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Work related etiology of amyotrophic lateral sclerosis (ALS): a meta-analysis

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Parole chiave: Sclerosi laterale amiotrofica, prodotti chimici organici, lavoratori, pesticidi, ELF-EMF

Abstract

Background. *The aim of this meta-analysis was to evaluate the association between ALS and occupational exposure to physical (ELF-EMF) and chemicals (solvents, heavy metals and pesticides) agents.*

Methods. *We considered articles published from 1980 up to April 2013; in total, 750 publications were evaluated. The studies had to satisfy the following criteria: 1) cohort or case-control studies; 2) the presence of individual exposures; 3) clinical diagnosis of sporadic ALS or sporadic ALS on the death certificate. We followed the evaluation of quality in two steps. The first step classified studies according to a rating system based on a mix of criteria developed by scientific organizations, especially developed for studies of risk factors for ALS. The ratings obtained range from I (highest) to V (lowest). The data on risk factors derived from studies with Armon ratings of I, II, and III can reach levels of evidence A (established risk factor), B (likely risk factor), or C (possible risk factor). The second step evaluated the exposure and a score from 1 to 4 was assigned to each item; an exposure with a score of 3 or 4 was considered sufficient. Different analyses were performed on ALS and exposure to metals, solvents, pesticides and electromagnetic fields. In our study the heterogeneity was assessed both by* χ^2*-based Q-tests and through the index of inconsistency* I^2 *while the measure RR/OR and CI of 95% to estimate the relationship between ALS and the various considered risk factors was employed.*

Results. *The association between exposure to pesticides and ALS as a whole is weak and not significant. With regard to the results of individual studies the following critical synthesis can be reported: 1) the selected studies showed a low level of association between ALS and electromagnetic fields; 2) as regards the solvents, the association with ALS in some studies is combined with a slightly increased risk, particularly in women, and in others a slight but significant linear association is observed; 3) for the metals, in some cases there was a stronger association in women than in men; for individual metals, there was an association especially with chromium and lead; 4) lastly, with regard to the products of agricultural pesticides in general, there was an association with ALS in men but not in women, with a dose-response relationship.*

Conclusions. *The lack of statistically significant association between occupational exposure and ALS is mainly due to the methodological diversity of the studies and the lack of prospective studies at the workplace.*

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Introduction

Under the generic name of motor neuron disease (MND) we include a set of heterogeneous disorders that recognize, as an element in common, the existence of a degenerative process of the nerve pathways related to motor neurons in the primary motor cortex and in the cortico-bulbar and cortico-spinal tracts. Clinical outcomes are represented by a progressive deterioration in the level of specific muscle groups to complete immobility. The clinical paradigm of MND is represented by amyotrophic lateral sclerosis (ALS), so that the MNDs are often designated with the dual definition of motor neuron disease/amyotrophic lateral sclerosis (MND/ALS). ALS is a progressive neurodegenerative disease of adulthood that is part of the group of disorders known as motor neuron disease; it is also known as Charcot's disease (named after the French neurologist who described it for the first time in 1860).

ALS is a rare disease and, in almost all cases, sporadic: in 90% of cases, ALS patients show no evidence in their medical history of other cases of illness in the family and are called sporadic cases.

Its incidence is fairly homogeneous and it occurs, in Europe and North America, at 1.7-2.3 cases per 100,000 individuals per year and its prevalence in Western countries is estimated at between 2.7 and 7.4 cases per 100,000 individuals (1, 2). In Italy the incidence of ALS is approximately 2–3 cases out of 100,000 per year, with a prevalence of approximately 7 cases per 100,000 (3).

The cause of ALS is mostly unknown, although some genetic risk factors have been identified. With regard to environmental factors, some recent literature reviews have found no significant associations between individual factors and the development of ALS. Most of the authors hypothesized a complex genetic-environmental interaction as a causal factor in the degeneration of motor neurons (4).

A growing number of working and environmental factors, causes of diseases (5-12) or early changes (13-19), were proposed over the years, but at present it has not been possible to establish any definitive causal link. (20-24). The more constant associations are exposure to pesticides, heavy metals including lead and mercury, heavy physical activity including professional football, head trauma, cigarette smoking and exposure to electromagnetic fields EMF-ELF (25). Most of the reviews on exposure to chemical and physical agents are narrative or semi-systematic (26, 27). To evaluate the existing evidence that occupational exposure to physical (ELF-EMF) and chemicals (solvents, heavy metals and pesticides) agents increases the risk of developing ALS, we performed a meta-analysis study, paying particular attention to the evaluation of exposures.

Materials and methods

Bibliographic search

We conducted a systematic search of peer-reviewed articles on the relations between occupational exposures and ALS, published in the scientific literature from 1980 until April 2013. The research was performed through the search engines databases PUBMED, EMBASE, CINAHL, and Cochrane.

The search string was made up of a combination of medical subject headings [MeSH] and words of text. The search terms for ALS, included "motor neuron disease", "motor neuron diseases", "amyotrophic lateral sclerosis", "progressive spinal muscular atrophy", "motor neuropathy", and ''motor neuropathies''. These terms were combined with boolean characters and with those relating to occupational exposures: workers, job, occupation, workplace exposure, work-related exposure, chemical, uses of specialty chemicals, organic chemicals, inorganic chemicals, toxic actions, pesticide(s), fungicide, herbicide, insecticide, solvent(s), benzene, styrene, glue, ethanol, ketone, toluene, xylene, metal(s), heavy metal(s), lead, mercury, arsenic, manganese, magnesium, aluminium, cadmium, nickel, welding, electromagnetic fields, electromagnetic, magnetic field, electric field, extremely low-frequency ELF, ELF-EMF, EMF.

Additional studies were identified by a manual search of the references in the original studies or related reviews.

In total, 750 publications were identified (PUBMED 413, EMBASE 298, CINAHL 15, Cochrane 24). After the elimination of duplicates, all items were selected on the basis of the criteria listed below.

