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ORIGINAL ARTICLE

Environmental and Occupational solvents exposure and amyotrophic lateral sclerosis: a systematic review and meta-analysis

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Abstract

Studies focusing on the association between environmental and occupational solvent exposure and amyotrophic lateral sclerosis (ALS) have yielded inconsistent results. Herein we present the results of a meta-analysis on the correlation between solvent exposure and ALS. We searched for eligible studies that reported ALS with exposure to solvents in PubMed, Embase, and Web of Science up to December 2022. The Newcastle–Ottawa scale was used to evaluate the quality of the article and a meta-analysis was performed using a random effect model. Thirteen articles, including two cohort studies and 13 case–control studies with 6365 cases and 173,321 controls were selected. The odds ratio (OR) for the association between solvent exposure and ALS was 1.31 (95% confidence interval [CI], 1.11–1.54) with moderate heterogeneity ($I^2 = 59.7\%$; $p = 0.002$). Subgroup and sensitivity analyses confirmed the results, and publication bias was not detected. These results indicated that environmental and occupational solvent exposure was associated with the risk of ALS.

Keywords Amyotrophic lateral sclerosis · Solvents · Meta-analysis

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by degeneration of motor neurons in the central nervous system [1]. The population incidence is 1–3 cases per 100,000 and has been on the rise in recent years [2]. Most previous studies have suggested that environmental [3, 4] and occupational [5] factors are important risk factors associated with ALS. Among the factors that may be associated with ALS, occupations are most often examined. Specifically, occupational exposure to heavy metals, pesticides, and solvents have been addressed [6–8]. Many studies have suggested that solvent exposure is a role in the development of ALS, but the results have been inconsistent. Recently, a meta-analysis by Wang [9] concluded that exposure to solvents is associated with ALS; however, the included studies up to 2010, and without nearly a decade of research, many of the studies involved a small number of ALS cases. Possible sources of heterogeneity were not explored based on confounding factors and publication bias was also not addressed. Previous studies have had insufficient epidemiologic evidence linking exposure to solvents and the occurrence of ALS. Therefore we performed a meta-analysis to further investigate the possible association between exposure to solvents and the risk of developing ALS.

Methods

Search strategy and selection criteria

According to the meta-analysis of observational studies in epidemiology [10], the strategy focused on the observational studies for solvent exposure associated with ALS disease occurrence and progression. we retrieved articles that identified an association between solvents and ALS in PubMed, Web of Knowledge, and the Springer databases. English articles regarding ALS and solvents were targeted. Searching covered single or combination words, including

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'amyotrophic lateral sclerosis' or 'motor neurone disease' or 'sporadic motor neuron disease' or 'ALS' with solvent exposure ('occupational' or 'environmental' or 'workplace' and 'chemical' or 'environmental toxins'). The following terms were excluded: 'animal experiment' and 'cell research'. The relevant articles are further identified by reading titles and abstracts. The retrieved articles were screened again according to inclusion criteria and we reviewed the reference list of retrieved articles to find potential articles. The cut-off time of search original manuscripts was December 31, 2022.

The selected articles met the following criteria: (1) the study assessed the relationship between solvents and ALS; (2) the publication was a case–control or cohort study; (3) the ALS outcome was a medical diagnosis (e.g. El Escorial criteria or International Classification of Diseases and Related Health Problems, Eighth Revision (ICD-8) or Tenth Revision (ICD-10)); and (4) outcomes had an OR or adjusted ORs and a corresponding 95% confidence interval (CI).

Quality assessment

Two authors independently selected relevant studies, assessed trial quality, and extracted data, including the first author's name, publication year, country, number of cases and controls, geographic area, OR, 95% CI, and adjusted factors. The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the included studies and a "star system" (range, 0–9) was developed for assessment [11]. There were 3 parts to assess a study, including selection, comparability and exposure (case–control study) or outcomes (cohort study), were the judging criteria of the NOS.

The quality of the articles was divided into high- (7–9 points), medium- (5–6 points), and low-quality studies (0–4 points), see supplementary table 3. The quality of selected articles is assessed independently by Guoqiang Zhang and Meng E, any inconsistencies are resolved through discussion.

Statistical analysis

Stata 13.0 was used to analyze data. The Q test and I^2 statistic was used to assess heterogeneity among the selected studies [12]. When the I^2 was ≥ 50%, a random-effects model was used. When the I^2 was < 50%, a fixed-effects model was used. Begg's and Egger's tests were used to detect publication bias [13, 14]. Sensitivity analysis was used to evaluate the stability of the meta-analysis by removing one study at the same time point adopted for testing [15].

