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REVIEW

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# Population-based study of environmental heavy metal exposure and hearing loss: A systematic review and meta-analysis

Fang Wang MSc | Frank Böhnke PhD | Katja Böck MD | Markus Wirth MD, PhD

Department of Otorhinolaryngology/Head & Neck Surgery, Klinikum rechts der Isar der Technischen Universität München, München, Germany

**Correspondence**
Fang Wang, Department of Otolaryngology/Head & Neck Surgery, Klinikum rechts der Isar der Technischen Universität München, Trogerstraße 32, zweite stock, Dr. FangWang Office, Munich 81675, Germany.
Email: harryfangfang520@163.com

## Abstract

**Background and Objectives:** Previous studies have shown an association between environmental exposure to heavy metals and hearing loss. However, the findings regarding the relationship between exposure to different metals and hearing loss development are inconsistent. To address this, we conducted a meta-analysis to explore the link between common heavy metal exposures and hearing loss. This study examined the effects of lead (Pb), cadmium (Cd), and mercury (Hg) pollution on hearing loss at various levels, and systematically reviewed the literature on manganese (Mn), barium (Ba), arsenic (As), and hearing loss.

**Methods:** We conducted systematic searches in five major databases, including PubMed, Web of Science, Embase, Cochrane Library, and Scopus. In addition, we searched three Chinese digital libraries: CNKI, Wanfang Data, and Wipu. From an initial pool of 649 articles, we carefully screened and selected 15 articles for further analysis. The effect sizes from these selected studies were synthesized through a meta-analysis to calculate the overall effect size.

**Results:** Our findings showed that: (1) There was a significant association between Pb and Cd exposure and hearing loss; (2) There is a proportional relationship between the increase of metal index detected in blood and hearing loss; (3) In the PTA measurement of hearing loss at different frequencies, the 4 kHz high frequency range had a stronger correlation with hearing loss than the low frequency, with OR 1.44 (1.22, 1.71); and (4) There was a more significant correlation between Barium (Ba) levels in nails and hair than in urine.

**Conclusions:** The study presented evidence of a significant association between human hearing loss and exposure to lead (Pb) and cadmium (Cd). It not only revealed a positive correlation between blood heavy metal concentrations and the incidence of hearing loss but also highlighted that long-term exposure indicators of heavy metals were more indicative of the correlation with hearing loss. Lastly, the study recommends utilizing high frequency 4 kHz for the effective assessment and diagnosis of hearing loss caused by exposure to heavy metals.

**KEYWORDS**
environmental exposure, hearing loss, heavy metals, meta-analysis, systematic review

## 1 | INTRODUCTION

Hearing loss (HL) is one of the most prevalent chronic conditions, with over 360 million people worldwide at risk of experiencing it. Projections suggest that by 2050, approximately 900 million individuals will be affected by HL, leading to substantial psychological and socio-economic burdens.[1] While HL has traditionally been associated with age and noise exposure, recent epidemiological studies have expanded this perspective, identifying ototoxic chemicals and environmental heavy metals such as arsenic, cadmium, lead, manganese, and mercury as potential contributors to auditory system impairment and subsequent HL.[2]

Previous research has reported a plausible link between environmental exposure to heavy metals and the risk of HL, with a particular emphasis on the ototoxic effects of lead, cadmium, arsenic, and mercury.[3–6] Studies have indicated a potential association between lead exposure and an increased risk of HL, particularly among children.[7] Animal models have demonstrated that lead exposure can impair axonal transport and suppress auditory processing near the cochlea.[8] Additionally, cadmium exposure has been shown to be toxic to the cochlea, and hearing changes have been observed in children exposed to environmental arsenic.[6,9] Other heavy metals, such as methylmercury, dimethylmercury, and mercuric sulfide, have also been found to impact of Brainstem Evoked Response Audiometry (BERA). Despite reports of potential associations between these heavy metals and HL, there remains controversy regarding the precise effects of different types of heavy metals and the duration of exposure on HL.[10] Furthermore, there is no consensus on the optimal frequency range (whether high-frequency or low-frequency) for detecting HL. Given the widespread presence of heavy metals in the environment, establishing the relationship between various levels of heavy metal exposure and the risk of HL is of paramount importance, and this constitutes the primary objective of our meta-analysis.