The publications were divided according to the field of interest: electromagnetic fields, solvents, metals and pesticides.

Selection Criteria

Studies, selected by two independent reviewers, had to satisfy the following criteria:

1) Cohort studies or case-control, experimental group composed of subjects occupationally exposed to the factors considered, the control group composed of non-exposed subjects;

2) The presence of single exposures: chemicals, pesticides, metals or ELF-EMF;

3) Clinical diagnosis of sporadic ALS or sporadic ALS on the death certificate (the studies conducted in Guam, Kii peninsula and other endemic areas were excluded);

4) Articles written in either English or Italian were considered.

Articles without data on prevalence, mortality or incidence of the disease, reviews, articles concerning laboratory animals or in vitro studies, clinical applications, studies, epidemiological studies of residential exposure, were also excluded. The authors of the publications for which the results were incomplete or could not be used because they were not expressed in a numerical form but only graphics were contacted in order to request and obtain, if available, the missing data.

The abstracts and subsequently the full texts of the remaining articles were assessed by two independent reviewers according to the evaluation of the quality specified.

Assessment of Study Quality

We followed the evaluation of quality suggested by Sutedja et al. (23), which includes two steps: the first classifies the studies selected and assesses them according to a rating system based on a mix of criteria developed by scientific organizations, in particular by the American Academy of Neurology, and developed specifically for the study of risk factors for ALS (26). This classification system consists of general methodological criteria (selection of the control group, high response rate, blinding, recall bias, quantification of exposure, confounding and bias, and appropriate analytical approach) and some specific criteria for ALS (ALS diagnosis in accordance with the criteria established, and previous exposure to the likely occurrence of organic disease). The ratings obtained vary from I (highest) to V (lowest). The data on risk factors derived from studies with Armon ratings of I, II, and III can reach levels of evidence A (established risk factor), B (likely risk factor), or C (possible risk factor). Studies with a rating of IV or V can result only in "unknown risk factor". The evaluation was performed independently by two reviewers. In the case of disagreement a brief exchange of views might achieve consensus but if this was not possible, a third reviewer was consulted.

The Armon criteria do not include exposure assessment, which is taken into account in the second step. The criteria used reflect current knowledge of the accuracy and reproducibility of the different approaches to exposure assessment and their potential as bias. The studies were distinguished according to the data: self-reported exposure, self-reported work tasks, exposure assessed in the workplace, information on the activities/work tasks included in medical records and risk or equivalent, deaths from exposure, environmental and biological monitoring.

A score from 1 to 4 was assigned to the various items. Studies with a score of 1 are considered low-explanatory; they include: 1) self-reported exposure, (differential non-responder bias), 2) job registry; 3) self-referential working history in the presence of objective documents. Studies with a score of 2 are classified as inaccurate and include: 1) self-reported work history (with or without mention of specific tasks) (non-responder bias differential although to a lesser extent with respect to self-reported exposures); 2) individual monitorings, (classification bias because of the temporal variability or intra-individual in the case of a biomarker). The measurement of biomarkers of exposure without external exposure information may provide inaccurate information, as an increase in the internal levels may be due to other sources or, in the case of metals, internal degenerative processes rather than external exposure. Studies with a score of 3 are deemed reliable but not agent-specific; work histories drawn from company documents are often accurate, but do not necessarily have a connection with occupational exposures.

The results of the exposure assessment are considered accurate and agent-specific and they reach a score of 4: 1) the working exposure matrix that allows the connection of occupations to profiles of environmental exposures by providing assessments (semi-) quantitative of exposure for each occupation; the quality is dependent on the quality of the work history and the assignment to a certain level may result in misclassification of exposure for individuals; 2) the case by case evaluation by experts; 3) the repeated sampling of biomarkers or environmental monitoring is agent-specific and will result in a minor underestimation of a dose-response relationship because of the reduced influence of temporal variability or intra-individual.

We included studies that meet both the methodological criteria and those of exposure. The studies were classified as evaluations of levels I, II, III or IV, according to the classification system of Armon et al. (26). The exposure assessment was considered sufficient if it reported a score of 3 or 4.

Different evaluations to understand the relationship between ALS and exposure to metals, solvents, pesticides and electromagnetic fields have been carried out.

Statistical Analysis

For each analysis, the calculation of the heterogeneity between studies was carried out (28). The most common test to assess heterogeneity is the χ^2 test. Under the assumption that the estimated effect of the treatment is the same (homogeneity between the estimates of the individual studies included in the analysis), or that the variability found between the results of individual studies are purely random, this test provides the difference between the observed and expected results. A high difference indicates it is unlikely that the effect of treatment is the same in all studies, a minor difference is instead indicative of random differences. In our study heterogeneity was assessed by χ^2-based Q-tests and through the computation of Higgins et al.'s index of heterogeneity or inconsistency index I^2, which measures the proportion of inconsistency of the individual studies that cannot be explained by sampling error. If the χ^2 test was significant ($p < 0.05$), heterogeneity was considered significant. The values of I^2 vary between 0% and 100%, with values of 25%, 50% and 75% respectively indicating low, moderate and high heterogeneity. To estimate the relationship between ALS and the various risk factors considered, measurement of the risk ratio

(RR), odds ratio (OR) and 95% confidence interval was employed; if the value of heterogeneity was not significant, the fixed-effect model was used for the analysis, otherwise, if the I^2 values were moderate to high, the random-effect model was applied.

Due to the heterogeneity of studies, it was not possible to perform a formal meta-analysis for some risk factors; in this case, for each study the estimated risk and the corresponding confidence intervals were indicated.

