Systematic Review and Meta-analysis of Environmental Toxic Metal Contaminants and the Risk of Ischemic Stroke

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Abstract

Background: Stroke is the second largest cause of mortality (WHO 2014) and long-lasting disability worldwide. Many risk factors are associated with stroke, such as age, gender, chronic illnesses, cardiovascular disease, lifestyle, and smoking. With global industrialization, the roles of environmental contaminants and their association with stroke are still unclear and have attracted much more attention. **Materials and Methods:** We conducted a systematic review on the environmental toxic metal contaminants and the risk of ischemic stroke. A comprehensive literature search was carried out till June 30, 2021 from databases such as PubMed, Science Direct, Embase, and Scopus. The quality of all the articles which met our inclusion criteria was assessed using Newcastle–Ottawa scaling, and four eligible studies were included for our systematic review. **Results:** The serum and urine cadmium concentrations were positively associated with the risk of ischemic stroke. There was an inverse association of serum and urine concentrations of mercury (Hg), serum concentration of gold and cerium with ischemic stroke, and the serum and urine concentrations of lead (Pb) had no association with ischemic stroke risk. **Conclusion:** The study showed strong associations between heavy metals and ischemic stroke, but more studies are required to prove the associations.

Keywords: Heavy metals, ischemic stroke, meta-analysis, metal contaminants, stroke, systematic review

Introduction

Stroke, a very debilitating illness, is currently one of the most common causes of health impairment worldwide.[1] In 2019, the global prevalence of stroke was 101.5 million people, but the prevalence of ischemic stroke was 77.2 million people, with 3.3 million people dying from ischemic stroke.[2] The risk of stroke is linked to myriad of factors, including age, gender, chronic illnesses (diabetes, hypertension), cardiovascular disease, lifestyle variables (obesity, stress), and smoking.[3-5] Stroke can be either ischemic or hemorrhagic, which can be distinguished by the blockage or rupture of blood vessels, followed by tissue damage or sometimes cell death. Ischemic stroke accounts for approximately 85% of all recorded instances, with hemorrhagic stroke accounting for the remaining 15%.[6] Ischemic stroke is a significant cause of disability and mortality globally, owing to the high sensitivity to even short (minutes) blood flow disruptions of the brain parenchyma.

The environment is constantly subjected to various chemical loads originating from natural and human sources. The release of these compounds from anthropogenic sources continues to rise due to growing industrialization and urbanization in many parts of the world. Heavy metals are a class of nonbiodegradable environmental pollutants widespread in nature. Though the negative consequences of their exposure, such as lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As), are well recognized, their use and quantities in the environment are growing day by day.[7] Furthermore, recent studies have linked persistent intoxication in humans to cardiovascular effects such as elevated blood pressure.[8] Heavy metal toxicity may also be linked to an increased risk of stroke because elements such as Pb, Cd, and Hg disrupt the vascular system.[9,10] In reality, the exposed people have a high frequency of noncommunicable illnesses like hypertension and diabetes.[11] Hypertension and diabetes can be recognized as risk factors for ischemic stroke. For instance, the mortality rate owing to ischemic stroke grew by 28% in Brazil's northern area, but reduced by 13%–25% in the country's south-eastern parts during the period 2000–2010.[12]

The pieces of evidence of involvement of heavy metals in ischemic stroke can be cited from different clinical and preclinical studies. Chronic exposure to Pb causes deficiency of antioxidants and disturbs the antioxidants' activity by replacing their active cofactor metals.[13] It is also found that the exposure

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of Pb in childhood results in a region-specific reduction in adult gray matter volume of participants, which is strongly linked with the small vessel disease.[14,15] Hg exposure may result in cerebral vasospasm, reduced nitric oxide (NO) bioavailability, increased oxidative stress, neuroinflammation, amyloid plaque formation, and cholinergic and serotonergic transmission disturbances.[16,17] Cadmium toxicity is the major contributor to cellular oxidative damage. In a study conducted in an animal model, 24-h exposure of Cd in the brain resulted in alteration of oxidative stress markers and brain inflammatory markers.[18]

Although numerous studies have been conducted on the toxicity of specific metals in the environment in biological systems, a comprehensive and systematic study investigating the association between heavy metal exposure and the risk of ischemic stroke has not been conducted. To our knowledge, this will be the first systematic study to analyze and evaluate the association between heavy metals and ischemic stroke risk.