To further explore the source of heterogeneity, we performed subgroup analysis according to the study design, geographic region, number of ALS cases, occupational exposure, adjusted factors(e.g. age, sex, and score).

Results

Study characteristics

Our search method and literature review process are shown in the Fig. 1. We identified 253 potential articles, 211 of which were removed due to duplication, or after reading the title and abstract. The full text of the remaining 42 articles was assessed; 16 were excluded that did not involve solvents, 13 were excluded that did not report ALS events, eight experimental research studies were excluded, and two were excluded that did not include ORs. Table 1 reports characteristics of included studies, thirteen [16–28] articles involving a total of 6365 cases with ALS and 173,321 controls were selected for the meta-analysis. Two cohort [19, 23] and 11 case–control studies [16–18, 20–22, 24–28] were selected. Ten studies were occupational exposure [17, 18, 20–23, 25–28] and three studies were no occupational exposure [16, 19, 24]. Six studies were conducted in the USA [18–20, 22, 25, 28], two in Italy [16, 26], two in Sweden [17, 24], Australia [21], the Netherlands [23] and Denmark [27]. Nine articles had a sample size ≥ 100 [18–21, 23–25, 27, 28] and four had < 100 [16, 17, 22, 26]. The studies conducted by Pamphlett [21] and Dickerson [27], which assessed sexed differences, were treated as independent case–control studies.

Meta-analysis results

The ALS pooled ORs for solvent exposure is shown in Fig. 2. Because of the heterogeneity ($I^2 = 59.7\%$; $P = 0.002$) between articles, a random model was used. Solvent exposure increased the risk of developing ALS (OR = 1.31, 95% CI = 1.11–1.52).

Subgroup and sensitivity analyses

Table 2 lists the data for subgroups. Based on study design (cohort and case–control study), the ORs were 1.22 (95% CI, 1.11–1.34 [n = 13]) and 1.14 (95% CI, 0.85–1.55 [n = 2]), respectively. Based upon occupational exposure (yes and no), the ORs were 1.20 (95% CI, 1.10–1.32 [n = 12]) and 1.33 (95% CI, 1.00–1.77 [n = 3]). Based upon geographic region (Europe and the USA), the ORs were 1.22 (95% CI, 1.10–1.36 [n = 9]) and 1.19 (95% CI, 1.01–1.41 [n = 6]), respectively. Based upon the number of cases (n ≥ 100 and n < 100), the ORs were 1.21 (95% CI, 1.10–1.32 [n = 11]) and 1.45 (95% CI, 0.88–2.39 [n = 4]), respectively. Based upon adjusted factors age and education, the ORs were 1.11 (95% CI, 1.01–1.28 [n = 10]) and 1.10 (95% CI, 0.98–1.26 [n = 8]), respectively.