Results

Electromagnetic fields

Among the 89 articles initially selected after removing duplicates, 22 were identified as eligible for meta-analysis; 28.3% of the studies examined the prevalence and approximately 61.9% examined mortality. Exposure metering was performed in only two studies. The measure of exposure is

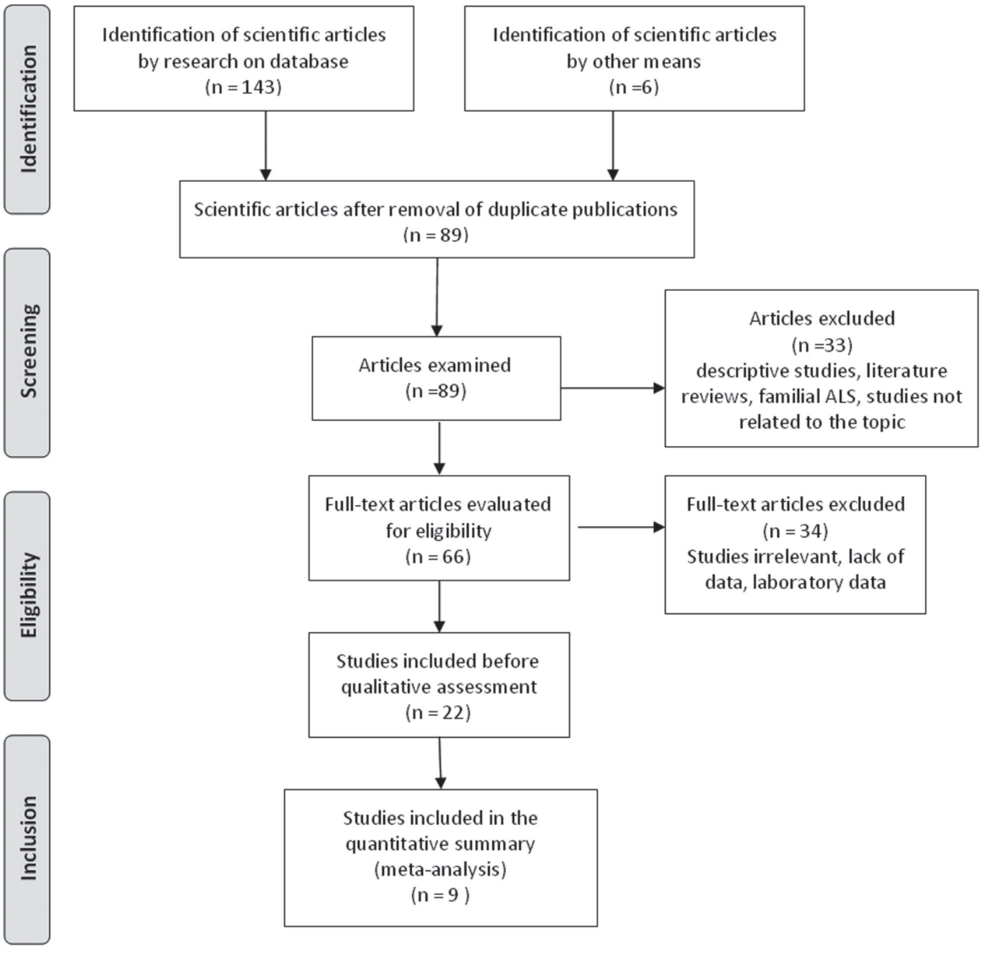

Fig. 1 – Flow diagram on EMF

defined in the other six cases according to a matrix of exposure, in one case it is based on evaluation by a hygienist and in eleven cases, according to the task. Among the latter, after the qualitative assessment previously described, nine were included in the meta-analysis (29-37) (Fig. 1).

In excluded studies (20, 23, 38-48) assessment of the exposure was made exclusively through the task, reported by the worker or derived from death certificates.

The nine included studies were case-control (n = 6) or cohort studies (n = 9) kind. The first study was published in 1998 and the most recent in 2011; five studies came from the USA and four from Europe, including Switzerland. All studies included covariants such as age and sex, and in some cases, socio-economic or educational level.

Among the included studies, seven surveys took into consideration the mortality, one study has considered the prevalence, and one survey has examined the incidence. Six studies evaluated exposure by JEM (job exposure matrix), two included the effective measurement of exposure and one was based on the assessment by an industrial hygienist.

The calculation of the χ^2 and I^2, shows a low heterogeneity (Fig. 2) for which the quantitative evaluation was performed using a fixed-effect model: the RR was equal to 1.33 CI (0.67, 4.14) showing a low level of association.

Therefore, we considered studies in which the measurement was performed; the calculation of χ^2 and I^2 shows an increase of heterogeneity (Fig. 3) that is close to the band of moderate heterogeneity for which the quantitative evaluation was performed with the random-effect model: the RR shows only a modest increase of 1.6 (95% CI 0.59–5.34).

Chemical agents

Solvents

Among the 79 papers initially selected after removing duplicates, 3 were identified as eligible for the meta-analysis after their qualitative assessment (Fig. 4). However, for uniformity we have included only the two case-control studies.

The three included studies are briefly described. The first (20), a case-control study based on the population, was conducted in three counties in the State of Washington to assess the associations between occupational exposures and risk of amyotrophic lateral sclerosis (ALS). The ALS cases (n = 174) were diagnosed by neurologists between 1990 and 1994 and controls (n = 348), matched by age (± 5 years) and sex, were identified through random generation of numbers [random digit dialling (RDD)] or the register of Medicare. The exposures were evaluated in a blinded fashion by a panel