Materials and Methods

Literature search

A systematic literature search for the review was done by the investigators (PD, PG) on June 30, 2021. The databases used were PubMed, Embase, Scopus, and Science Direct; the MESH terms used for the search were heavy metals [TIAB] AND cerebral stroke [TIAB] OR ischemic stroke [TIAB]. Out of 182 results from PubMed, 30 were found relevant. Three articles were included for the systematic review and other articles were excluded as they fell under the exclusion criteria. The search in the Science Direct database provided 83 results, out of which one article was included for the systematic review and others were excluded due to insufficient information and duplication. The search in Embase database showed 30 results, out of which two were relevant but were excluded due to repetition. The search in Scopus resulted in 40 results, out of which one article was relevant but was excluded due to duplication. All the articles published from 1998 to 2021 were included [Figure 1]. The systematic review has been registered in PROSPERO with registration id: CRD42021267391.

Inclusion and exclusion criteria

The inclusion criteria for the search were all the case–control studies conducted in human adults (age above 18 years) and the studies that gave a direct link between ischemic stroke and heavy metals. All the preclinical studies, model studies, reviews, case reports, newsletters, and the studies from which the association between ischemic stroke and heavy metals cannot be extracted were excluded. The search was restricted to articles in English language.

Study selection and data extraction

The two investigators (PD, PG) independently searched for suitable studies in the four databases. The systematic search was well assisted by the thoroughly defined inclusion and exclusion criteria. After screening for population, abstract, and title of the study, each article's relevant information was added to the well-defined table for further easy analysis and understanding. The table included information like author's name, year of publishing, duration of the study, study design, sample size, age and sex, heavy metals, sample collection, assay method, confounders adjusted, the conclusion from the study, relevant result, and limitation of the study.

Quality assessment

Newcastle–Ottawa scale is an easy and convenient tool to calculate the quality of the nonrandomized studies, including case–control and cohort studies. The reviewers (PD, PG) ensured the quality of all the case–control studies included in the systematic review by Newcastle–Ottawa scaling.

Results

Through the systematic search, 335 records were gathered from a different database. Out of these, four records seemed to link to the topic directly and were chosen for the systematic review. The general characteristics of the included studies are described in Table 1. Out of four studies, two were nested case–control and two were case–control design. All the studies were published between 2005 and 2020.

Two studies focused on the heavy metal Cd among the four eligible studies.

In the studies conducted by Borné *et al*.,[19] Cd levels were measured in 4156 subjects (39.2% men; mean standard deviation [SD] age 57.3±5.9 years) without a history of stroke. The patients were followed up for a mean of 16.7 years, during which 221 patients developed ischemic stroke. The result showed a positive association between serum Cd concentration and ischemic stroke (hazard ratio [HR]: 1.66, 95% confidence interval [CI]: 1.01–2.72). Incidence of ischemic stroke was associated with both carotid plaque (HR: 1.44, 95% CI: 1.09–1.90; $P = 0.009$) and Cd (HR for quartile [Q] 4 vs. Q1–3: 1.95, CI: 1.33–2.85; $P = 0.001$), after adjustment for risk factors. There was a significant interaction between Cd and plaque, concerning the risk of ischemic stroke ($P = 0.011$). After adjustment for risk factors, subjects with plaque and Cd in Q4 had an HR of 2.88 (CI: 1.79–4.63) for ischemic stroke, compared to those without plaque and Cd in Q1–Q3.