## 2 | METHODS

### 2.1 | Literature search

The current scientific literature was systematically searched to identify original peer-reviewed studies exploring the relationship between different heavy metal exposures in the environment and HL. This review was conducted based on the guidelines of the 2022 Preferred Reporting Project Systematic Review and Meta-Analysis Protocol (PRISMAP) statement. The systematic literature search was conducted in May 2023 and included five major English-language digital libraries (PubMed, Web of Science, Embase, Cochrane Library, and Scopus) as well as three Chinese-language digital libraries (Zhiwang, Wanfang, and Wipu). Search terms included "heavy metals," "environmental exposure," "lead," "cadmium," "mercury," "arsenic," "manganese," "iron," "barium," "Hearing loss," "Hearing loss," "Hearing impairment" and "Deafness." These words were used to develop search strings and were combined in different ways using Boolean operators such as "AND" and "OR". We paid particular attention to studies assessing the intersection of these two topics and manually searched the relevant reference lists, thoroughly screening the full text of identified publications for primary data.

First, we used the EndNote software to organize the literature retrieved from electronic databases and excluded duplicate articles. Subsequently, two professionally trained researchers (F.W. and F.B.) carefully analyzed the data in this literature, and we conducted an in-depth review of each study included in the analysis to ensure the validity of all data and to verify the conformity of each participant. In the process of data analysis, we considered a number of key factors, including the year of publication of the article, the last name of the first author, the context of the study, the level of exposure to the various heavy metals (in milligrams per deciliter [mg/dL]), the number of participants, the definition of HL (in terms of pure-tone averaging thresholds (PTAs) >25 decibels), the estimate of the effect size, the 95% confidence intervals (CIs), and the used adjustment model (for studies that included multiple adjustment models in a single article, we chose those with the most comprehensive adjustment of variables to extract data). Also, because the method of defining HL varied across studies, we also documented in detail the specific definitions used in the original studies. Any disputes that arose during the interpretation of the data were resolved by our two researchers through a consultative discussion.

### 2.2 | Inclusion and exclusion criteria

#### 2.2.1 | Inclusion criteria

(1) Published studies should be original cohort studies, case–control studies, or cross-sectional studies; (2) the study should be on the effects of heavy metal exposure on hearing, and the topic of the study should cover, but not be limited to, the following keywords: "lead," "cadmium," "mercury," "arsenic," "manganese," "iron," "barium," and hearing-related terms such as "hearing loss," "hearing decline," and "deafness"; (3) The study must provide exact measurements of the

levels of specific heavy metals in the body, such as biomarker tests in blood, hair, nails, urine, and bone; (4) the definition of HL should be based on a pure tone average threshold (PTA) exceeding 25 dB; (5) studies need to provide adjusted OR and their 95% CI; and (6) the study should detail its methodology, including critical steps such as sample selection, diagnostic guidelines and statistical analysis.

### 2.2.2 | Exclusion criteria

(1) Animal experiments or mechanistic studies; (2) literature not related to the study topic; (3) studies investigating environmental factors other than heavy metals; (4) studies that did not provide OR and 95% CI; and (5) publications include reviews, conference papers, commentaries or, case reports.

## 2.3 | Statistical analysis

In our study, we utilized Stata (version 17.0; Stata Corp LP, College Station, TX, USA) for statistical analyses, summarized the ORs associated with HL in the eligible heavy metal exposure studies, and calculated the overall effects and their 95% CIs. To manage the heterogeneity across studies, we employed a random-effects model within the SPSS software, which accommodates the variability within and across individual studies. Heterogeneity was quantified using the $I^2$ statistic, representing the proportion of overall variation across studies attributable to heterogeneity rather than chance. $I^2$ values of 0%, 25%, 50%, and 75% correspond to non-existent, low, moderate, and high heterogeneity, respectively.