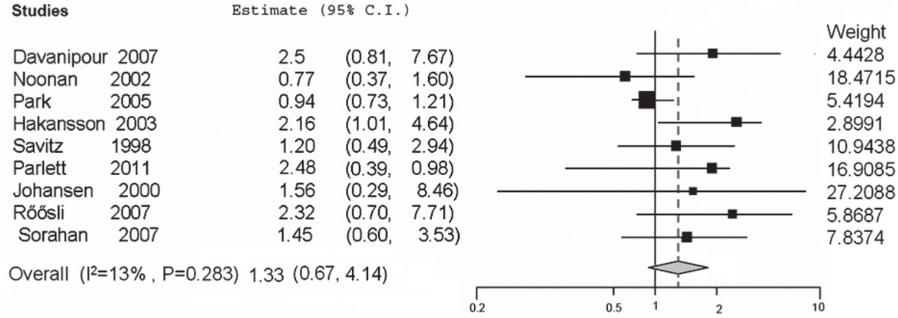

Fig. 2 - Forest Plot on the exposure to ELF and ALS

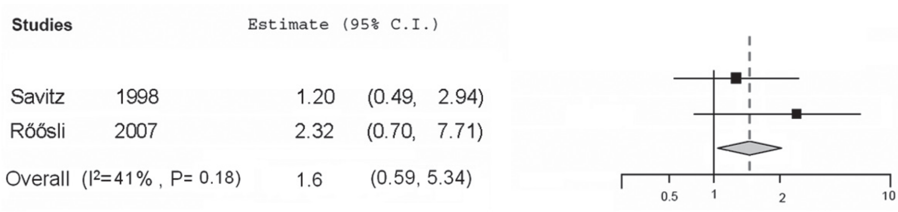

Fig. 3 - Forest Plot on the exposure to ELF and ALS after JEM exclusion

of four industrial hygienists. Comparisons between cases and controls were made for exposures that occurred after 15 years of age and at least 10 years prior to the date of diagnosis.

The association between exposure and ALS was not significant both in sexes taken together: OR 1.2 (95% CI 0.8-1.9) and separately (men OR 1.3, 95% CI 0.7-2.3; women OR 1.1, 95% CI 0.6-2.2). We point out that the same assessments performed for data on exposures, self-reported by the workers, were associated with a slightly increased risk of ALS (OR = 1.6, 95% CI 1.1-2.5),

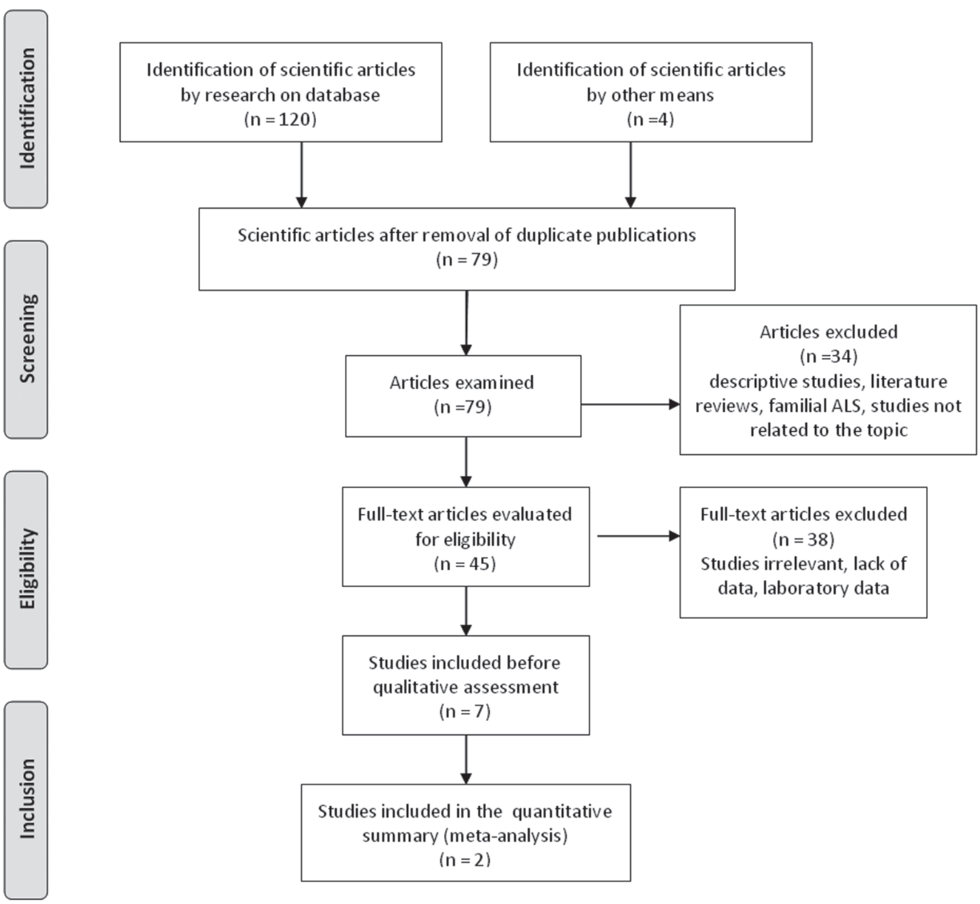

Figure 4 - Flow diagram on solvent

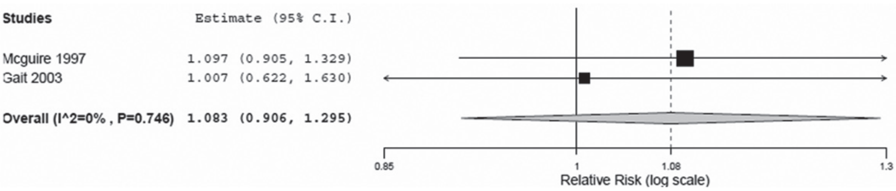

Fig. 5 - Forest plot on the exposures to solvents and ALS

determined in particular by the risk in women (OR = 2.4, 95% CI 1.3-4.3), but not in men (OR = 1.1, 95% CI 0.6-2.1).

The second study of Gait et al. (49), also a case-control type, used death certificates of 22,526 employees in the archives and pension funds of an engineering company in the UK. The deaths occurred between 1967 and 1997; the study included 228 male subjects: 22 cases of MND and 206 controls. Occupational exposure was assessed in a blinded fashion, by an industrial hygienist on the basis of the company's business data. The exposure was coded qualitatively as present or absent, and where possible, the durations of exposure were summed to provide the total exposure for each individual. The level of exposure was coded as high, low or not present. Only 10 cases (46%) and 93 controls (45%) were exposed to solvents with no evidence of increased risk of death from MND (OR = 1.12 95% CI 0.45-2.78) after adjustment for age and place of work. Even taking into account the duration of exposure, any increase in mortality was not possible to show (0.01-10 years OR 1.44, 95% CI 0:48-4:30; 10-20 years OR = 0.89, 95% CI 0:18-4:37; > 20 years OR = 0.99, 95% CI 0:19-5:02).