The other study conducted by Chen *et al*.[20] investigated the relationship between urine Cd concentration and the risk of ischemic stroke. Out of 2540 participants from a random cohort 660 incidents of ischemic stroke was found. This case–control population was chosen from a Reasons for Geographic and Racial Differences in Stroke (REGARDS) study cohort. This study showed that the creatinine-corrected urine Cd concentration was significantly associated with ischemic stroke (HR: 1.82, 95% CI: 1.06–3.11). The adjustment with the cofounders was significantly related to the P value of 0.0004.

The study conducted by Medina-Estévez *et al*.[21] analyzed 45 inorganic elements to find their relationship with stroke. The study was done in 92 patients and 86 controls. The study concluded a positive association of Pb with ischemic stroke in

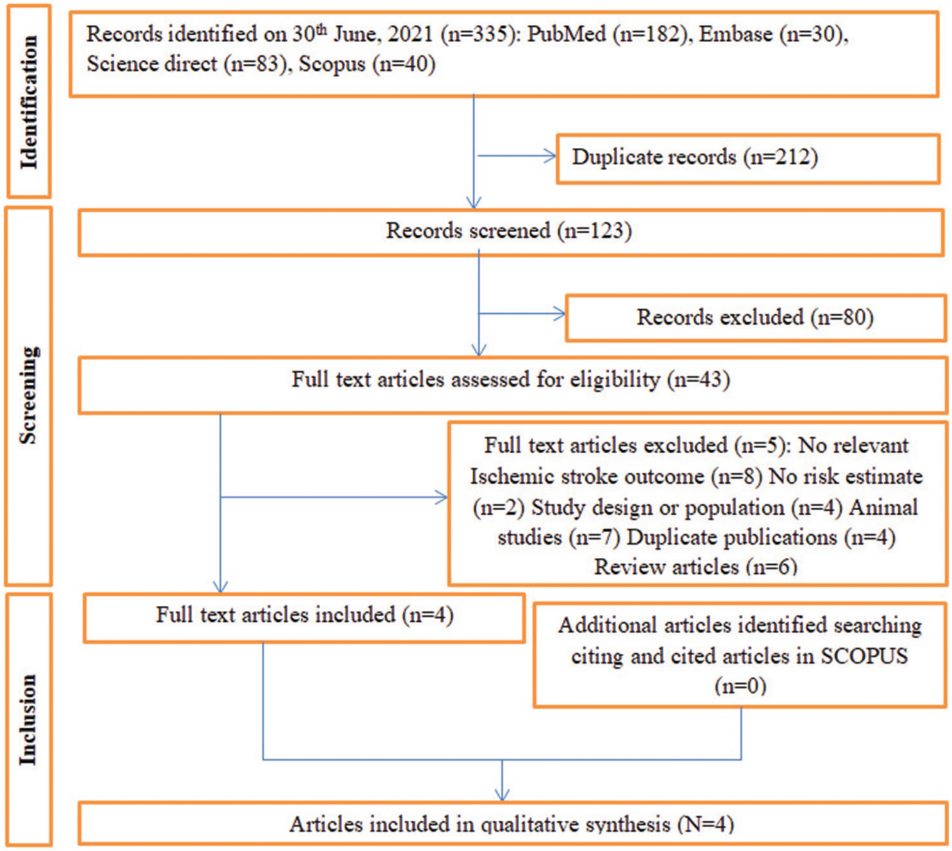

Figure 1: Study flowchart

univariate and multivariate analyses (odds ratio [OR] = 1.65, 95% CI: 1.09–2.50 and OR = 1.91, 95% CI: 1.20–3.04, respectively). They also suggested an inverse association of gold (Au) and cerium (Ce) with ischemic stroke in multivariate analysis (OR = 0.81, 95% CI: 0.69–0.95 and OR = 0.50, 95% CI: 0.31–0.78, respectively).

While the case–control study by Lin *et al*.[10] showed the inverse association of serum and urine levels of Hg with ischemic stroke patients (*P*-values 0.032 and 0.006, respectively). They also found no significant difference in serum and urine Pb (S-Pb) and As (S-As) levels in either group. Thirty-three patients selected were the first-ever acute ischemic stroke patients, while 39 healthy controls were selected.

