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Review

Exposure to lead increases the risk of meningioma and brain cancer: A meta-analysis

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ABSTRACT

Objective: To analyze the relationship between environmental lead exposure and various types of brain tumors.
Methods: Search databases PubMed, Web of Science, Embase and Chinese National Knowledge Infrastructure (CNKI) as of July 1, 2019. Stata 15.0 software was used for analysis.
Results: In the case control, lead exposure was associated with gliomas and meningiomas 0.82 (95 % CI: 0.69, 0.95) and 1.06 (95 % CI: 0.65, 1.46). In the cohort study, lead exposure was associated with brain cancer and meningiomas 1.07 (95 % CI: 0.95, 1.19) and 1.06 (95 % CI: 0.94, 1.17). The risk of childhood brain tumors associated with parental lead exposure was 1.17 (95 % CI: 0.99, 1.34).
Conclusions: Lead may be a risk factor for meningiomas and brain cancers. However, the glioma results suggest that lead may be a protective factor, which needs to be further studied.

1. Introduction

Lead is a toxic metallic chemical element, which is widely used as industrial raw material in industrial production [1]. People can be exposed to lead in many ways, but various in different countries [2]. As long as the human body is exposed to lead and absorbed, it will affect the health of various systems of the body, including the nervous system, digestive system and reproductive system. Studies have shown that lead exposure in both occupational and general populations can cause risk of cardiovascular disease, nerve injury, kidney injury, cancer and diabetes mellitus and other systemic diseases [3].

In most research on lead toxicity has been emphasized with attention being given to the brain, since the central nervous system the main target of lead toxicity. In the brain, lead can cause damage to the prefrontal cortex, hippocampus and cerebellum, which can lead to a variety of neurological disorders [4]. Long-term exposure to lead has been reported to increase the risk of brain tumors [5]. Brain is the most common site of central nervous system (CNS) malignant tumors [6], and brain tumors are likely to have functional sequelae [7]. The brain tumors account for only 1.4 % of all cancers, however it is a high incidence disease group that cannot be ignored [7]. Meningioma is the most common primary brain tumor [8]. There is a general lack of understanding of brain tumors in current life, leading to the death of many patients without early diagnosis and treatment.

There have been meta-analyses of risk factors for neurological diseases associated with lead exposure [9–11]. This study was a comprehensive review of brain tumor risk in people exposed to lead.

2. Methods

The study was registered in PROSPERO (CRD42019141399). Its experimental design, implementation and results of this study were based on the preferred reporting project of systematic review and meta-analysis (PRISMA) guidelines [12].

2.1. Search strategy

Keywords were used to search PubMed, Web of Science, Embase and Chinese National Knowledge Infrastructure (CNKI) databases until July 1, 2019. English search terms for PubMed, Web of Science, and Embase are (1) brain cancer OR cerebral cancer OR brin cncer OR brain tumor; (2) lead exposure; and (3) (1) AND (2). Chinese retrieval strategy of CNKI database are brain tunmor and lead.

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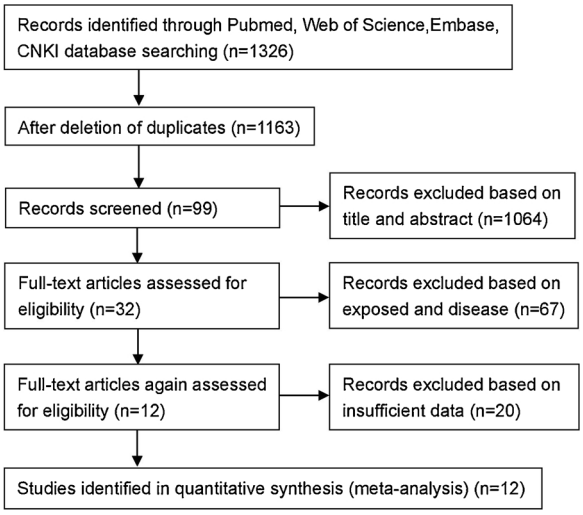

Fig. 1. Literature screening flow chart.

2.2. Document selection

Studies unrelated to lead and brain tumor risk were excluded based on titles and abstracts. Data extraction was made according to the following criteria: (1) specify exposure to lead; (2) the research object is the population; (3) the outcome of the brain tumor; (4) the literature has risk ratio (RR) or odds ratio (OR) value and corresponding 95 % confidence interval (CI), or it can be obtained through calculation; (5) Sample size > 500. Exclusion criteria: (1) literature of the same study or the same institution at different times; (2) problems existed in the research, such as design defects, poor literature quality and unmodifiable errors in statistical methods; (3) through the database and contact with the author who cannot get the full text; (4) review literature.