Park et al., (31) in a cohort study about neurodegenerative diseases and work, examined the mortality odds ratio (MOR) through the examination of death certificates in 2,614,346 workers in 22 US states between 1992 and 1998, finding 6,347 deaths ascribed to ALS-MND. The index of exposure to solvents was modelled in the logistic regression as a continuous variable that assumes discrete values as 0-9. The total exposed to solvents among cases of ALS-MND was 1,194, whereas in the category of maximum exposure it was possible to observe a slight but significant linear association (MOR 1.16, 95% CI 1:01-1:34).

In the meta-analysis the two case-control studies were included (20, 49). For the low heterogeneity observed, the quantitative evaluation was performed by the binary fixed-effects method (Het. p-value 0.746, I^2 0%). These results included 62 events out of 196 cases and 213 controls with 554 events on RR of 1.083 (95% CI 0.91-1.3). Figure 5 shows the relative forest plot which visually confirms the lack of association. After quality assessment, six were excluded from the meta-analysis (22, 39, 41, 50-51).

Metals

Among the 93 papers initially selected after removing duplicates, two were identified as eligible after the qualitative assessment (Fig. 6) so they were included in the meta-analysis.

The two studies considered are those previously described by McGuire et al. (20), and Gait et al. (49). With regard to self-reported exposure to metals, McGuire indicates an association between ALS and exposure to metals with OR 1.6 (95% CI 1-2.5). Considering the two sexes separately, the association was more significant in women OR 2.3 (95% CI 1.1-4.7) than in men (OR 1.2, 95% CI 0.7-2.1). Considering the individual metals, always self-reported exposure, there was an

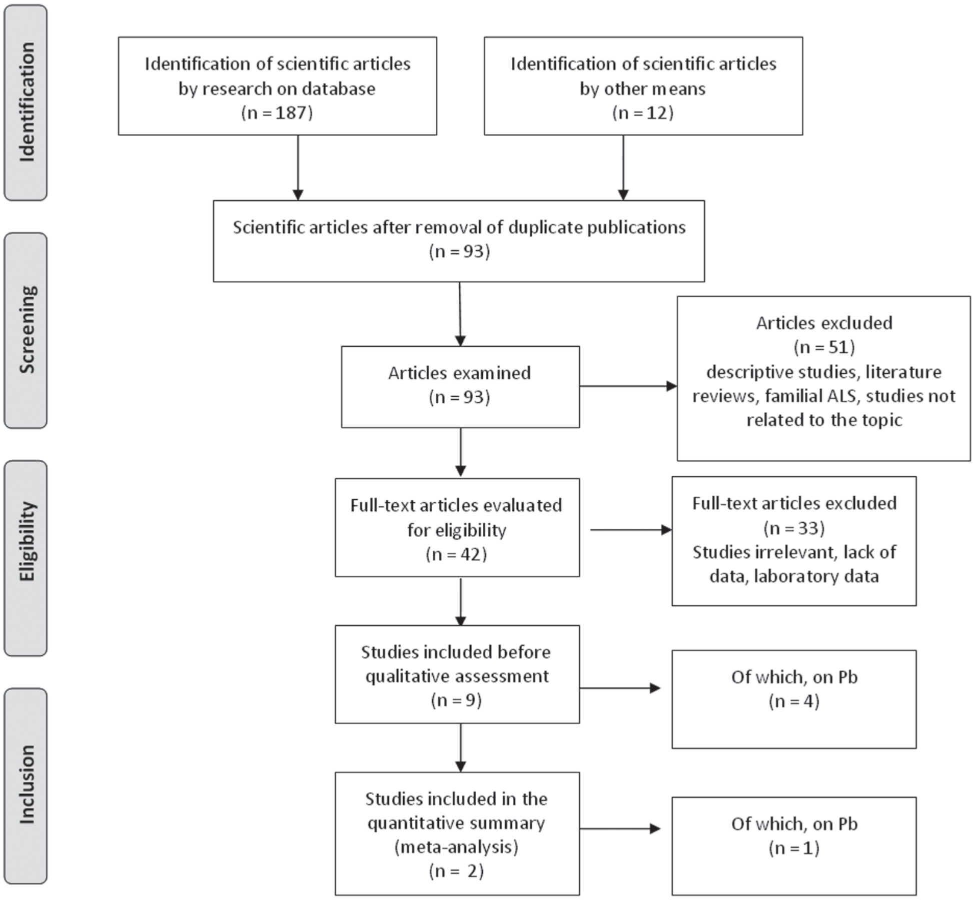

Fig. 6 - Flow diagram on metals

association for chromium (OR = 2.5, 95% CI 1.0-6.7) and lead (OR = 1.9, 95% CI 1.0-3.6). The exposure to Pb also including lead paint and leaded gasoline vapours was also considered; the overall assessment of the two studies shows an association between exposure and ALS (OR = 1.6, 95% CI 1.04-2.5 95), with no differences between the sexes. There was a dose-response relationship: low exposure OR 1.0 (95% CI 0.5-1.8) and high exposure OR 2.4 (95% CI 1.4-4.1) (p-trend = 0.001), with a similar trend for both men and women.

However, if we consider the results based on the evaluation of the expert panel, the association between ALS and exposure to metals is poor (OR = 1.2, 95% CI 0.8-1.9), even considering the sexes separately; the OR associated with any lead exposure was 1.2 (95% CI 0.7-2.0) without any dose-response relationship.