Pathogenesis

Cd has been associated with proinflammatory effects in experimental and human studies. It has been shown to increase the necrosis and apoptosis in macrophages exposed to increased Cd levels. Additionally, Cd inhibits fibroblast proliferation and collagen synthesis in vascular cells. These effects could severely impair the function of endothelial cells and reduce the stability of the carotid plaque.[22,23] Cadmium is supposed to be genotoxic and promotes DNA damage along with gene deletion and adverse transcriptional and cytoplasmic changes in various rodent cultured cells such as ovarian, myoblasts, liver cells, and osteoblasts. These changes could lead to enhanced apoptosis along with impaired proliferation and differentiation.[24,25]

However, other heavy metals like Pb and Hg seem to have a protective role in endothelial function. However, metals like lead also cause cell damage, apoptosis, and chromosomal abnormalities at a toxic dosage. The dichotomy of having a protective role in vascular endothelium on one hand to cellular damage on the other may be dose dependent, with the latter being obvious at toxic dosages.[26,27] *In vitro* studies have demonstrated that the impairment of vascular endothelial layer caused by Cd toxicity is antagonized by Zinc (Zn) through prevention of Cd-induced de-endothelialized area formation along with a detachment of [3H] thymidine-labeled endothelial cells. Zn further reduces the incorporation of [3H] thymidine into the growing cells, and it also prevents Cd-induced cell damage indicated by the activity of lactate dehydrogenase. In animal models, Zn supplementation has been shown to have antioxidative effects mainly by preventing the Cd-induced changes in lipid peroxidation and other lipid compounds. Additionally, zinc causes decreased Cd accumulation, thereby reducing the Cd-induced apoptosis by 1.5–2-folds.[28]

Meta-analysis

In the association between heavy metals and ischemic stroke analysis, we observed a 17% reduction in the risk of ischemic stroke with Risk Ratio 0.83(RR=0.83, 95% CI: 0.76–0.90). In

Table 1: General characteristics of the included studies

Author's name	Study duration	Heavy metal analyzed	Study design	Case–control sample size	Sex and age	Method of exposure assessment (blood, urine, diet)/assay method	Confounders adjusted
Borné *et al*.[19] (Sweden)	1991-2010	Cadmium	Nested case–control	221 IS patients 3935 nonischemic stroke patients	Male and female	Blood/inductively coupled plasma mass spectrometry	Age, sex, waist circumference, smoking status, diabetes mellitus, BP, BP-lowering drugs, low-density lipoprotein, high-density lipoprotein, lipid-lowering drugs, and C-reactive protein
Chen *et al*.[20] (USA)	January 2003-October 2007	Cadmium	Nested case-control	680 IS patients, 1860 controls	Male and female ≥45 years of age	Urine/NHANES method with a NEXION 300X quadrupole inductively coupled plasma mass spectrometry	Age, sex, race (black or white), age-sex and age-race interactions, and region (Stroke Buckle, the rest of Stroke Belt, or non-Stroke Belt region)
Lin *et al*.[10] (Taiwan)	2012-2013	Pb, Hg, As, and Cd	Case–control	33 acute IS patients/39 healthy controls	Male and female	Serum and urine/inductively coupled plasma mass spectrometry	-
Medina-Estévez *et al*.[21] (Spain)	April 2017 and April 2018	Ag, As, Ba, Be, Cd, Co, Cu, Hg, Mn, Pb, Pd, Se, Sb, Sr, Th, U, V, Zn, Au, Bi, Ce, Dy, Er, Eu, Fe, Ga, Gd, Ho, In, La, Lu, Nb, Nd, Os, Pr, Pt, Ru, Sm, Sn, Ta, Tb, Tm, Y, Yb	Case-control study	92 IS patients/83 healthy controls	Male and female ≥18 years of age	Blood	Smoking, arterial hypertension, dyslipidemia, and coronary cardiopathy