2.3. Data extraction and quality assessment

Careful data extraction was carried out for the literature included in the study, and the accuracy was guaranteed by two independent authors. Extraction from literature: first author and publication time, study period, region, gender, age, population number, OR/RR and corresponding 95 % CI, and covariates. In addition, all included studies were evaluated using the Newcastle-Ottawa scale (NOS). NOS table scores ranged from 0 to 9, and high-quality studies were defined as 6–9 [13]. High-quality studies were included in this meta-analysis.

2.4. Meta-Analysis

PRISMA checklist was used for subgroup analysis, heterogeneity test and publication bias assessment [12]. Data analysis was performed using Stata 15.0 software. The heterogeneity of the study was assessed using the Q and I^2 squared statistics. If $P > 0.05$ and $I^2 < 50$ % of Q statistics indicate low heterogeneity in the included studies, the fixed effect model should be selected, while the random effect model should be selected [14]. Potential publication bias was assessed using Begg's funnel plots, $P > 0.05$ indicated no publication bias.

3. Results

3.1. Study characteristics

According to the retrieval strategy in Fig. 1, there are 12 studies that meet the requirements [15–26]. This included 7 case-control studies and 5 cohort studies, and 3 of the 7 case-control studies looked at the relationship between childhood brain tumors and parents' risk of lead exposure. The characteristics of these studies are summarized in Table 1, including first author and publication time, study period, region, gender, age, and population number. 7 studies were conducted in the United States, and 11 studies were published after 2000. NOS scores of 11 studies rangedd from 6 to 9, indicating good quality of included literature.

3.2. Meta-analysis of lead exposure and brain tumor risk

Fig. 2A shows the association between lead exposure and adult brain tumor risk in case-control studies when all types of brain tumors were analyzed together, OR = 1.00 (95 %CI: 0.92, 1.07).

After identifying tumor types, the risk OR of lead exposure with glioma and meningioma was 0.82 (95 % CI: 0.69, 0.95) and 1.06 (95 % CI: 0.65, 1.46), respectively. Fig. 2B shows the association between lead exposure and adult brain tumor risk in cohort studies, RR = 1.08 for all brain tumors (95 % CI: 0.96, 1.19), and risk RR for brain cancer and meningioma was 1.07 (95 % CI: 0.95, 1.19) and 1.06 (95 % CI: 0. 94, 1.17), respectively. Fig. 2C shows the relationship between parental lead exposure and the risk of childhood brain tumors, OR = 1.17 (95 % CI: 0.99, 1.34). Parents' exposure to lead may be a risk factor for brain tumors in children. Meta-analyses of case-control studies suggest that lead exposure may not be a risk factor for all brain tumors, but results of cohort studies suggest that lead is a risk factor for brain tumors. This may be because case-control studies and cohort studies focus on different types of tumor outcomes.

Table 1
The characteristics of 12 studies.

First author (year)	Time period	Area	Sex	Age	Sample size	NOS
Case-control study						
Parent ME (2017) [15]	2000-2004	*	M/F	30-69	1800/5160	8
Bhatti P (2011) [16]	1994-1998	US	M/F	> 19	506/505	6
Rajaraman P (2006) [17]	1994-1998	US	M/F	> 18	686/799	7
Cocco P (1999) [18]	1984-1992	US	F	–	375/1459	6
Cohort study						
Steenland K(2017) [19]	1975-2012	US	M	–	88000	7
Liao LM (2016) [20]	1996-2000	China	F	40-70	73363	7
McElvenny DM (2015) [21]	1975-2012	Brtitish	M/F	–	9122	6
van Wijngaarden E (2006) [22]	1979-1990	US	M/F	–	637162	6
Navas-Acie´n A (2002) [23]	1971-1989	Sweden	M	25-64	1516552	7
Case-control : Parents with lead[$]						
von Ehrenstein OS(2016) [24]	1990-2007	US	M/F	< 6	26/19765	6
Keegan TJ (2013) [25]	1962-2006	Brtitish	M/F	< 15	11119/11039	6
Kerr MA (2000) [26]	1976-1987	US	M/F	< 15	183/372	6

- Indicates that it was not clearly indicated in the study; M male, F female;
[$] These case-control studies looked at parents' exposure to lead and their children's risk of developing brain tumors;
* The study was conducted in seven countries: Australia, Canada, France, Germany, Israel, New Zealand and the UK.