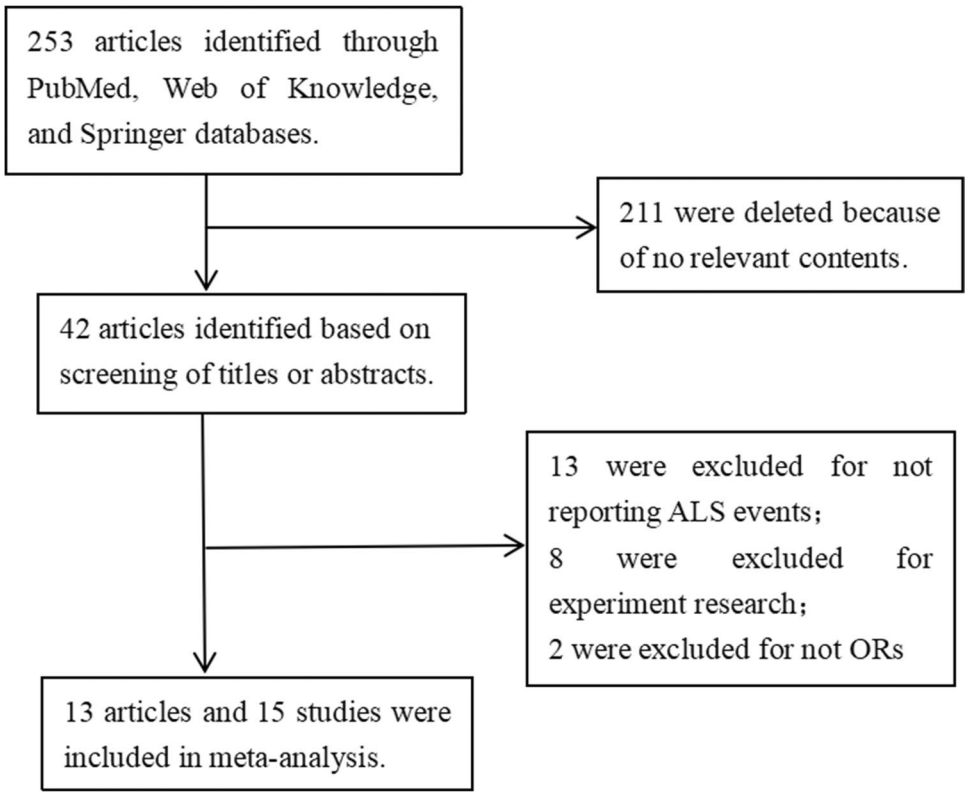

Fig. 1 Selection of studies for inclusion in meta-analysis

Table 1 Characteristics of the included studies

Author (year)	Years	OR	95% CI	Type of study	Case	Control	Area	Adjusted	Score
Savettieri G(1991) [16]	NA	2.14	0.60–7.20	Case–control	46	92	Italy	NA	moderate
Gunnarsson LG(1992) [17]	NA	1.40	0.60–3.00	Case–control	92	372	Sweden	NA	moderate
McGuire V(1997) [18]	1990–1994	1.60	1.10–2.50	Case–control	174	348	USA	Age and education	high
Weisskopfl MG(2009) [19]	1989–2004	1.04	0.73–1.49	cohort	142	1014	USA	Age, sex, smoking, military service, education, alcohol, occupation, vitamin E, and all other chemical classe	high
Fang F(2009) [20]	1993–1993	1.00	0.50–2.10	Case–control	109	253	USA	Age, sex, residence, smoking, and educational level	high
Pamphlett P(2012) [21]	2000–2011	Men,1.96 Women,1.71	1.46–2.61 1.22–2.40	Case–control	380 234	377 401	Australian	NA	moderate
Malek AM(2014) [22]	2008–2010	1.00	0.36–2.86	Case–control	66	66	USA	NA	moderate
Koeman T(2016) [23]	1987–2003	1.46	0.81–2.61	cohort	136	4344	Netherland	Age, education	high
Andrew AS(2017) [24]	2009–2015	2.03	1.23–3.44	Case–control	224	295	Sweden	Age, sex	high
Peters TL(2017) [25]	1991–2010	0.92	0.77–1.09	Case–control	2647	13,378	USA	Age sex, and education	moderate
Filippini T(2020) [26]	2002–2012	1.68	0.59–4.78	Case–control	95	135	Italy	Age sex, and education	high
Dickerson AS(2020) [27]	1982–2013	Men,1.25 Women,1.04	1.02–1.52 0.69–1.56	Case–control	1639	151,974	Denmark	Age, sex, residence, socioeconomic	high
Goutman SA(2022) [28]	2010–2020	1.03	0.80–1.34	Case–control	381	272	USA	Age, sex, and military service	moderate

