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REVIEW ARTICLE

Lead exposure and its association with neurological damage: systematic review and meta-analysis

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Abstract

Lead (Pb) is one of the most toxic and abundant elements in the earth's crust, which is pointed out that the intoxication caused by it may damage biological systems. This systematic review with meta-analysis aimed to evaluate the association between Pb exposure and neurological damage. This work was executed according to PRISMA guidelines, and seven online databases were consulted. Based on the PECO strategy, studies presenting humans as participants (populations) exposed to Pb (exposure) compared to non-exposed to Pb (control) evaluating the neurological impairment (outcome) were included. The quality and risk of bias were verified by Fowkes and Fulton checklist. Two meta-analyses were conducted considering Digit Symbol and Profile Mood tests. The certainty of the evidence was evaluated with the GRADE tool. This review identified 2019 studies, of which 12 were eligible according to the inclusion criteria. Eight were considered with a low risk of bias. All the studies elected showed that exposure to Pb is associated with neurological damage, but the meta-analysis did not show any difference for the evaluated tests, and the certainty of the evidence was considered very low. Nevertheless, the included studies showed that Pb occupational exposure is associated with neurological damage, and the main parameters evaluated for possible neurological damage were related to mnemonic aspects, reaction time, intelligence, attention disorders, and mood changes. Thus, our results revealed that a definitive demonstration of an association of Pb and neurological changes in humans is still a pending issue. Future studies should take into consideration more confident methods to answer this question.

Keywords Lead · Occupational · Exposure · Neurological · Damage · Neurotoxic · Systematic review · Association

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Introduction

Lead (Pb) is a blue-white metal that gained popularity during the industrial revolution due to its low melting point, malleability, and non-corrosive properties (Lessler 1988). It is one of the most toxic metals, widely dispersed in the environment and used for over 9000 years by mankind (Lessler 1988).

This metal can be found in the environment in a natural way and through anthropogenic actions, thus causing numerous health risks since it is not an essential element to the human body (ATSDR 2005; Flora et al. 2012; WHO 1995). For this reason, several measures have been taken to reduce the use of Pb. However, several industries still use it on a large scale. In recent years, they have been the main responsible for the spread of considerable amounts of Pb in some cities of the United States (USA). This culminated in long-term environmental and occupational exposures that promote severe neurotoxic responses (Li et al. 2016; Maloney et al. 2018).

In 1993, the US Occupational Safety and Health Administration Pb standards reported that workers could contain up to 40 μg/dl of Pb in their blood. Many studies have begun to elucidate the mechanisms and damage caused by exposure to Pb, showing that a cumulative dose of Pb can cause cognitive dysfunction or decrease. Levels below 18 μg/dl were presented as causing damage in exposed adult workers (Liu et al. 2013).

Exposure to Pb has decreased continuously over the last 20 years (Control and Prevention 2012), and, currently, concerns are related to the health effects that can be caused by past exposure (Khalil et al. 2009; Schwartz et al. 2000). Among the chemical agents, Pb most commonly causes contamination. Through inhalation or digestion, this metal enters into the organism and can cause damage to various existing systems, including the central nervous system (CNS) and culminating in neurological damage (Moreira and Moreira 2004). Although recent studies show a predisposition to cardiovascular and renal diseases (Navas-Acien et al. 2007), the damage described in the literature is often associated with neurological damage, among which there are changes in memory, learning (Chen et al. 2019; Liu et al. 2013; OĞUZ et al. 2018), and, changes in neurotransmission that can cause mood changes, fatigue, depression, and attention deficits (Baker et al. 1985; Kabir et al. 2021; Patrick 2006). Furthermore, the neurological disorder is explained by the activation of oxidative stress (OS), which is caused by increased activity of oxidative parameters such as lipid peroxidation or by direct modification of protein chains by reactive oxygen species (ROS) or reactive nitrogen species (RNS). The increase in OS is due to the increase of pro-oxidant factors, as free radical formation via the Fenton reaction in the presence of redox-active trace metals, and reduced antioxidant competence (Narayanan et al. 2020). Apart from all these diseases, exposure to Pb for long periods may cause an increase in infertility, cataract, and muscular disorders (Seppäläinen and Hernberg 1980).

Thus, our systematic review aimed to answer the question "Is there any association with exposure to Pb and neurological damage in humans?" To answer this question, we include studies showing humans with clinical signs of neurological damage and exposed to Pb. In answering this question, we seek to bring clarification with clinical evidences of Pb toxicity in humans.

Materials and methods

Registration

This systematic review was registered under the code/number CRD42017067230 in the International Prospective Registration database for Systematic Reviews (PROSPERO). It was carried out following the Preferred Reporting Requirements for Systematic Review (PRISMA) (Moher et al. 2010).

Eligibility criteria

This review was developed using the PECO strategy to look for observational studies with humans (P) that were exposed (E) or non-exposed (C) to Pb and evaluated the association with neurological impairment (O). The studies used in this review presented clinical data that met the inclusion criteria.

Strategy search, selection, and eligibility criterion

The following electronic databases were used: Pubmed, Scopus, Web of Science, Cochrane, and Lilacs. Searches in grey literature were also conducted (OpenGrey and Google Scholar). The search strategy was initially predefined based on a convergence of MeSH and entry terms focused on neurological impairment related to Pb exposure. The words used were previously defined and adapted to the syntax rules corresponding to each bibliographic database. After searches, an alert was created in each database to monitor the appearance of new eligible articles. The searches were performed until September 2020 (Table S1).

All retrieved articles were exported to bibliographic reference software (EndNote, version X7, Thomson Reuters, Philadelphia, USA), where duplicates were removed automatically and manually. Then, the articles were analyzed by title and abstract, observing their eligibility. Later, the studies were read in full to select those that met the eligibility criteria (Fig. 1). All references of the articles were analyzed to search for studies that fit within the criteria and thus could be part of this systematic review.

