating that it may be difficult to disentangle these two exposures [Huss et al., 2013].

A Danish study assessed neurological diseases in a cohort of workers who had survived electrical injuries, and observed increased risks for some conditions such as migraine or vertigo [Grell et al., 2012]. However, ELF-MF exposures for these workers were not taken into account. In addition, workers in electrical occupations will also likely be exposed to other factors associated with the use of electricity, such as electric fields, imperceptible contact currents, nuisance shocks, or other chemical exposures [Bracken et al., 2009]. These exposures, however, have not yet been covered in most epidemiological studies. Application of a "shock-JEM" (a job-exposure matrix for electric shocks) in addition to the assessment of ELF-MF exposure did not provide clear evidence for or against an effect of shocks on ALS [Fischer et al., 2015; Huss et al., 2015; Koeman et al., 2017]. The study by Koeman et al. [2017], where chemical exposures were taken into account, in addition to ELF-MF and shocks, pointed toward an independent effect of ELF-MF that could not be explained by other exposures.

The assessment of the disease outcome also differed between the studies. Some studies used a physician's diagnosis (ALS incidence), whereas others used information provided on death certificates (ALS mortality). ALS is likely to be reasonably well-captured on death certificates. Accordingly, our study

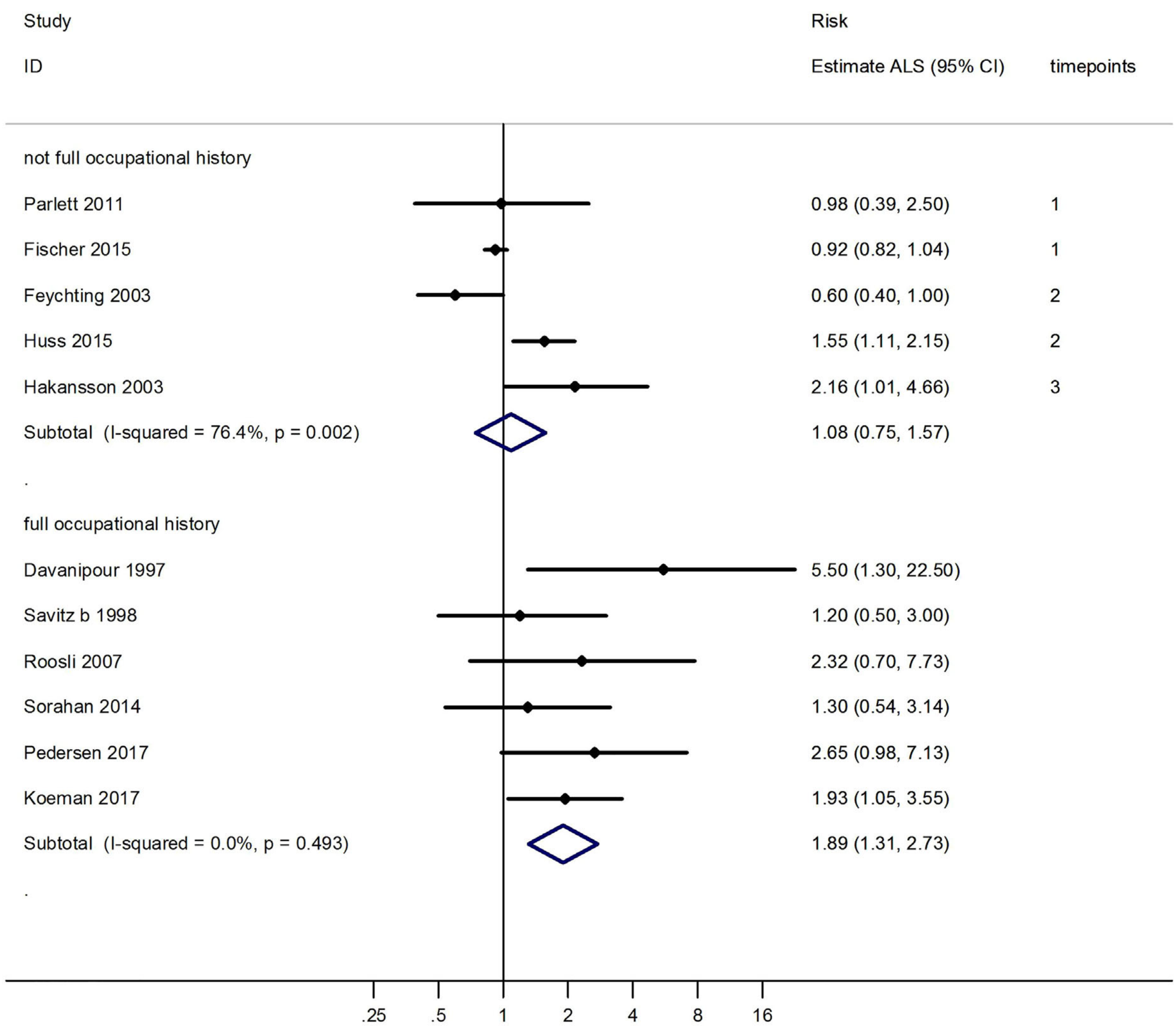

Fig. 3. Highest-longest occupational exposure to ELF-MF and the risk of ALS, stratified by full or non-full occupational history (time points indicate the number of points in time that occupations were recorded per subject).

provided no evidence that results differed significantly depending on whether the outcome was assessed from death certificates or not.

In conclusion, in our meta-analysis we observed elevated risks of ALS for persons employed in electrical occupations and occupationally exposed to ELF-MF. Increased risks due to ELF-MF exposure emerged from studies that were able to evaluate only the full occupational history. Studies that evaluate self-reported exposure or assign exposure levels based on occupations that were extracted from death certificates appear to be non-informative and should be excluded from future meta-analyses. Moreover, future studies should improve on ELF-MF exposure assessment, in particular on quantitative measures of exposure, including duration of exposure. Temporal effects of exposure should be evaluated in order to identify etiologically relevant time windows. Whether ELF-MF are the relevant exposure, or whether they are just a proxy for another, more important exposure (e.g., electrical injuries), remains an open research question.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.