VOCs, Volatile organic compounds; NA, not give

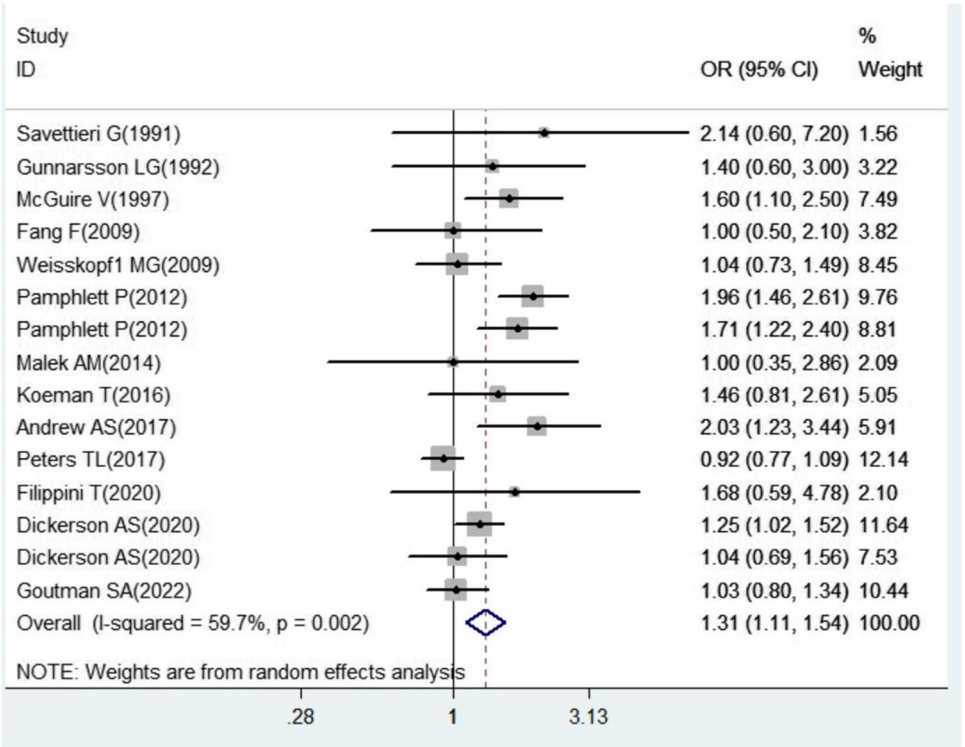

Fig. 2 Forest plot of meta-analysis

Table 2 Stratified meta-analysis of solvents exposure and the risk of ALS

Stratifications	No. Studies	Effect Estimates		Heterogeneity		
		OR	(95% CI)	χ^2	*P*	I^2 (%)
Study design						
Cohort study	2	1.14	(0.84, 1.55)	0.94	0.332	0.00
Case–control study	13	1.22	(1.11, 1.34)	33.63	0.001	64.3
Geographic regions						
European	9	1.22	(1.10, 1.36)	26.46	0.001	69.8
USA	6	1.19	(1.01, 1.41)	8.22	0.144	39.2
Number of case						
N ≥ 100	11	1.21	(1.10, 1.32)	33.31	0.000	70.0
N < 100	4	1.45	(0.88, 2.39)	0.94	0.815	0.00
Exposure						
Occupational	12	1.20	(1.10, 1.32)	29.35	0.002	62.5
No-occupational	3	1.33	(0.99, 1.77)	4.99	0.083	59.9
Sex						
Men	5	1.28	(1.08, 1.51)	0.77	0.943	0.00
Women	2	1.36	(0.97, 1.90)	5.13	0.024	80.5
Adjusted						
age	10	1.11	(1.01, 1.28)	16.26	0.062	44.7
education	8	1.10	(0.98,1.26)	10.60	0.157	34.0
Score						
High	7	1.32	(1.14, 1.53)	6.03	0.420	0.40
Moderate	8	1.16	(1.03, 1.29)	28.81	0.000	73.9

Sensitivity analysis (Fig. 3) confirmed that the results were stable by deleting one study at a time. The over pooled OR and ORs ranged from 1.27 (95% CI, 1.07–1.50) to 1.37 (95% CI, 1.18–1.59).

Publication bias

As shown in Fig. 4, we did not detect any evidence of publication bias (Begg's test, P = 0.428; Egger test, P = 0.159).

Discussion

Solvents have been shown to be neurotoxic [29]. Previous studies have been shown that exposure to solvents can lead to cognitive impairment [30], Alzheimer's disease [31], and Parkinson's disease [32]. Solvents are suspected to have a role in ALS, but the reported outcomes have been inconsistent. Our results showed that solvent exposure is associated with ALS (OR, 1.31; 95% CI, 1.11–1.52) and are similar to the results reported by Wang [9] (OR, 1.43; 95% CI, 1.10–1.86). We replaced a previous study [33] with a newer study [21] from the same sample because the most recent study had a larger sample size. In addition, we updated eight [21–28] articles that were not included in the previous meta-analysis [9]. Due to moderate heterogeneity, we performed subgroup and sensitivity analyses. The subgroup analysis show that all of the variables significantly affected the association between solvent exposure and ALS, with the exception of the small number of ALS patients (< 100) in the cohort studies (n = 2). The results of this meta-analysis were stable according to the sensitivity analysis, and no article had substantially influenced the overall OR (1.27–1.37). Our study provides further evidence that exposure to solvents can cause ALS. It is important to understand the influence of non-genetic factors on ALS. It is critical to identify factors that should be avoided to decrease ALS risk and prevent disease.

ALS has been known to result from neurotoxins for 150 years; however, the onset and progression of ALS is not well understood. Although genetic and environmental factors have an important role in ALS [34], only 5%–10% of ALS cases can be attributed to familial genetic susceptibility [35]. Until now, many studies have evaluated occupational and environmental with ALS, such as exposure to heavy metals and pesticides from occupational activities [36]. Risk factors for the development and progression of ALS may be related to the misfolding process of prion-like transmission proteins, which is relevant to ALS, Alzheimer disease, and Parkinson disease [37]. Cu/Zn superoxide dismutase (SOD1) [38] and TDP43 [39] are known to misfold and aggregate under various cellular stress conditions. Ataxin-2 may participate in the expression of 'seeding' proteins or co-factors in their generation [40]. Exposure to heavy metals and solvents can lead to post-translational modification or oxidize protein in vivo and could be associated with the formation of a productive nidus or 'seed' that can propagate misfolding intra- and inter-cellularly [41].