All assessments, including database searches, study selection, risk of bias assessment, and data extraction, were performed independently by two reviewers (LGE and MKMF)

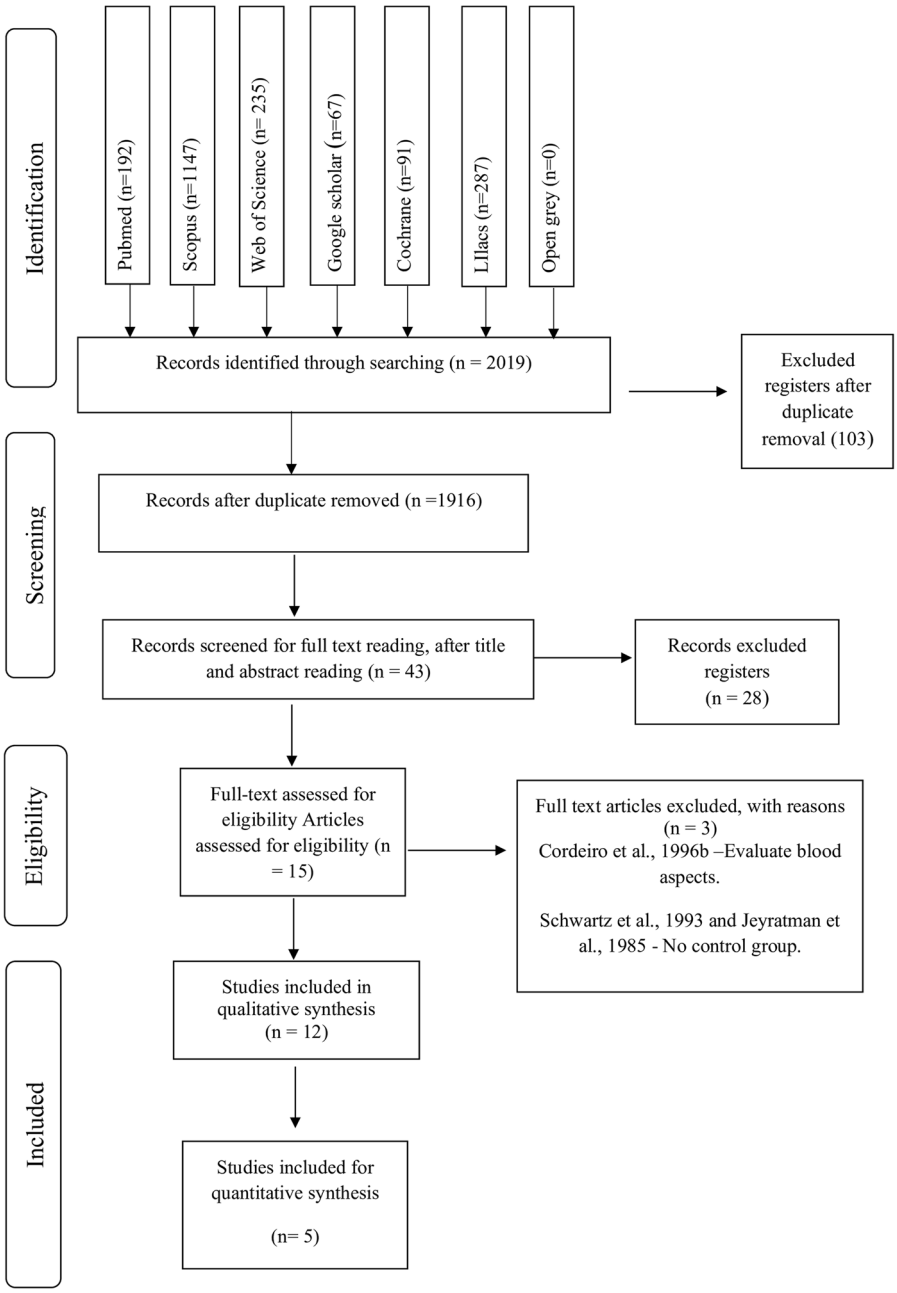

Fig. 1 Flowchart diagram of literature search according to PRISMA guidelines

and checked by a third reviewer for the possible discrepancy between assessments (DRF).

Data extraction and risk of bias

To evaluate the methodological quality and the risk of bias, the checklist by Fowkes and Fulton (1991) was used, which has domains that cover the type of study and its design, characteristics of the control group, and the integrity and/or distortion influences. This checklist was largely used in systematic reviews focused on observational studies (Castro et al. 2020; de Oliveira Ferreira et al. 2019; Nascimento et al. 2019; Puty et al. 2019).

After evaluating each criterion, different characters were used to assign no problem (0), major problems (++), or minor problems (+) in each study. This categorization was used to assess whether the methods in each study were adequate to produce valid information and whether the expected results were able to demonstrate some conclusion. In the items where the questions did not apply to the type of study, the acronym NA (not applicable) was used (Fowkes and Fulton 1991).

After a detailed evaluation of the methods and results, the studies were analyzed to verify the possibility of risk of bias,

confusion, or chance of occurrence. To determine the value of the study, three questions, in summary, were answered: "Are the results erroneously biased in a certain direction?" "Are there any serious confusing or other distorting influences?" "Is it likely that the results occurred by chance?" "YES" and "NO" were the answers to those questions. If the three questions were answered "NO," the article presents a low risk of bias (Fowkes and Fulton 1991) (Table S2).

Quantitative analysis (meta-analysis)

Data from the included studies were analyzed using Review Manager software (Review Manager v. 5.3, The Cochrane Collaboration; Copenhagen, Denmark) to evaluate the Digit Span and Profile Mood test results between participants exposed and non-exposed to Pb. The main results of each test analyzed by the studies were evaluated in two different random effects meta-analyses: Digit Span test and Profile Mood test. The mean and standard deviation of the score of each test and the total number of individuals in the control and Pb groups were used. The analyses were subgrouped according to study type when applicable.

As the studies reported the outcome using similar methods for all parameters, the mean difference (MD) was applied, with 95% confidence interval (95% CI). If some of the information needed for the meta-analysis was absent from the selected studies, the authors were contacted to provide the missing data.

Heterogeneity was tested using the I^2 index, and, if possible, sensitivity analyses were conducted to estimate and verify the influence of studies, one by one, when the heterogeneity was substantial or considerable (50 to 100%) (Higgins 2011). Random effects models were employed, considering that the studies were not functionally equivalent in which the objective was to generalize the results from the meta-analysis (Borenstein et al. 2011).

Certainty of evidence (GRADE tool)

The certainty of evidence was evaluated according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). This approach aims to evaluate the certainty of the evidence of the results found on the meta-analysis considering the risk of bias, inconsistency, indirectness, and imprecision. Evidence from randomized controlled trials starts at "high," while observational data starts at "low," because of residual confounding factors. The level of the evidence varies from very low to high depending on whether there are serious or very serious issues related to the parameters cited above and on the dose-effect parameters, the presence of confounding factors, and the magnitude of the effect (Brasil 2014).