Author's name	Conclusion	Result	Limitations	Newcastle-Ottawa	Sensitivity	Specificity
Borné *et al*.[19] (Sweden)	The cadmium concentration was relatively high for the IS patients and the association remained significant after adjustment for age, sex, and other risk factors. Carotid plaque was also associated with IS, after adjustments for risk factors. When the plaque and cadmium were combined and simultaneously adjusted for risk factors, they exhibited a significant association	There was a significant interaction between cadmium and plaque with respect to the risk of IS	Some of the risk factors are changed during long follow-up, which may affect the cadmium concentration	8	-	-
Chen *et al*.[20] (USA)	This study showed that the creatinine-corrected urine cadmium concentration was significantly associated with IS	This study suggested that cadmium exposure may be an independent risk factor for IS	Urinary cadmium concentration was measured only at baseline. The study did not consider the within-person variation	7	-	-
Lin *et al*.[10] (Taiwan)	The study proved the positive association of lead with stroke in univariate and multivariate analyses. Also suggested an inverse association of gold and cerium with stroke in multivariate analysis	The study found low levels of serum and urine Hg in first-ever patients with AIS, providing new evidence of dysregulated heavy metals in patients with AIS	The study was conducted in a single center with relatively small sample size	9	-	-

Contd...

Table 1: Contd...

Author's name	Conclusion	Result	Limitations	Newcastle-Ottawa	Sensitivity	Specificity
Medina-Estévez *et al*.[21] (Spain)	There was an inverse association of serum and urine levels of Hg with IS (P-values 0.032 and 0.006, respectively). Also suggested that there was no significant difference in serum Pb (S-Pb), As (S-As), and Cd (S-Cd) levels and urine Pb (U-Pb), As (U-As), and Cd (U-Cd) levels in either group	These findings provided new evidence of the potential association of dysregulated heavy metals and other elements in patients with stroke, whose ability to cross the blood–brain barrier has been previously suggested	The study did not provide any information about the mechanism of these elements in stroke	9	-	-

BP=blood pressure, IS=ischemic stroke, NHANES=National Health and Nutrition Examination Survey, AIS= Acute Ischemic Stroke. Ag (silver), As (arsenic), Au (gold), Ba (barium), Be (beryllium), Bi (bismuth), Cd (cadmium), Ce (cerium), Co (cobalt), Cu (copper), Dy (dysprosium), Er (erbium), Eu (europium), Fe (iron), Ga (gallium), Gd (gadolinium), Hg (mercury), Ho (holmium), In (indium), La (lanthanum), Lu (lutetium), Mn (manganese), Nb (niobium), Nd (neodymium), Ni (nickel), Os (osmium), Pb (lead), Pd (palladium), Pr (praseodymium), Pt (platinum), Ru (ruthenium), Se (selenium), Sb (antimony), Sn (tin), Sr (strontium), Ta (tantalum), Tb (terbium), Th (thorium), Tm (thulium), U (uranium), V (vanadium), Y (yttrium), Yb (ytterbium), Zn (zinc)

the subgroup with the measure of association, we observed a significantly higher HR (HR: 1.67, 95% CI: 1.20–2.15); however, a protective effect was noted in the pooled OR analysis (OR = 0.81, 95% CI: 0.74–0.88) [Figure 2].

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to assess and integrate the scientific data from epidemiological research on the association between heavy metal exposure and stroke risk. Atherosclerotic plaque is a well-known and crucial factor for cerebral ischemic stroke. In numerous investigations, Cd has been proven to cause vascular disorders in animals, such as atherosclerosis. The presence of Cd in the environment has been linked to a substantial increase in the incidence of stroke.[29,30] Experimental evidence revealed that Cd could affect endothelial function at doses lower than the reference values.[31] Heavy metals have differed in their effects on the risk of stroke. Cadmium reduces endothelial function, while other heavy metals like zinc and lead have a protective effect and antagonize the adverse impact of cadmium on endothelial function.[22,23,28] The study conducted by Borné *et al*.[19] hurt which was followed over some time the study confirmed that both large artery address chlorosis and small artery occlusion seem to be associated with the presence of plaque and high cadmium concentration. However, there was a nonsignificant association of plaque with cadmium in cardioembolic stroke. Smoking is known to increase cadmium exposure. Although the study adjusted for smoking status, still there could be residual confounding for the same. However, the number of pathogenic subtypes was small and the result of specific subtypes must be interpreted with caution.