In addition, to assess possible publication bias, we drew the funnel plots. We applied Egger's test to explore whether there was a tendency to favor the publication of statistically significant studies, which is a critical step to ensure our analysis's accuracy and our conclusions' reliability. Also, we conducted subgroup analyses to examine differences in the relationship between heavy metal exposure and HL in specific subgroups, which included subgroups categorized by type of heavy metal, site of measurement, and frequency of hearing tests. It enhanced our understanding of the data and provided a more precise basis for scientific insight.

# 3 | RESULTS

As shown in Figure 1, we found 626 potentially relevant papers using the search strategy of keywords. Upon eliminating 129 duplicates, 497 papers underwent preliminary scrutiny of their titles and

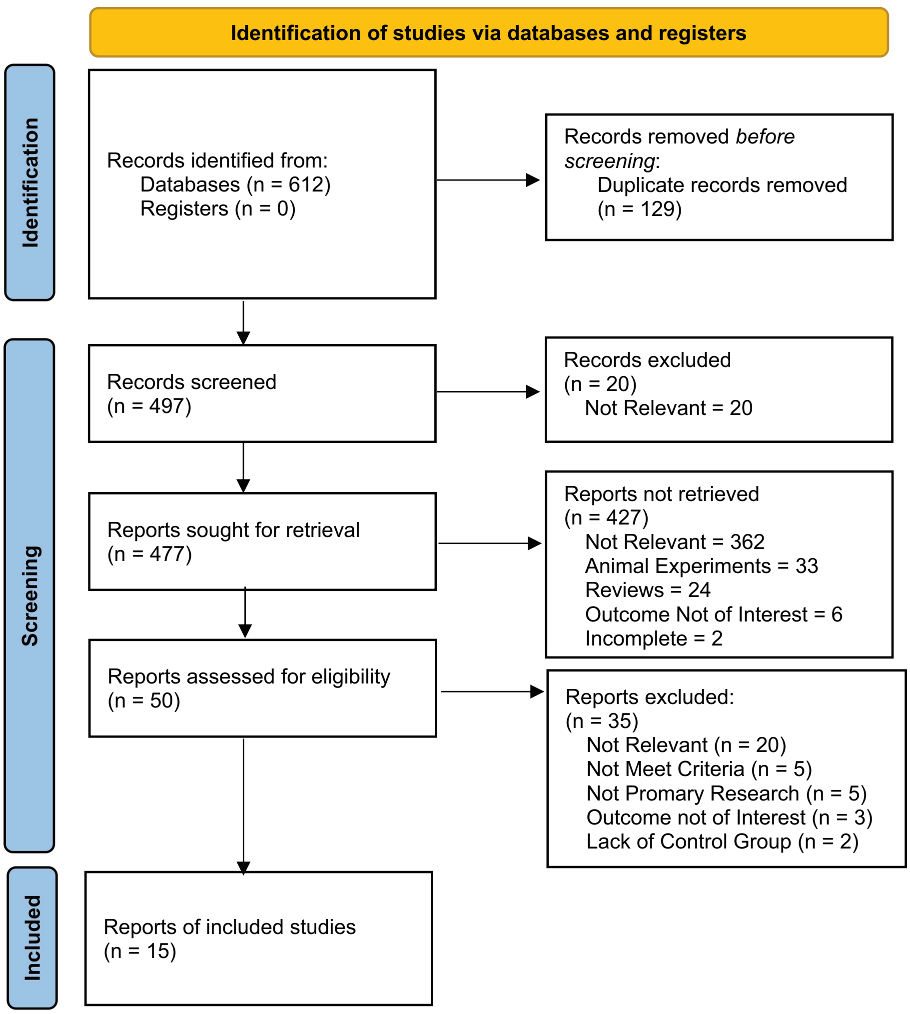


FIGURE 1 Flow diagram.