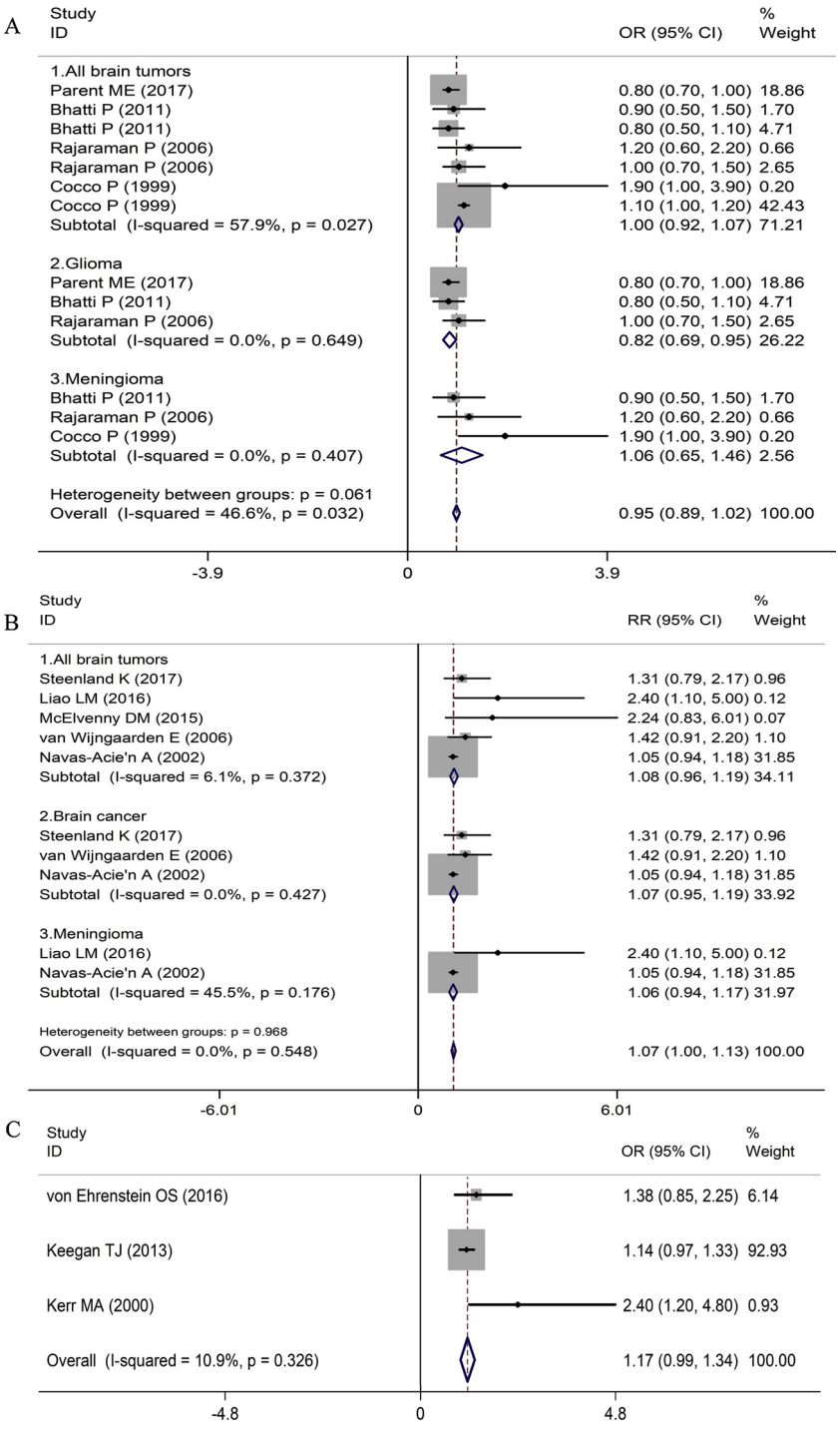

Fig. 2. Pooled random-effects OR/RR (95 % CI) of brain tumor risk with lead exposure.

3.3. Heterogeneity and publication Bias

Fig. 2A Significant heterogeneity was found in 7 studies of all tumor types in the case-control group ($P < 0.05$, $I^2 = 57.9$ %). It was found that the study period, population size and age difference may be the reasons for heterogeneity. Heterogeneity can be explained by subgroup analysis.

Begg's funnel charts show asymmetry, but no statistically significant publication bias. The results of Egger's regression confirmed an association between lead exposure and brain tumors (all $P > 0.05$). P values are 0.059, 0.221 and 0.296 respectively.

4. Discussion

To investigate the relationship between lead exposure and brain tumor risk in population, a meta-analysis of 12 studies was conducted. The study included all previous eligible case-control and cohort studies from which OR/RR, and its corresponding 95 % CI were extracted or calculated. Brain tumors were classified, and subgroup analysis was carried out when the conditions were met.