The study of Gait et al. (49) showed a total of 13 (59%) cases exposed to metals compared to 131 (64%) controls with OR = 0.88, 95% CI 0.35-2.22), no relationship between MND and duration or extent of exposure, even the 37 workers with higher exposure were in the control group. When it relates to the meta-analysis, considering the low heterogeneity the binary fixed-effect model was used. Heterogeneity Q (df = 8) Het. p-value I^2 1.154 0.283 13%

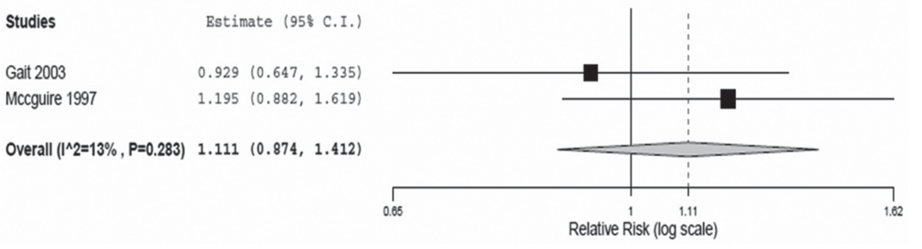

Fig. 7 - Forest plot on the exposure to metals and ALS

In the meta-analysis, 62 events on 196 cases and 213 controls on 554 events were included with a RR = 1.11 (95% CI 0.874-1.412). Figure 7 shows the forest plot which confirms the lack of association between exposure to metals and ALS.

After quality assessment, seven were excluded from the meta-analysis (38, 39, 50-54).

Pesticides

Among 107 papers selected after removing duplicates, two were identified as eligible for the meta-analysis after the qualitative assessment (Fig. 8). After quality assessment, fifteen were excluded from the meta-analysis (21, 22, 38, 39, 41, 50-53, 55-60). The two included studies are briefly illustrated.

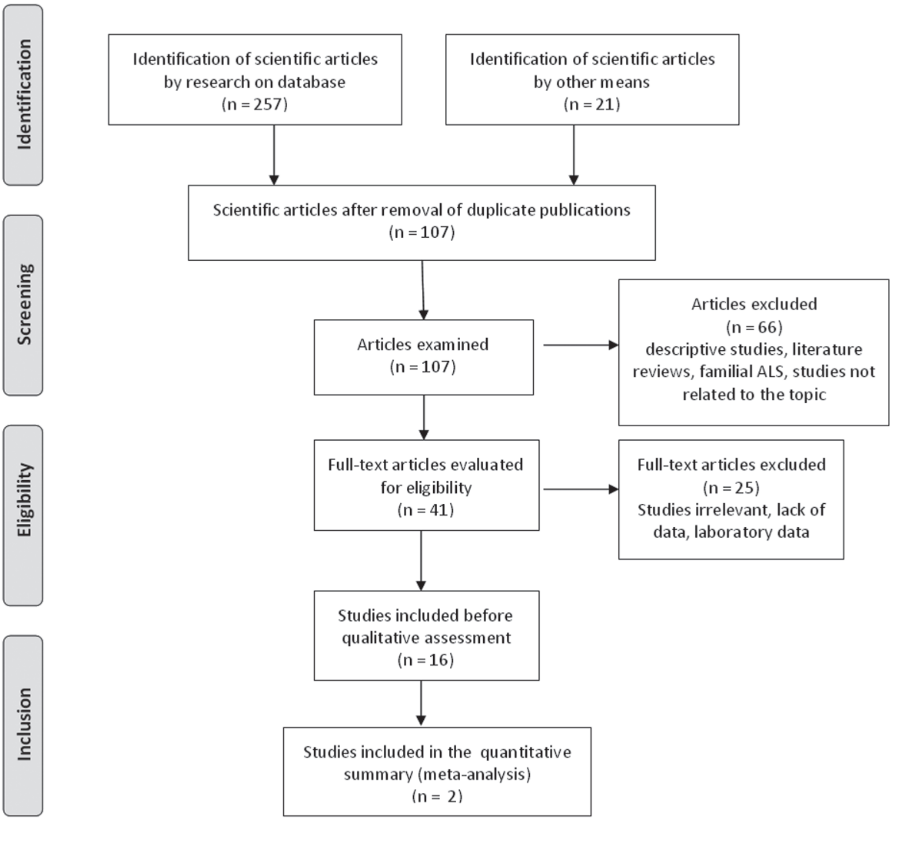

Fig. 8 - Flow diagram on pestecides

The first study is that of McGuire et al. (20) previously described. With regard to the relationship between exposure to pesticides and ALS, the study examined different exposure categories: agricultural chemicals in general, fertilizers, and pesticides. The exposures were assessed jointly and separately in both sexes, in the two modes and a self-report assessment by a panel of experts. They also considered exposures outside of work.

Considering the self-reported exposure to agricultural chemicals in general, there was an association with ALS in men (OR = 2.1, 95% CI 1.1-3.8), but not in women (OR = 0.8, 95 % CI 0.3-2.4), with a dose-response (p = 0.02). In men, the comparison between the groups not exposed to low exposure shows OR = 1.5 (95% CI 0.6-4.1), and between non-exposed to high exposure, OR = 2.7 (95% Cl 1.3-5.7). The self-reported exposure to the individual groups of agricultural chemicals is not associated with an increased risk of ALS.

On the basis of the panel's assessment, the exposure to agricultural chemicals is associated with ALS limited to men (OR = 2.4, 95% CI 1.2-4.8) (women OR = 0.9, 95% CI 0.2-3.8) with the presence of a dose response (p = 0.03).

The exposure to fertilizers was then examined, and pesticides considered both globally and in subgroups as herbicides, fungicides, insecticides and other pesticides. On the basis of the assessments made by the panel, we found a slight association for fertilizers (OR = 1.4, 95% CI 0.7-2.3) and herbicides (OR = 1.7, 95% CI 0.7-3.9) in men with no significant dose-response relations. The association between exposure to pesticides and ALS as a whole is significant (OR 2.5, 95% CI 1.2-5.1, p = 0.02) as well as that between exposure to pesticides and ALS (OR 2.5, 95% CI 1.2-5.3, p = 0.05).