Results

Study selection

Searches totaled 2019 identified studies. After the removal of 103 duplicates, 1916 remained for reading the titles and abstracts. After this stage, 43 studies were screened by title and abstract readings. Then, 28 studies were excluded, remaining 15 studies for the full-text analysis stage. Among these, three studies were excluded because one evaluated blood aspects (Cordeiro et al. 1996b) and two did not have a control/comparison group (Jeyaratnam et al. 1985; Schwartz et al. 1993). Therefore, twelve (Baker et al. 1984; Baker et al. 1985; Baker et al. 1983; Balbus et al. 1998; Cordeiro et al. 1996a; Jeyaratnam et al. 1986; Murata et al. 1995; Schwartz et al. 2001; Seo et al. 2015; Valciukas et al. 1978; Valciukas et al. 1980; Yi-lan et al. 1985) articles were eligible for qualitative analysis (Fig. 1).

Results of individual studies

The association of exposure to Pb with neurological damage was found in all articles included in this review (Baker et al. 1984, Baker et al. 1985, Baker et al. 1983, Balbus et al. 1998, Cordeiro et al. 1996a, Jeyaratnam et al. 1986, Murata et al. 1995, Schwartz et al. 2001, Seo et al. 2015, Valciukas et al. 1978, Valciukas et al. 1980, Yi-lan et al. 1985) as can be seen in Table 1 which shows the summary of characteristics of the studies included.

Among the studies elected, all of them were performed with factory workers (Baker et al. 1984, Baker et al. 1985, Baker et al. 1983, Balbus et al. 1998, Cordeiro et al. 1996a, Jeyaratnam et al. 1986, Murata et al. 1995, Schwartz et al. 2001, Seo et al. 2015, Valciukas et al. 1978, Valciukas et al. 1980, Yi-lan et al. 1985); one of them was performed in factories of Pb batteries (Seo et al. 2015); one was performed in Pb-using facilities (Schwartz et al. 2001); four only described the participants as workers (Baker et al. 1984; Baker et al. 1985; Baker et al. 1983; Cordeiro et al. 1996a); one was performed in a company of Pb-based stabilizers (Jeyaratnam et al. 1986); another with female workers from Shanghai batteries, TV, and embroidery factories (Yi-lan et al. 1985); one was performed with workers from a chemical manufacturing facility that produced tetraethyl Pb (Balbus et al. 1998); two were with secondary Pb smelter workers (Valciukas et al. 1978; Valciukas et al. 1980); and finally, one was performed with female glass workers exposed solely to Pb (Murata et al. 1995). The population included was composed of adults from 21 to 60 years of age. The studies were performed in countries of two continents, including South Korea (Schwartz et al. 2001; Seo et al. 2015), Brazil (Cordeiro et al. 1996a), USA (Baker et al. 1984; Baker et al. 1985; Baker et al. 1983; Balbus et al. 1998; Valciukas et al. 1978; Valciukas et al. 1980),

Table 1 Characteristic of samples and data of included studies

Author/year/country/study design	Participants			Lead exposure type	Metal quantification	Neurological tests	Statistical analysis	Results
	Source of the exposed sample	Sample size	Age mean (SD) in years					
Seo et al. 2015 [36] South Korea Case-control	Factories of lead batteries	84 Exposed: 43 Control: 41	Exposed: 60.1 ± 4.9 Control: 58.3 ± 5.2	Occupational	Blood (atomic absorption spectrophotometer)	WCST test; MRI and experimental paradigm	Student's *t*-test Multiple linear regression analysis $p < 0.05$	The averages of reaction times and the percentage of correct answers in experimental runs revealed to be significantly different between exposed and control participants.
Schwartz et al. 2001 [35] South Korea Cross-sectional	Lead-using facilities	938 Exposed: 803 Control: 135	Exposed: 40.4 ± 10.1 Controls: 34.5 ± 9.1	Occupational	Blood (atomic absorption spectrophotometer) Tibia (X-ray fluorescence)	Profile of Mood States; simple reaction time; Digit Span test; Wechsler Memory Scale; Santa Ana dexterity test; Digit Symbol substitution test; Benton Visual Retention Test	Multiple linear regression analysis $p < 0.05$	Exposed subjects performed significantly worse than controls on the following tests: simple reaction time, Digit Span, Benton Visual Retention, Colored, Digit Symbol Substitution, Purdue Pegboard, and grip strength.
Baker et al. 1984 [28] Massachusetts, USA Case-control	Workers	160 Exposed: 99 Control: 61	Exposed: 40.4 ± 10.1 Controls: 34.5 ± 9.1	Occupational	Blood and urine analyses	Wechsler Memory Scale (WMS) subtest, Wechsler Adult Intelligence Scale (WAIS), continuous performance test, Santa Ana dexterity test, Profile of Mood States (POMS)	Multiple regression analysis $p < 0.05$	Impairment in neurobehavioral function was particularly apparent in performance on tests of verbal concept formation, selected memory tests, and mood profile
Jeyaratnam et al. 1986 [33] Singapura Case-control	Workers from a company of lead-based stabilizers	85 Exposed: 49 Control: 36	Exposed: 26.1 ± 7.6 Controls: 29.8 ± 6.4	Occupational	Blood (atomic absorption spectrophotometer)	Digit Symbol (DSy), Bourdon-Wiersma vigilance test (B-W VT), Digit Span (DSp), Visual Tracing Test (VTT), Trail Making Test (TMT), Santa Ana dexterity test (SA), line pursuing test (LPT), flicker fusion test (FFT)	Student's *t*-test $p < 0.05$	Compared with the control group, the exposed group was significantly poorer in perceptual-motor speed, sustained attention, and concentration as measured by Digit Symbol and Bourdon-Wiersma (speed).
Yi-lan et al. 1985 [39] China Case-control	Female workers from Shanghai batteries, TV, and embroidery factories	105 Exposed: 53 Control: 52	Not related	Occupational	Blood (atomic absorption spectrophotometry) and urine (dithizone colorimetry)	Electrophysiology exams and behavioral function evaluation	Correlation Multiple regression analysis $p < 0.05$	The data showed that the motor and sensory conduction velocities of the median nerve in the lead-exposed groups were slower than those of the reference group, but that the ulnar nerve's motor conduction velocity was the same in all three groups.
Cordeiro et al. 1996 [32] Brazil Cross-sectional	Workers	40 Exposed: 20 Control: 20	Not related	Occupational	Pb-S, ALA-U, and δ-aminolevulinic dehydratase enzyme activity (ALAD)	Wechsler Memory Scale; memory auditive test; concentration attention test; sub-test Digit Symbol; Intelligence Scale	Correlation Multiple regression Student's *t*-test $p < 0.05$	The lead workers showed memory, mood, and motor coordination disorders. Comparing these results with those obtained from the control group, a significant difference was observed.
Baker et al. 1985 [29] USA	Foundry workers	50 Exposed: 36	Not related	Occupational	Blood lead concentrations and zinc	Verbal ability: vocabulary and similarities Memory:	Pearson correlation	The data showed dose-dependent decrements in mood, visual/motor performance, memory, and verbal