In another study done by Medina-Estévez *et al*.[21] of case–control type, the authors tried to investigate the association of 45 inorganic elements with stroke in 92 patients and 83 controls. Blood levels of lead were significantly higher and associated with stroke patients, while gold and cerium were higher in controls and were inversely related to ischemic stroke. Modifiable risk factors were different between the groups, but the sample size of the study was small. Similarly, the study tried to investigate 45 inorganic elements, and the combined effect of these elements is unknown.[21]

Chen *et al*.[20] conducted a case-cohort study including 680 incident ischemic stroke patients out of 2540 participants. After adjustment for confounders, urinary cadmium was associated with an increased incidence of ischemic stroke. However, the observed association was more pronounced among participants in the lowest tertile of serum zinc values. Still, this effect was attenuated and found to be nonsignificant in never smokers. However, in this study, urinary cadmium was only measured at baseline and within-person variation may affect the findings of the study. Moreover, like other observational studies, residual confounding factors from dietary and environmental factors cannot be ruled out.

Lin *et al*.[10] investigated the relationship between the amount of heavy metals and stroke incidence. Consecutive patients of acute ischemic stroke onset within 1 week were selected. The serum levels of lead, mercury, arsenic, and cadmium were determined. The study conducted by Lin *et al*.[10] was the first one that reported the association of low levels of urinary and serum mercury in the first-ever ischemic stroke. Several studies have reported that Hg is not associated with ischemic stroke,[32-34] but one study conducted by Wennberg *et al.*[35] reported that there is a protective association between serum Hg (sHg) and myocardial infarction. While non-significant differences were seen in the serum and urine levels of lead, arsenic, and cadmium. The study had several limitations including a small sample size and the possibility of recall bias for covariates like alcohol consumption, smoking habits, and fish consumption. Also, a single blood and urine sample does not reflect the total body burden.[10]

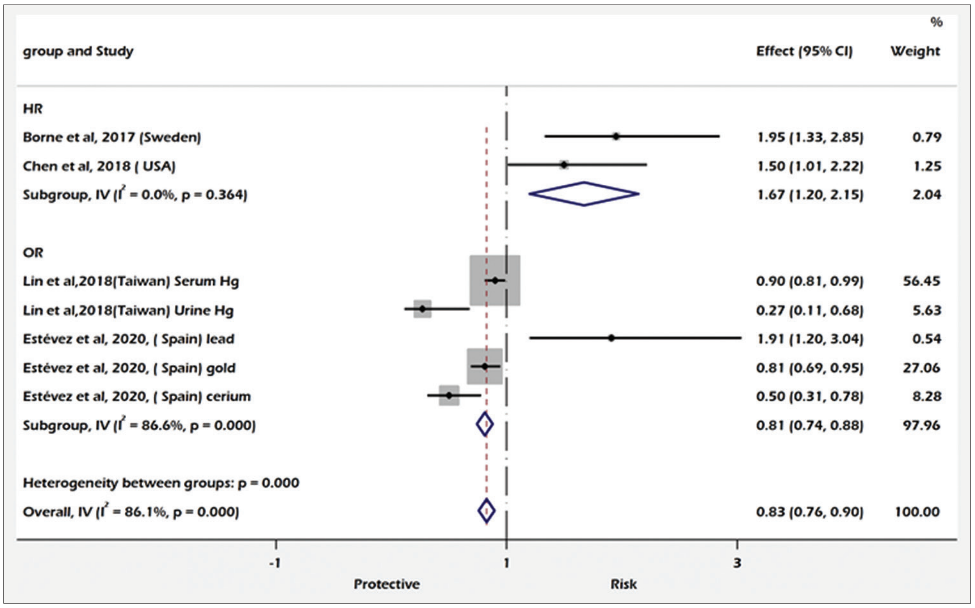

Figure 2: Forest plot of pooled random-effects ORs (95% CI) for the association between heavy metal concentrations and ischemic stroke. CI = confidence interval, OR = odds ratio

There are a few strengths of our review and meta-analysis. First and foremost, this is the first systemic review that compiles all the published literature linking heavy metals and their association with ischemic stroke. Our study also highlighted the plausible pathogenic mechanism of heavy metals causing ischemic stroke, which is mostly derived from the studies published on animal models.