The associations between exposure to agricultural chemicals in the home, the workplace, and in both places from the age of 15 years of age at the date of commencement of the study, were also examined. Each type considered was compared with the data of the non-exposed. The highest relative risk was associated with work and non-work combined exposure to agricultural chemicals, with a significant trend in both sexes combined (OR 3.5, 95% CI 1.6-7.8, p = 0.04) and slightly above the limit only for men (OR 3.8, 95% CI 1.4-10.1, p = 0.06). Considering the relationship between exposure and age there was a higher risk for exposures that occurred in the interval between 22 and 32 years.

The qualitative evaluation was excluded from the assessment of the study cohort of Kamel et al. (60) conducted in Iowa and North Carolina. The cohort was recruited from the years 1993-1997 (61) and it includes 52,394 users of agricultural pesticides and 32,345 of their spouses. 97% of users were men and 99% were married women. The inclusion in the study was based on a survey of the clinical case history. Mortality data are those available for the cohort until 7 February, 2010 from the state data and the National Death Index. Forty-one subjects were identified with ALS on the basis of death certificates, 37 as the main cause and 4 as a contributory cause.

The remaining cohort members were considered as controls (84,698 subjects). The members of the cohort provided information on the use of pesticides (years, days per year of use) and they calculated the total number of days of use of any pesticide during their lifetime (minimal use <25 days; higher> 25 days). The members of the cohort also provided information on the use of 50 specific pesticides, and this information allowed the construction of variables based on the chemical and functional classes.

In the AHS cohort, there were no significant differences compared to gender, state residency, ethnicity, education, alcohol use and smoking among cases and controls and, as expected, cases were older than controls. There were no differences between cases and controls among those who had used pesticides for more or less than 25 days.

Among the cases, the use of insecticides compared to controls, (OR 1.3, 95% CI 0.6-2.9) in particular organochlorines (OR 1.6, 95% CI 0.8-3.5), herbicides (OR 1.6, 95% CI 0.7-3.7) and fumigants (OR 1.8, 95% CI 0.8-3.9) was more frequent.

The authors also took into account some specific pesticides: for organochlorines aldrin, dieldrin, DDT, toxaphene it was possible to detect an OR > 2.0 although not significant, was not modified by adjustment for confounding factors and by the exclusion of two cases, where the death occurred less than two years after inclusion in the cohort.

Analysing the data on subjects aged > 60 years, they found higher OR (1.8), for dieldrin (2.6), and toxaphene (3.9), but not for DDT (0.8) or for organochlorines as a group (1.3). Analysing only the men, they found elevated OR for organochlorines as a group (2.0), aldrin (2.4), dieldrin (3.0), DDT (2.4), and toxaphene (2.2).

As regards the meta model, it is characterized by a high heterogeneity for which the use of the binary random-effects model was necessary.

The calculation of the χ^2 and I^2 shows a moderate heterogeneity ($\chi^2 = 0.043$; Q (df = 1) = 1.837; Het. p-value 0.175; I^2 46%) for which the quantitative evaluation was performed by the binary random effects method: the association between exposure to pesticides and ALS as a whole is weak and not significant (RR 1.088 CI 95% 0.749-1.580) (Fig. 9).

The individual exposures were not considered because McGuire provides data only for men while the Kamell data refer to the two types together.

Discussion and conclusion

Discussion

Our meta-analytic study examined the major working risk factors in literature whose association with ALS is hypothesized: physical (ELF-EMF) and chemicals (solvents, heavy metals and pesticides) agents.

With regard to exposure to ELF-EMF, our data indicate a slight and non-significant association and they confirm the findings reported by Zhou et al. (63) and Vergara et al. (64) in two recent meta-analyses.

Zhou et al. (63) suggest a slight but significant increase in the risk of ALS among patients with tasks involving exposure to relatively high levels of ELF-EMF. However, the same author points out that since the magnitude of the estimated RR is relatively small, the intervention of bias related for example to electrical shock or other unidentified variables associated to the tasks performed rather than exposure to ELF-EMF cannot be excluded. Zhou's study has also not carried out any assessment of quality and both studies bearing a self-reported exposure, and studies in which the exposure was assessed by repeated measurements or JEM, are included.

According to Vergara et al. (64), the associations between occupational exposure

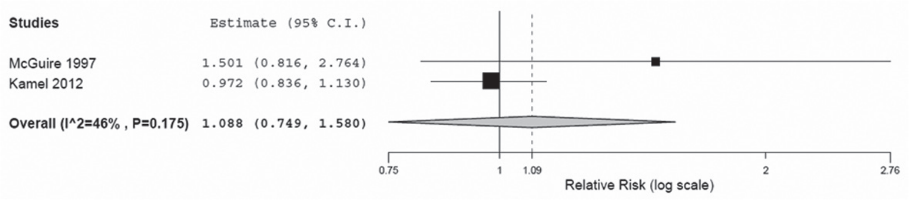

Fig. 9 - Forest plot on the exposure to pesticides and ALS

to EMF and MND are weak and do not support the pathogenetic hypothesis in particular when we consider the exposures not self-reported, but linked to repeated measurements or JEM.

The confounding factors related to exposure to ELF-EMF and outside work due to power lines, electric transportation systems, household appliances, are then considered. These sources unrelated to the job may in some cases be of the same level of those related (65).

Epidemiological studies of death may also be affected by other confounders such as trauma, electrical shock, co-exposure to chemicals such as organic solvents, metals and agricultural chemicals (1, 66).

The possible role of occupational chemical agents has received great attention in the last decades. The meta-analysis that we conducted for solvents, metals and pesticides, although performed on a very limited number of studies, did not show significant associations between ALS and exposure. The majority of eligible studies were eliminated by the evaluation of quality in particular for the deficiencies in the assessment of workplace risks. In almost all cases of self-reporting, the exposure assessment is reported by patients or their relatives.