Table 1 (continued)

Author/year/country/study design	Participants			Lead exposure type	Metal quantification	Neurological tests	Statistical analysis	Results
	Source of the exposed sample	Sample size	Age mean (SD) in years					
Case-control		Control: 14			protoporphyrin (ZPP) concentrations	Digit Span; Digit Symbol recall; difficult paired-associate learning test; paired associate learning Visual reproduction: immediate recall; delayed recall; Benton visual retention Visual/motor function: block design; continuous performance test; Digit Symbol substitution; Santa Ana dexterity test Mood: Profile of Mood States	and linear extrapolation $p < 0.05$	concept formation. Attendant improvement in indices of tension (20% reduction), anger (18%), depression (26%), fatigue (27%), and confusion (13%) was observed.
Baker et al. 1983 [30] USA Cohort	Foundry workers	164 Exposed: 103 Control: 61	35.46	Occupational	Blood and urine analyses	Wechsler Adult Intelligence Scale; Wechsler Memory Scale; continuous performance (CPT); Santa Ana dexterity test; Profile of Mood States; nerve conduction tests	Multiple linear regression analysis $p < 0.05$	Results show increased rates of depression, confusion, anger, fatigue, and tension among workers with blood levels over **40** mcg/dl. Other aspects of neurobehavioral function, including verbal concept formation, memory, and visual/motor performance, were also impaired.
Balbus et al. 1998 [31] USA Cohort	Workers from a chemical manufacturing facility that produced tetraethyl lead	284 Exposed: 222 Control: 62	Not related	Occupational	Recent blood lead (PbB) and peak urine lead level	Simple visual reaction time (SVRT)	Multiple linear regression $p < 0.05$	Mean reaction times in response to moderate and long interstimulus intervals were mainly associated with lead exposure; this suggests that interstimulus interval duration modifies the relationship between lead exposure and simple visual reaction time performance. In SVRT protocols, stronger associations between reaction time and lead exposure may be found.
Murata et al. 1995 [34] China Case-control	Female glass workers exposed solely to lead	51 Exposed: 36 Control: 15	Exposed: 21–35 years Control: 22–29 years	Occupational	Blood lead (BPb) by flameless atomic absorption spectrophotometry	Electrocardiographic R-R interval variability (CV_{RR}) and visual and brainstem auditory evoked potentials (VEP and BAEP)	Pearson's product--moment $p < 0.05$	The CV_{RR}, C-CV_{LF}, C-CV_{HF}, and LF/HF ratio in the exposed group were significantly lower than those in the unexposed group. Also, the exposed group had more complaints of subjective symptoms and signs than did the unexposed group. On the other hand, no significant differences in either VEP or BAEP latencies were found between the two groups.
		307		Occupational				

Table 1 (continued)

Author/year/country/study design	Participants			Lead exposure type	Metal quantification	Neurological tests	Statistical analysis	Results
	Source of the exposed sample	Sample size	Age mean (SD) in years					
Valciukas et al. 1978 [37] USA Cross-sectional	Secondary lead smelter workers	Exposed: 90 Control: 217	Exposed: 42.8 ± 12.1 Control: 43.3 ± 11.5		Blood lead levels (atomic absorption spectrophotometry)	Block design test (BD), Digit Symbol test (DS), Embedded Figures Test (EF), Santa Ana dexterity test with the dominant hand (DH) and both hands (BH)	Multiple linear regression $p < 0.05$	Lower performance test scores were consistent with a sizeable prevalence of central nervous system symptoms among secondary lead smelter workers. Moreover, lead workers without central nervous system symptoms also showed decrements in performance test scores, which were also correlated with elevated zinc protoporphyrin levels.
Valciukas et al. 1980 [38] USA Cross-sectional	Secondary lead smelter workers	141 Exposed: 90 Control: 51	Not related	Occupational	Blood lead levels (atomic absorption spectrophotometry) and zinc protoporphyrin (ZPP) levels	Block design, Digit Symbol, and Embedded Figures Tests	Multiple linear regression $p < 0.05$	Workers chronically exposed to lead at levels that until recently had been accepted as "safe" are at risk of developing brain dysfunction. The findings suggest that the higher the degree of lead absorption, the higher the degree of risk.

WCST Test, Weschler Test; *MRI*, magnetic resonance imaging; *SVTT Protocols*, simple visual reaction time protocols; $CV_{RR:\ R\text{-}R}$, interval variability; $C\text{-}CV_{LF}$ and $C\text{-}CV_{HF}$, two component Cvs of the CV: reflecting sympathetic and parasympathetic activities, respectively; *VEP* or *BAEP*, visual and brainstem auditory evoked potentials

China (Murata et al. 1995; Yi-lan et al. 1985), and Singapore (Jeyaratnam et al. 1986), comprising 2918 patients (sum of the 12 studies).

From these studies, six were case-control (Baker et al. 1984; Baker et al. 1985; Jeyaratnam et al. 1985; Murata et al. 1995; Seo et al. 2015; Yi-lan et al. 1985), four cross-sectional (Cordeiro et al. 1996a; Schwartz et al. 2001; Valciukas et al. 1978; Valciukas et al. 1980), and two cohorts (Baker et al. 1983; Balbus et al. 1998). Most of the articles analyzed the amount of Pb in the exposed group employing blood and urinary dosages. Some even performed a complete blood count to identify other possible alterations. Regarding neurological tests, many studies used questionnaires as a prior evaluation. For the main analyses, the main tests were Wechsler's tests, mainly Digit Symbol, and Profile Mood.

All the studies elected had a group of workers not exposed, called the control group. This control group was confirmed through the dosage of Pb in blood and compared to the exposed group.

One of the studies analyzed was Baker et al. (1983), which analyzed 61 workers belonging to the control group and did a blood dosage and found that the values of the control group, or non-exposed group, were 18.6 μg/dl (mean) and 3–36 μg/dl (range), while the exposed group presented 33.89 μg/dl (mean) and 8–80 μg/dl (range).