In addition, exposure to cigarette smoke [3] and extremely low frequency electromagnetic radiation [42] are important risk factors associated with ALS. Furthermore,

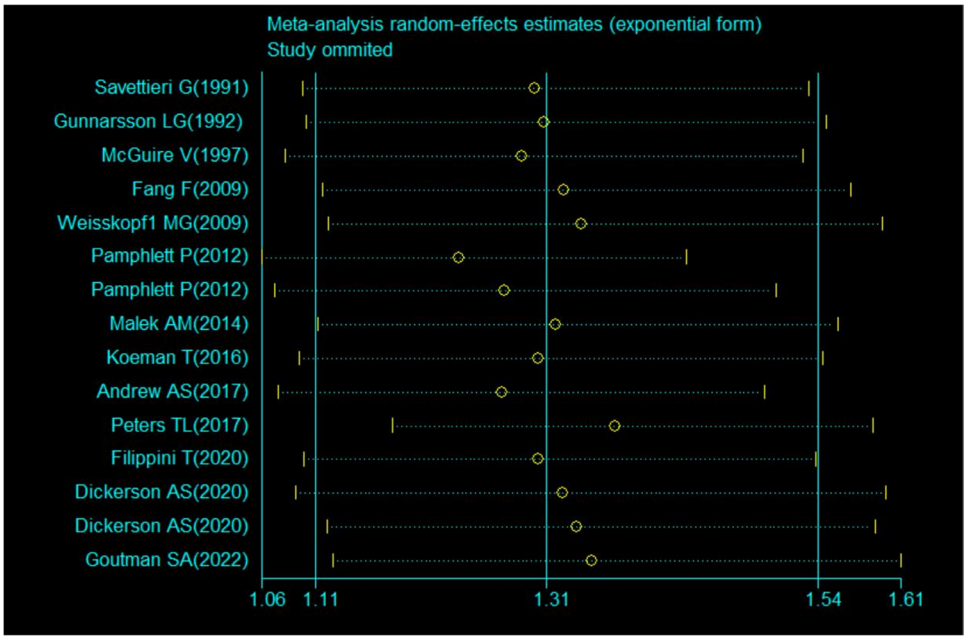

Fig. 3 The result of sensitivity analysis

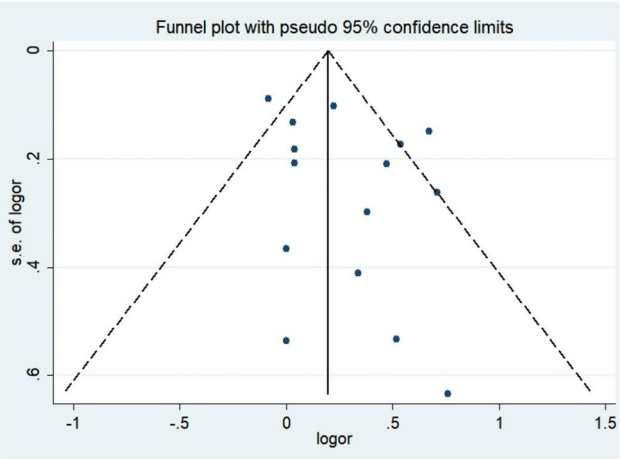

Fig. 4 The funnel plot of meta-analysis

our previous study confirmed that environmental/ occupational lead exposure is positively proportional to the risk of ALS [43]. A few limitations of our study should be noted. First, ALS is usually diagnosed within 1 year of the of clinical symptom onset and there is no specific diagnostic test for ALS. Misdiagnosis or misclassification is estimated to account for approximately 10% of all ALS cases. Second, there are many kinds of industrial solvents (especially for toluene and xylene); however, the industrial solvents were not specified in the original articles. Third, three of the 13 articles did not adjust for confounding factors. We also performed the analysis by adjusting factors (age, sex, smoking); however, it was difficult to identify the other risk factors that may lead to ALS.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-023-06718-8.

Author contributions Guoqiang Zhang and Xin Zhou conceived the study. Meng E participated in the statistical analysis. Guoqiang Zhang and Meng E drafted the article. All authors read and approved the final version of the manuscript.

Data availability This paper is meta that all data are fully available without restriction.

Declarations

Ethical approval Not required, as this is a review of existing literature.

Consent to participate This paper did not contain human participants enrolled by any of the authors.

Conflict of interest The authors have no conflicts of interest to declare.

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