The risk relationship between heavy metals and brain tumors has been reviewed, but only one article looked at the risk of lead and brain tumors [5], even if the brain has the highest concentration of lead in the body except bones and teeth [27]. Lead poisoning was diagnosed

internationally with blood lead level ≥100 μg/L [28]. Only 2 of the 12 included articles calculated the population's lead exposure, with cumulative exposure of ≥100 Mg/m3-y and blood lead level of 260 μg/L, respectively. Although most of the included studies did not calculate lead exposure, but they looked at the risk relationship between lead and two types of brain tumors.Therefore, this study conducted a subgroup analysis to analyze the risk relationship between lead exposure and different types of brain tumors.

In case-control and cohort studies, the risk relationship between lead exposure and meningiomas was consistent (OR/RR = 1.06). Moreover, meta-analysis showed that lead exposure may be a risk factor for meningiomas. In the case-control study, the risk of lead exposure and glioma OR = 0.82, suggesting that lead may be a protective factor for glioma; in the cohort study, lead exposure may be a risk factor for brain cancer (RR = 1.07). The results of gliomas' meta-analysis are inconsistent with other types of brain tumors, which may be related to the type of brain tumors. The most common endogenous brain tumors in adults are gliomas, such as glioblastoma and astrocytoma, which appear in the entire nerve axis and exhibit different biological behavior [29].

Three studies in the meta-analysis were about the risk of brain tumors in children and parents after exposure to lead. Lead can be easily transferred from the mother to the fetus through the placenta [30]. When the mother is exposed to lead, the concentration of lead in the fetus is very close to that of the mother. Because lead accumulates in the body for a long time, even if mothers stopped contacting lead many years ago, fetal lead toxicity will occur [31,32]. The meta-analysis showed that the risk of brain tumors in children after parental exposure to lead OR = 1.17, suggesting that parental exposure to lead may be a risk factor for brain tumors in children.

5. Conclusions

This meta-analysis also has some limitations, including the lack of consistency in each study, the study cycle, population size and age differences may affect the results of the study. However, considering the difficulty of large-scale epidemiological research, the inclusion analysis was chosen. More research is needed on the risk relationship between brain tumors and lead exposure after classification.

Meta-analysis showed that lead was a risk factor for meningioma and brain cancer, and when parents were exposed to lead, their children had a higher incidence of brain tumors. The results of glioma suggest that lead may be a protective factor, which needs further study and analysis. Lead exposure is still an important public health issue. It is hoped that this meta-analysis can provide some theoretical basis for lead exposure to brain tumors.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

References

[1] A. Mathee, Towards the prevention of lead exposure in South Africa: contemporary and emerging challenges, Neurotoxicology 45 (2014) 220–223.

[2] E. Obeng-Gyasi, Sources of lead exposure in various countries, Rev. Environ. Health 34 (2019) 25–34.

[3] K. Rehman, F. Fatima, I. Waheed, M.S.H. Akash, Prevalence of exposure of heavy metals and their impact on health consequences, J. Cell. Biochem. 119 (2018) 157–184.

[4] K.S. Liu, J.H. Hao, Y. Zeng, F.C. Dai, P.Q. Gu, Neurotoxicity and biomarkers of lead exposure: a review, Chin. Med. Sci. J. 28 (2013) 178–188.

[5] M. Caffo, G. Caruso, G.L. Fata, et al., Heavy metals and epigenetic alterations in brain tumors, Curr. Genomics 15 (2014) 457–463.

[6] T.A. Dolecek, J.M. Propp, N.E. Stroup, C. Kruchko, CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009, Neuro Oncol 5 (2012) 1–49.

[7] M.M. Vargo, Brain tumors and metastases, Phys. Med. Rehabil. Clin. N. Am. 28 (2017) 115–141.

[8] A.R. Fathi, U. Roelcke, Meningioma, Curr. Neurol. Neurosci. Rep. 13 (2013) 337.

[9] G. Van Maele-Fabry, L. Gamet-Payrastre, D. Lison, Residential exposure to pesticides as risk factor for childhood and young adult brain tumors: a systematic review and meta-analysis, Environ. Int. 106 (2017) 69–90.

[10] T. Vlasak, G. Jordakieva, T. Gnambs, et al., Blood lead levels and cognitive functioning: a meta-analysis, Sci. Total Environ. 668 (2019) 678–684.

[11] B.Q. Guo, H.B. Li, Y.Y. Liu, Association between hair lead levels and autism spectrum disorder in children: a systematic review and meta-analysis, Psychiatry Res. 276 (2019) 239–249.