Baker et al. (1985) analyzed 14 controls and 36 exposed. During the study period, 1980–1982, a reduction in the participants' blood dosage of Pb was noticed because of the countless implementations that the industry in question made with the objective of reducing exposure to Pb and improving working conditions. Therefore, the levels of the control group were 25.1 μg/dl (10–42) in the first year of research, 22.9 μg/dl (7–37) in the second year, and 21.5 μg/dl (8–31) in the last year of research.

Cordeiro et al. (1996a) analyzed 20 controls and 20 exposed where the blood values of Pb were 10.29 μg/dl, with standard deviation of 30.01, maximum value of 16.9 g/dl, and minimum value of 4.5 μg/dl for the control group. The exposed group presented 49.44 μg/dl mean, with 6.83 standard deviation, 58.8 μg/dL as the maximum value, and 35.7 μg/dL as the minimum value.

Another elected study was Jeyaratnam et al. (1986), which analyzed 36 exposed and 15 controls. The mean found was 6.3 μg/dl (4.7–8.6) in the control group and 55.6 μg/dl (25.8–79.3) in the exposed group.

Balbus et al. (1998) correlated Pb values in blood with reaction time. The work did not present blood dosage values but presented graphs with the correlation and the reaction time and concludes that this correlation is true.

In another study, Schwartz et al. (2001) analyzed 803 exposed and 135 controls, where the mean Pb values in blood in the exposed group were 32 μg/dl (15 standard deviation) and in the control group 5.3 μg/dl (1.8 standard deviation).

Seo et al. (2015) analyzed 43 exposed and 41 controls; from the blood tests, we can see that the exposed presents superior results when compared to the control group. The exposed group presented 4.47 μg/dl (0.88–17.82), while the control group presented 2.30 μg/dl (1.27–6.27).

Another analyzed study was Valciukas et al. (1978), where the values were given in percentage. Ninety workers of the exposed group were analyzed, and about 17% presented values below 40 μg/dl, 20% values between 60 and 79 g/dl, and 61% values between 40 and 59 μg/dl. In the control group, 217 workers were analyzed, and about 94% presented values lower than 40 μg/dL and 2% values between 40 and 59 μg/dL.

Valciukas et al. (1980) analyzed 80 exposed workers and 51 control workers, but the blood dosage values of the control group were not informed at work. On the other hand, the values informed from the exposed group are consistent with the values found in the literature when it comes to Pb intoxication.

Finally, Yi-Lan et al. (1985) analyzed about 53 exposed workers and 52 workers belonging to the control group. The exposed group presented a mean of 61.87 μg/dl with SD of 33.05, and the control group presented mean values of 22.06 μg/dl and SD of 12.31.

To confirm the appearance of neurological damage, a series of cognitive tests were performed. Some studies (Baker et al. 1985; Cordeiro et al. 1996a; Jeyaratnam et al. 1986; Schwartz et al. 2001; Valciukas et al. 1978) used the Digit Symbol as the evaluation test. In addition to the Digit Symbol, two of the articles also used Profile of Mood State (POMS) as the evaluation method (Cordeiro et al. 1996a; Schwartz et al. 2001). Finally, Schwartz et al. (2001) and Cordeiro et al. (1996a) also used the Weschler Memory Tests.

Qualitative synthesis

The main methodological problems detected in the studies were related to confounding factors (all). Majority of these studies carried out analyzes to reduce distortions, contributing to reducing the possibility of bias (Baker et al. 1984; Baker et al. 1983; Cordeiro et al. 1996a; Jeyaratnam et al. 1986; Murata et al. 1995; Schwartz et al. 2001; Seo et al. 2015; Valciukas et al. 1978; Valciukas et al. 1980; Yi-lan et al. 1985).

Furthermore, it was identified inadequate sampling method (Balbus et al. 1998; Jeyaratnam et al. 1986; Murata et al. 1995) and problems in the correspondence/randomization criterion (Baker et al. 1983; Balbus et al. 1998; Jeyaratnam et al. 1986; Murata et al. 1995; Schwartz et al. 2001; Seo et al. 2015; Yi-lan et al. 1985).

An association between exposure to Pb and neurological damage was found in all 12 studies (Baker et al. 1984; Baker et al. 1985; Baker et al. 1983; Balbus et al. 1998; Cordeiro

et al. 1996a; Jeyaratnam et al. 1986; Murata et al. 1995; Schwartz et al. 2001; Seo et al. 2015; Valciukas et al. 1978; Valciukas et al. 1980; Yi-lan et al. 1985), and the main parameters evaluated for possible neurological damage were related to mnemonic aspects (Baker et al. 1984; Baker et al. 1983; Schwartz et al. 2001; Seo et al. 2015), reaction time (Murata et al. 1995; Schwartz et al. 2001), intelligence (Baker et al. 1984; Baker et al. 1983; Cordeiro et al. 1996a; Valciukas et al. 1978; Valciukas et al. 1980), attention disorders (Baker et al. 1984; Cordeiro et al. 1996a; Jeyaratnam et al. 1986), and mood changes (Baker et al. 1984; Baker et al. 1985; Baker et al. 1983).

The quality evaluation of each study is in Table 2. Of the 12 studies, 4 were categorized as presenting high risk of bias (Baker et al. 1985; Balbus et al. 1998; Jeyaratnam et al. 1986; Yi-lan et al. 1985) and 8 as presenting low risk of bias (Baker et al. 1984; Baker et al. 1983; Cordeiro et al. 1996a; Murata et al. 1995; Schwartz et al. 2001; Seo et al. 2015; Valciukas et al. 1978; Valciukas et al. 1980). Although low-risk studies have shown some problems related to sample size, correspondence/randomization of a control group, dropouts, lack of data, and confounding factors, they were not considered to be significant problems for reducing methodological quality, due to the control of these factors in the studies.

Meta-analysis

Digit Symbol

Four studies reported the performance of the Digit Symbol test. However, one study (Cordeiro et al. 1996a) was excluded from the analysis because it used the Wechsler Adult Intelligence Scale to evaluate this parameter (Fig. 2).

Individuals exposed to Pb (n = 941) have not shown a statistical difference in the mean scores compared to subjects not exposed to Pb (n = 196) (MD = − 3.23 [− 16.50, 10.04]; I^2 > 95%; p = 0.63).