It must be pointed out that there are no studies in the literature on the meta-analytic relationship between ALS and exposure to metals and solvents: the systematic evaluations conducted by Sutedja et al. (23, 24) showed that the inclusion of solvents and metals among the risk factors for ALS is often generated from the inadequacy of exposure assessment methods. Even in the study of Sutedja et al., (24) when the various studies were assessed for quality, their number was drastically reduced particularly in relation to assessments of employment.

Currently, in the literature there is a limited number of epidemiological studies that investigate the relationship between exposure to pesticides and risk of developing ALS, and to date only two meta-analyses have investigated this association (61, 67). Sutedja conducted two systematic reviews of the literature that did not include a meta-analysis due to the heterogeneity of studies (23-24).

Our data indicate a very weak and non-significant association between exposure to pesticides and ALS both for pesticides taken together and insecticides, herbicides and fungicides considered separately.

Malek et al., (67) reported an association between exposure to pesticides and risk of ALS in men (OR 1.88, 95% CI 1.36-2.61), although it does not identify the chemical class of pesticides considered.

Even Kamel et al., (31) reported an association between occupational exposure to pesticides and ALS (OR 1.9, 95% CI 1.1-3.1) without specifying the class of pesticides considered. In the two meta-analysis an assessment of quality was not performed, and other literary studies report only a binary exposure (yes / no) to pesticides.

The use of the proposed method by Sutedja et al. (24) in our meta-analysis definitely reduces the risk of bias in studies of mortality, but it greatly reduces the number of studies that can be included in the quantitative synthesis making it difficult to demonstrate a size effect. The potential relationships between exposure to pesticides and ALS are extremely difficult to establish in the absence of data concerning the class of pesticides, the chemical name of the substance or duration of exposure.

Our study demonstrates that further studies are needed with a prospective target group exposed to elucidate the relationships considered, in particular, it is necessary to obtain a more accurate assessment of exposures, not through self-reported data but for example through the blinded assessment by a panel of industrial hygienists as indicated by McGuire et al. (20).

A closer collaboration between neurologists and occupational physicians seems appropriate, whereas the majority of studies excluded (68, 69), reported unsuitable data. The agricultural labour was considered as a factor risk, being a vague term and a possible source of misunderstandings.

Apart from some advanced working realities, the creation of an exposure matrix is extremely difficult due to: a) the extreme heterogeneity in the manner and amount of the different pesticides used and b) the almost total absence of data of the biological monitoring.

Farm workers may be exposed to more than one pesticide, often simultaneously, with the result of additive or potentiating effects.

Conclusions

Our study does not indicate significant associations between occupational exposure and ALS, also in relation to the extreme diversity of methodological studies considered. However, it highlights, because of the importance and consequences of the disease in question, the need for prospective studies that involve not only an accurate assessment of the clinical picture, but also of occupational exposure.

Riassunto

Eziologia lavorativa SLA: metanalisi

Obiettivi: L'obiettivo della meta-analisi è di valutare l'associazione tra la SLA e l'esposizione lavorativa ad agenti fisici (EMF-ELF) e chimici (solventi, metalli pesanti e pesticidi).

Metodi: Abbiamo preso in considerazione gli articoli pubblicati fino ad aprile 2013. Sono state valutate in totale 750 pubblicazioni. Gli studi dovevano soddisfare i seguenti criteri: 1) studi di coorte o caso-controllo; 2) presenza di esposizioni singole; 3) diagnosi clinica di SLA sporadica o SLA sporadica sul certificato di morte. Abbiamo seguito la valutazione di qualità in due step. Il primo step classificava gli studi secondo un sistema di rating basato su un mix di criteri elaborati dalle organizzazioni scientifiche, sviluppato appositamente per gli studi dei fattori di rischio SLA. I rating ottenuti variano da I (il più elevato) a V (il più basso). I dati sui fattori di rischio derivanti da studi con rating Armon di I, II, e III possono raggiungere livelli di evidenza A (fattore di rischio accertato), B (fattore di rischio probabile), o C (fattore di rischio possibile).

Il secondo step ha valutato l'esposizione ed è stato assegnato ad ogni articolo un punteggio da 1 a 4: è stata considerata sufficiente un'esposizione con punteggio di 3 o 4. Sono state effettuate analisi differenti relative a SLA ed esposizione a metalli, solventi, pesticidi e campi elettromagnetici. Nel nostro studio l'eterogeneità è stata valutata sia attraverso χ-based Q-tests e sia attraverso l' indice di inconsistenza I^2 mentre per stimare le relazioni tra SLA e i vari fattori di rischio considerati è stata impiegata la misura del RR/OR e CI 95%.

Risultati: L'associazione tra esposizione a pesticidi nel loro insieme e SLA è debole e non significativa. Per quanto riguarda i risultati dei singoli lavori si può riportare la seguente sintesi critica: 1) gli studi selezionati hanno mostrato un basso livello di associazione tra SLA e i campi elettromagnetici; 2) per quanto riguarda i solventi la presenza di SLA in alcuni studi è associata ad un lieve aumento del rischio, in particolare nelle donne, mentre in altri mostra una lieve ma significativa associazione lineare; 3) per quanto riguarda i metalli in alcuni casi si osservava un'associazione più forte nelle donne che negli uomini; per i singoli metalli, si evidenzia un'associazione soprattutto per cromo e piombo; 4) infine per quanto riguarda i pesticidi agricoli in generale, si evidenzia una associazione con la SLA negli uomini, ma non nelle donne, con una relazione dose risposta.

Conclusioni: La mancata associazione statisticamente significativa tra esposizione professionale e SLA si ritiene possa essere riferibile soprattutto alla diversità metodologica degli studi considerati ed alla mancanza di studi di tipo prospettico in ambito lavorativo.

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