[12] L.A. MoherD, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews andmeta-analyses: the PRISMA statement, Int. J. Surg. 8 (2010) 336–341.

[13] C.K. Lo, D. Mertz, M. Loeb, Newcastle-Ottawa scale: comparing reviewers' to authors' assessments, BMC Med. Res. Methodol. 14 (2014) 45.

[14] R. DerSimonian, N. Laird, Meta-analysis in clinical trials revisited, Contemp. Clin. Trials 45 (2015) 139–145.

[15] M.E. Parent, M.C. Turner, J. Lavoué, et al., Lifetime occupational exposure to metals and welding fumes, and risk of glioma: a 7-country population-based case-control study, Environ. Health 16 (2017) 90.

[16] P. Bhatti, P.A. Stewart, M.S. Linet, A. Blair, P.D.I. nskip, P. Rajaraman, Comparison of occupational exposure assessment methods in a case-control study of lead, genetic susceptibility and risk of adult brain tumours, Occup. Environ. Med. 68 (2011) 4–9.

[17] P. Rajaraman, P.A. Stewart, J.M. Samet, et al., Lead, genetic susceptibility, and risk of adult brain tumors, Cancer Epidemiol. Biomarkers Prev. 15 (2006) 2514–2520.

[18] P. Cocco, E.F. Heineman, M. Dosemeci, Occupational risk factors for cancer of the central nervous system (CNS) among US women, Am. J. Ind. Med. 36 (1999) 70–74.

[19] K. Steenland, V. Barry, A. Anttila, et al., A cohort mortality study of lead-exposed workers in the USA, Finland and the UK, Occup. Environ. Med. 74 (2017) 785–791.

[20] L.M. Liao, M.C. Friesen, Y.B. Xiang, et al., Occupational lead exposure and associations with selected cancers: the shanghai men's and women's health study cohorts, Environ. Health Perspect. 124 (2016) 97–103.

[21] D.M. McElvenny, B.G. Miller, L.A. MacCalman, et al., Mortality of a cohort of workers in Great Britain with blood lead measurements, Occup. Environ. Med. 72 (2015) 625–632.

[22] E. van Wijngaarden, M. Dosemeci, Brain cancer mortality and potential occupational exposure to lead: findings from the National Longitudinal Mortality Study, 1979-1989, Int. J. Cancer 119 (2006) 1136–1144.

[23] A. Navas-Acién, M. Pollán, P. Gustavsson, B. Floderus, N. Plato, M. Dosemeci, Interactive effect of chemical substances and occupational electromagnetic field exposure on the risk of gliomas and meningiomas in Swedish men, Cancer Epidemiol. Biomarkers Prev. 11 (2002) 1678–1683.

[24] O.S. von Ehrenstein, J.E. Heck, A.S. Park, M. Cockburn, L. Escobedo, B. Ritz, In Utero and Early-Life Exposure to Ambient Air Toxics and Childhood Brain Tumors: A Population-Based Case-Control Study in California, USA, Environ. Health Perspect. 124 (2016) 1093–1099.

[25] T.J. Keegan, K.J. Bunch, T.J. Vincent, et al., Case-control study of paternal occupation and social class with risk of childhood central nervous system tumours in Great Britain, 1962-2006, Br. J. Cancer 108 (2013) 1907–1914.

[26] M.A. Kerr, P.C. Nasca, K.A. Mundt, A.M. Michalek, M.S. Baptiste, M.C. Mahoney, Parental occupational exposures and risk of neuroblastoma: a case-control study (United States), Cancer Causes Control 11 (2000) 635–643.

[27] L.D. White, D.A. Cory-Slechta, M.E. Gilbert, et al., New and evolving concepts in the neurotoxicology of lead, Toxicol. Appl. Pharmacol. 225 (2007) 1–27.

[28] Centers for Disease Control and Prevention, Lead, (2017) https://www.cdc.gov/nceh/lead/.

[29] S. Brandner, Z. Jaunmuktane, Neurological update: gliomas and other primary brain tumours in adults, J. Neurol. 265 (2018) 717–727.

[30] E. Rossipal, M. Krachler, F. Li, D. Micetic-Turk, Investigation of the transport of trace elements across barriers in humans: studies of placental and mammary transfer, Acta Paediatr. 89 (2000) 1190–1195.

[31] D. Bellinger, Teratogen update: lead and pregnancy, Birth. Defects. Res. A. Clin. Mol. Teratol. 73 (2005) 409–420.

[32] H. Hu, M.M. Tellez-Rojo, D. Bellinger, et al., Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development, Environ. Health Perspect. 114 (2006) 1730–1735.