Profile of Mood States

Two studies were included in this analysis (Cordeiro et al. 1996a, Schwartz et al. 2001). Individuals exposed to Pb (n = 823) have not shown a statistical difference in the mean scores compared to subjects not exposed to Pb (n = 155) (MD = − 15.76 [− 37.02, 5.5]; I^2 > 99%; p = 0.15) (Fig. 3).

Certainty of evidence

The certainty of evidence related to the Digit Symbol test in terms of risk of bias was serious due to the problems with the sampling method in one of the studies, exclusion/inclusion criteria, problem in control randomization, presence of confounding factors, and absence of reducing analysis of these factors. Regarding the inconsistency presented as very serious, it was due to the heterogeneity index (I^2) was high (95%). Finally, the imprecision was very serious because the confidence interval of the meta-analysis was wide. There was a big difference between the number of exposed cases and the control group. This way, the certainty of the evidence was very low.

Regarding Profile Mood certainty of the evidence, the risk of bias was not serious, but the inconsistency was serious because the heterogeneity index (I^2) was 99%. Finally, the analysis regarding imprecision was considered serious due to the confidence interval of the meta-analysis was very wide. There was a big difference between the number of exposed cases and the control group. Thus, the level of certainty was very low (Fig. 4).

Discussion

This systematic review aimed to summarize evidence from epidemiological studies of humans that evaluated the association between Pb exposure and neurological damage. Twelve studies were selected; all of them showed an association between Pb exposure and neurological damage, but 9 of them were low risk of bias, according to qualitative analysis. For the quantitative analysis, four studies made it possible to compile their results and were included in the meta-analysis. The findings of meta-analysis did not show a statistical difference between the groups (Pb vs control). The level of evidence reported between the studies was very low. It is worth mentioning that this systematic review and meta-analysis is the first to be elaborated on this theme.

The systematic review is one of the types of bibliographic research, which aims to gather several similar materials from several authors and perform a statistical analysis in case of meta-analysis. It is considered a secondary research because it uses primary studies to make the analysis. In general terms, the systematic review includes research to answer a key question, making a critical study of the literature. It has a guiding question and the main objective to make a review project. After this, the literature is searched through databases to find similar studies, and then established methodological criteria are applied to prepare an analysis.

Considering the importance of this topic to public health, it can be highlighted that Pb toxicity affects several biological systems, especially the CNS, which is one of the main target organs (Maloney et al. 2018). In this perspective, Pb can promote changes in the biochemical homeostasis of neural cells through some mechanisms of molecular action. Among these, we can highlight Pb binding to the sulfhydryl groups present in several proteins and cellular enzymes, which can result in the structural and functional alteration of these biomolecules

Table 2 Checklist of quality assessment and risk of bias evaluation of included studies according to Fowkes and Fulton (1991)

Guideline	Verification list	Baker et al. 1983 [30]	Baker et al. 1984 [28]	Baker et al. 1985 [29]	Balbus et al. 1998 [31]	Cordeiro et al. 1996b [32]	Jeyaratnam et al. 1986 [33]	Murata et al. 1995 [34]	Schwartz et al. 2001 [35]	Seo et al. 2015 [36]	Valciukas et al. 1978 [37]	Valciukas et al. 1980 [38]	Yi-Lan et al. 1985 [39]
Is study design appropriate to objectives?	Objective common design	-	-	-	-	-	-	-	-	-	-	-	
	Prevalence cross-sectional	-	-	-	-	-	-	-	-	-	-	-	
	Prognosis cohort	-	-	-	-	-	-	-	-	-	-	-	
	Treatment controlled trial	-	-	-	-	-	-	-	-	-	-	-	
	Cause cohort, case-control, cross-sectional	0	0	0	0	0	0	0	0	0	0	0	0
Study sample representative?	Source of sample	0	0	0	0	0	0	0	0	0	0	0	0
	Sampling method	0	0	0	+	0	+	0	0	0	0	0	0
	Sample size	0	0	++	0	0	0	+	0	0	0	0	0
	Entry criteria/exclusion	0	0	0	0	0	+	0	0	0	0	0	0
	Non-respondents	0	0	0	0	0	0	0	0	0	0	0	0
Control group acceptable?	Definition of controls	0	0	0	0	0	0	0	0	0	0	0	0
	Source of controls	0	0	0	0	0	0	0	0	0	0	0	0
	Matching/randomization	+	+	+	+	0	+	+	+	+	0	0	+
	Comparable characteristics	0	0	0	0	0	0	0	0	0	0	0	0
Quality of measurements and outcomes?	Validity	0	0	0	0	+	0	0	0	0	0	0	0
	Reproducibility	+	+	0	+	0	0	0	0	0	0	0	0
	Blinding	0	0	0	0	0	0	0	0	0	0	0	0
	Quality control	0	0	0	0	0	0	0	0	0	0	0	0
Completeness	Compliance	+	+	+	0	0	0	0	0	0	0	0	0
	Dropouts	0	0	++	0	0	0	0	0	0	0	0	0
	Deaths	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Missing data	+	+	+	0	0	0	0	0	0	0	0	0
Distortion influences?	Extraneous treatments	0	0	0	0	0	0	0	0	0	0	0	0
	Contamination	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Changes over time	0	0	0	++	0	0	0	0	0	0	0	0
	Confounding factors	++	+	+	+	+	+	+	+	+	+	+	+
	Distortion reduced by analysis	0	0	+	+	0	+	0	0	0	0	0	+
Summary questions	Bias: Are the results erroneously biased in certain direction?	NO	NO	YES	YES	NO	YES	NO	NO	NO	NO	NO	NO
	Confusion: Are there any serious confusing or other distorting influences?	NO	NO	YES	YES	NO	YES	NO	NO	NO	NO	NO	YES
	Chances: Is it likely that the results occurred by chance?	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO

0 = no problem; + = minor problem; ++ = major problem; NA = not applicable

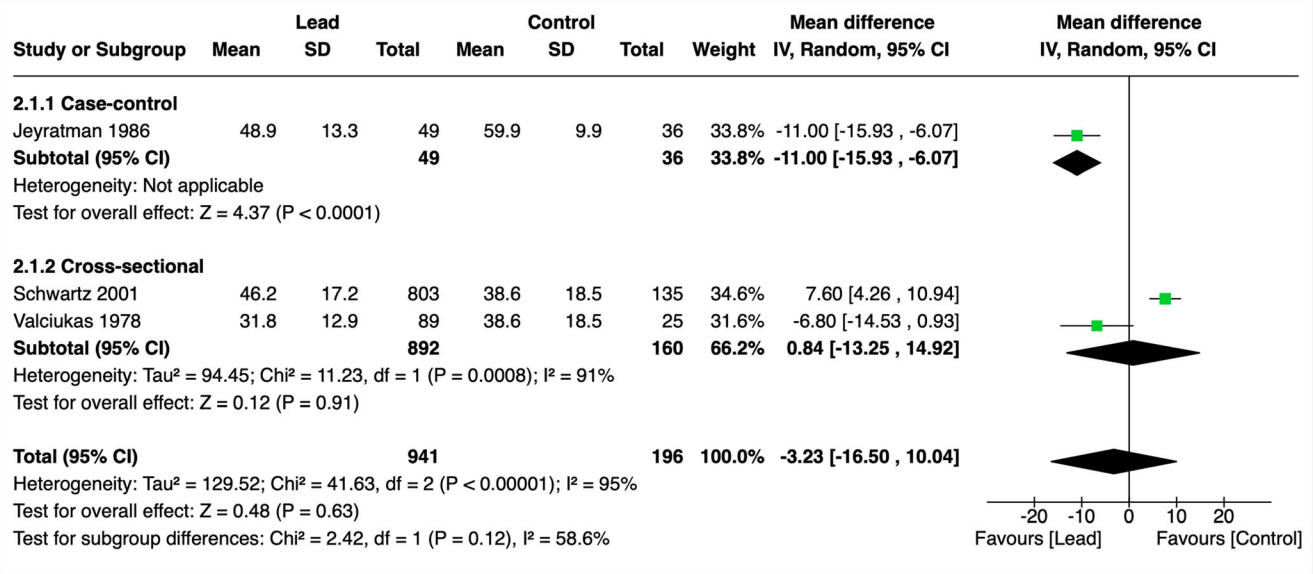

Fig. 2 Forest plot of studies that used Digit Symbol

and consequent homeostatic imbalance (Mitra et al. 2017). As a result, a change in the cellular redox system can occur with the increase of reactive oxygen species and the reduction of cellular antioxidant capacity, configuring oxidative stress (Gomes et al. 2018). This mechanism acts on the oxidation of several biomolecules affecting cellular functions that can result in irreversible processes such as apoptosis (Ayyalasomayajula et al. 2019). Besides, Pb ability to alter the metabolism of calcium ions (Ca^{2+}) in the cell can compromise regulatory functions such as cell signaling and molecular transport (Kasten-Jolly and Lawrence 2018).

Monitoring Pb levels in populations susceptible to exposure is an important tool to understand how Pb is harmful to living beings. The maximum permissible limit recommended by the World Health Organization is 40 μg/dl. Above these levels, scientific evidence supports that subclinical effects may occur in contaminated individuals (WHO 1986).

Since Pb contamination is a global problem, many countries are implementing new policies to reduce Pb contamination sources with the help of environmental and public health organs. Because of this, studies on this subject are relevant for use as a source of information for health and environmental organs since several countries do not yet have real data on Pb poisoning in humans (Schifer et al. 2005).

As a consequence of Pb contamination, all the cellular framework may result in neurological damage that involves the memory, motor coordination, and psychological behavior of individuals who have been exposed to Pb for long periods (Cordeiro et al. 1996a). Our review gathered the findings of studies that evaluated the association between exposure to Pb and neurological damage following the evidence-based research protocol, using selection methods and critical analysis of the main findings in a systematic way, and following the PRISMA protocol (Moher et al. 2010).

For the preparation of this review, we adopted the inclusion/exclusion criteria according to our initial question's relevance. Studies with children were excluded, and only studies with adults were included, regardless of gender. Studies that presented a control group composed of individuals not exposed to Pb and similar socioeconomic characteristics to the group of individuals exposed to Pb were also adopted as inclusion criteria.

All included studies analyzed individuals who were exposed to Pb in an occupational context. Our findings support the idea

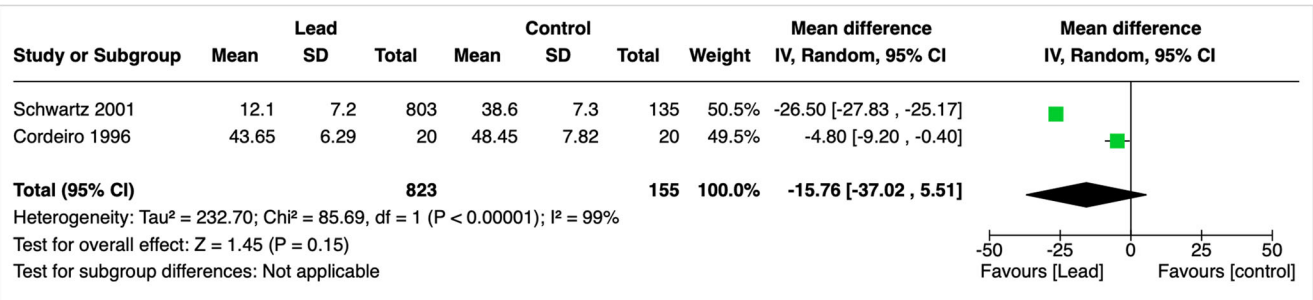

Fig. 3 Forest plot of studies that used Profile of Mood States

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lead	No lead	Relative (95% CI)	Absolute (95% CI)		
Digit symbol												
3	observational studies	serious [a]	very serious [b]	not serious	serious [c]	All plausible residual confounding would reduce the demonstrated effect	941	196	-	mean **3.23 lower** (16.5 lower to 10.04 higher)	⊕◯◯◯ VERY LOW	Not Important
Profile Mood												
2	observational studies	not serious	very serious [b]	not serious	serious [c]	All plausible residual confounding would reduce the demonstrated effect	823	155	-	mean **15.76 lower** (37.02 lower to 5.51 higher)	⊕◯◯◯ VERY LOW	Not Important

Fig. 4 Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) instrument. *CI*, confidence interval. [a]One of the articles presented problems with sampling method, exclusion/inclusion criteria, problem in control randomization, confounding factors, and absence of reduction analysis of these factors. [b]The heterogeneity index (I^2) was over 90%. [c]The confidence interval of the meta-analysis was very wide, and there was a big difference between the number of exposed cases and the control group

that exposure to Pb in adults can cause neurological damage. The neurological manifestations caused by this exposure were mood disorders, in which these workers reported symptoms consistent with those of depression, fatigue, tension, anger, and confusion in all studies. Other parameters were affected, such as short-term memory (partially visual memory), psychomotor speed and dexterity, and verbal concepts. Of the 12 articles elected, the majority of them showed decreased cognition and motor loss, in addition to language deficits.