There are several limitations of the present review and meta-analysis. First, the studies are too less in number (only four) to draw conclusive evidence from the review. Secondly, two of the four included studies carried out by Medina-Estévez *et al*.[21] and Chen *et al*.[20] were performed in a small number of patients (92 and 33, respectively), which were significant limitations of the included studies. Third, only one of the studies reported by Borné *et al*.[19] was done prospectively where the patients were followed up for significant duration till they developed ischemic stroke and the Cd levels were measured. At the same time, all the other studies were case–control studies done in a relatively small sample size, which would challenge the external validity of the published studies. Fourth, two studies have used the patients' serum, while the other two have used urine to estimate the heavy metals. Different mediums of measurement can lead to a discrepancy in the interpretation of results.

Previous studies from different cohorts have reported a link between Cd in the blood and cardiovascular illness, particularly carotid plaque.[36,37] Even though causality cannot be established in the study, there are numerous negative consequences of Cd that may raise the risk of stroke. The current findings by Borné *et al*.[19] demonstrated that Cd and carotid plaque have a synergistic effect on the risk of ischemic stroke in the future. Because the entire population was exposed to Cd through their diets and Cd is very slowly removed from the human body, this finding might have significant public health consequences.[19]

The relationship between Cd exposure and the risk of ischemic stroke was maintained among ever smokers and significantly reduced among never smokers in stratified analyses, even though the interaction test was not statistically significant. Aside from the comparatively low amount of Cd exposure among never smokers, the discrepancy might be attributed to the fact that nonsmokers usually lead healthier lifestyles, including eating nutritious food. In addition, detailed information on smoking was collected in the present study, which enabled us to reduce the residual confounding and study the effect of modification by smoking status.

To our knowledge, the study conducted by Chen *et al*.,[20] is the first long-term study that links urinary Cd and the risk of ischemic stroke. Although previous studies have been done, they have focused on all strokes, and hence, there was a lack of information on the stroke types and the Cd concentration measured in the diet. Urinary Cd has been shown to represent long-term exposure and total body load in studies,[38] which is essential for understanding the health effects of Cd exposure in the average population. The current study is noteworthy since it is the first to show that Zn has an inhibitory impact on Cd toxicity in humans. Because bioaccumulation of Cd in the human body is challenging to eliminate effectively,[39] this result has significant clinical and public health implications.

Exposure to toxicological heavy metals including Pb, Hg, As, and Cd is progressively related to cardiovascular and stroke risks.[40-42] For example, various epidemiological studies have shown that higher Pb levels are associated with an increased risk of ischemic stroke.[43,44] Furthermore, Pb exposure has been linked to an increase in the incidence of cardiovascular disease as well as stroke.[45,46] Since a few studies are available in different databases, our review was solely based on observational data that the unmeasured confounders might affect. Therefore, further conclusive trials and research are needed to validate the study in the general population. This will also help us know the risk of adverse health consequences even at a relatively low exposure to these toxic metals. This will guide setting up appropriate legislation, preventive strategies, and standards to tackle the global determinant of ischemic stroke.

Conclusion

Serum and urine Cd concentrations are positively associated, while serum and urine Hg concentrations are inversely related to the risk of ischemic stroke. However, this systemic review does not find any convincing evidence to refute or support the association of any heavy metal as a causative agent of ischemic stroke. A single study revealed that the serum and urine concentration of Pb had no association with ischemic stroke risk. However, more extensive prospective cohort studies are required in larger populations to prove the causal association of metals with acute ischemic stroke.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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