The evaluation of methodological quality was performed using the Fowkes and Fulton protocol (Fowkes and Fulton 1991). A low risk of bias was observed in most studies (Baker et al. 1984; Baker et al. 1983; Cordeiro et al. 1996a; Murata et al. 1995; Schwartz et al. 2001; Seo et al. 2015; Valciukas et al. 1978; Valciukas et al. 1980; Yi-lan et al. 1985). Although some problems were still present in the research design and execution of these studies, biased results were avoided due to the presence of control over the study confounding variables. This analysis allowed the observation of the main aspects regarding the study design, definition of the samples, reliability of the outcomes, and influence of distortions. Besides these results, three studies presented several methodological problems resulting in a high risk of bias (Baker et al. 1985; Balbus et al. 1998; Jeyaratnam et al. 1986), due to problems in the sample size, randomization, drop-outs, presence of confounding factors, and the absence of analysis to reduce these factors.

Regarding the neurological tests adopted by the studies, the high variability of tests was reported across the studies. Among the most used tests in the studies are the Digit Symbol and POMS. The Digit Symbol is a neuropsychological test sensitive to brain damage, dementia, age, and depression. However, it is not sensitive to the location of brain damage, although it is the most used in the analysis (Benedict et al. 2017). It consists of pairs of symbols and digits, followed by a list of digits (Benedict et al. 2017). Three articles used the Digit Symbol test: Jeyaratnam et al. (1986), Schwartz et al. (2001), and Valciukas et al. (1978). The POMS is a psychological rating scale used to assess transient and distinct moods. POMS measures six different dimensions of mood changes over a period (Langdon et al. 2012). These include stress or anxiety, anger or hostility, vigor or activity, fatigue or inertia, depression or discouragement, and confusion or bewilderment. A five-point scale ranging from "nothing" to "extremely" is administered by the experimenters to the patients to assess their mood (Yokoyama et al. 1990). The articles analyzed with this test were those by Schwartz et al. (2001) and Cordeiro et al. (1996a).

The meta-analysis was hard to conduct, because of the different methodology of evaluation adopted among the studies, or due to the lack of standard deviation data and clinical heterogeneity among them. In this sense, the analysis of the certainty of evidence evaluated by the GRADE tool was very low, not only due to the small number of articles but also because of the high risk of bias, inconsistency, and imprecision. The serious risk of bias on the Digit Symbol test was because Jeyaratnam et al. (1986) had a problem with the sampling method and did not show clearly the exclusion and inclusion criteria. Also, they had an issue in control randomization, presence of confounding factors, and absence of reduction analysis of these factors. Besides, both Digit Symbol and Profile Mood tests had a high heterogeneity index (I^2), which affected the inconsistency, and a wide confidence interval from the meta-analysis results, with a big difference between the number of exposed cases and the control group, affecting the imprecision of the evidence.

Thus, these two tests may not be the best choice for the neurological analysis of those exposed to Pb. Most of the articles included in this review showed an association between Pb and neurological damage that could not be proven on the statistical

analysis and had a very low level of evidence. If there was a standardization of tests or if more suitable neurological tests were used, such as the Mini-Mental State Examination (MMSE), it would be more appropriate to perform a quantitative analysis. The MMSE allows assessing cognitive function, which is often applied in clinical settings for detecting cognitive impairment, dementia progress follow-up, and monitoring of treatment response (Tombaugh et al. 1996). In the presence of a better protocol of standardization, even for the tests included in the meta-analysis, the results would probably be similar among the studies, reducing confounding factors and statistical and methodological heterogeneity.

During the formulation of this manuscript, some situations appeared, making it difficult to analyze such articles listed as final. All of them use neurological tests as a clinical analysis method to confirm damage or reduction of motor and cognitive activity of the sample group, whether exposed or control, but little is explained about each one of the methodologies, and, when comparing the articles with each other, a lack of pattern is noticed, resulting in barriers to a final analysis. The tabulation of results is also an important point to be taken into consideration since there is a lack of test values presented in the methodology, and there is no standard value for comparison, such as Balbus et al. (1998), Valciukas et al. (1978), and Valciukas et al. (1980), which do not present the dosage values of Pb in blood.

Finally, our evaluation confirms that there is an association between exposure to Pb and the appearance of neurological damage in exposed workers. However, these studies need to undergo new methodological evaluations to improve the understanding of persistent doubts and thus, clarify the mechanisms and events associated with this exposure. Thus, studies that aim to show whether Pb is associated with neurological damage in the exposed population should take into consideration an appropriate study project, seeking to minimize the confounding factors highlighted here in this review, such as the neurological tests chosen and employed in each article. We also would like to recommend that the studies choose reference subjects that are similar to the study group with monitoring of Pb levels in both groups and also suggest that all analyses should be performed in subgroups according to a standardized age range in future studies inside this topic.

Conclusion

This systematic review and meta-analysis gather epidemiological evidences showing that exposure to Pb can impair the neurological function of humans living in exposed areas, especially factory workers. However, in our meta-analysis, there was no statistical difference, and the analysis of the level of evidence showed very low certainty. Therefore, the evidence gathered in this review about this association must be interpreted with caution, and in addition, more robust observational studies still need to be done to better clarify this association. Although final papers relate neurological damage to exposure to Pb, more research is needed on this relationship using more sensitive methodological tools. It is important to emphasize the importance of further assessment and analysis to better elucidate the possible mechanisms involved and whether there is an association between Pb exposure and neurological damage.

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Code availability Not applicable

Authors' contribution Walessa Alana Bragança Aragão and Déborah Ribeiro Frazão: Methodology, Software; Luciana Guimarães Eiró: Data curation, Writing — Original draft preparation; Maria Karolina Martins Ferreira: Visualization, Investigation; Rafael Rodrigues Lima, Lucianne Cople Maia and Nathalia Carolina Fernandes Fagundes: Supervision; Rafael Rodrigues Lima: Conceptualization; Nathalia Carolina Fernandes Fagundes: Software, Validation; Renata Duarte Souza-Rodrigues, Rafael Rodrigues Lima and Lucianne Cople Maia: Writing — Reviewing and Editing. All authors read and approved the final manuscript.

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Data Availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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