abstracts. From this cohort, 447 papers were excluded for various reasons: misalignment with the study's focus, utilization of animal models, or their classification as systematic or literature reviews. A subsequent thorough review of the full text of the remaining 50 papers resulted in the further exclusion of an additional 35 papers for not meeting our inclusion criteria, with the following reasons for exclusion: (1) the study content was irrelevant ($n = 20$); (2) the definition of HL was not the same as our criteria ($n = 5$); (3) the study did not provide an OR or 95% CI ($n = 5$); (4) the study was a review article ($n = 3$); and (5) there was a lack of a control group ($n = 2$). After careful screening, 15 articles were finally included in our analysis. Controversial points throughout the process were discussed and resolved by our two reviewers.

This study covered 15 studies published between 2009 and 2022, 11 of which were conducted in Asia (Japan,[6,11,12] Korea,[3,9,13,14] and China[5,7,15,16]) and 4 in the United States.[4,17–19] Of these studies, 10 articles identified lead and cadmium as the main or one of the risk factors for HL. Two papers focused on the effects of mercury, one of which was analyzed independently in adults and one in adolescents, and thus were considered two separate studies. For other elements, such as arsenic, manganese, and zinc, there is only one published paper on each element.

All studies used PTA (the gold standard of hearing test) to assess HL degree. Four of the studies categorized HL into three categories: low frequency, speech frequency, and high frequency, while the remaining studies focused on HL in the speech frequency range. Of these studies, only one was conducted exclusively on males, on workers in a heavy metal smelting plant.[17] The other studies included participants of both sexes. Of the 15 studies, three were prospective assessments, including one cohort study[19] and two case–control studies.[15,16] In addition, the remaining studies retrospectively assessed the history of HL through a cross-sectional study design. The characteristics of the studies are summarized in Table 1.

## 3.1 | Meta-analysis results

### 3.1.1 | Cadmium

A total of 10 studies involving 38,591 participants were included to assess the impact of cadmium exposure on HL. Figure 2 demonstrates a significant increase in the prevalence of HL in the cadmium-exposed group compared to the control group, with an OR of 1.03 (95% CI 0.95–1.12). There was moderate heterogeneity observed between the two groups ($I^2 = 39.6\%$).

### 3.1.2 | Lead

A total of 10 studies involving 36,517 participants were included to assess the impact of lead exposure on HL. Figure 3 reveals a significant increase in the occurrence of HL in the lead-exposed group compared to the control group, with an OR of 1.09 (1.03–1.16). Notably, there was no heterogeneity detected between the two groups ($I^2 = 0.0\%$).

### 3.1.3 | Mercury

A total of 3 studies involving 8575 participants were included to assess the impact of mercury exposure on HL. Figure 4 shows that blood mercury levels were associated with a protective effect on hearing, with an OR of 0.81 (0.70–0.94). Similar to lead exposure, no heterogeneity was observed between the two groups ($I^2 = 0.0\%$).

## 3.2 | Subgroup analyses

### 3.2.1 | Frequency

To assess the association strength between lead exposure and hearing loss at different frequencies, we categorized the data into quintiles of lead concentration (Q1 to Q5) for both left and right ears across various frequencies (500kHz, 1kHz, 2kHz, 4kHz), resulting in groups A1-D1, A2-D2…A8-D8. In the subgroup analysis based on Pb exposure frequency, Figure 5 demonstrates that when measuring HL caused by heavy metal exposure using pure-tone audiometry (PTA), the higher frequency of 4 kHz was more indicative of the level of hearing impairment compared to other lower frequencies. For 0.5 kHz, the OR was 1.08 (0.49–2.38); for 1 kHz, the OR was 0.95 (0.78–1.17); for 2 kHz, the OR was 1.17 (0.99–1.38); for 4 kHz, the OR was 1.44 (1.22–1.71); and for 6 kHz, the OR was 1.13 (0.95–1.34).

### 3.2.2 | Short/long-term exposure

In the analyses of short-term and long-term exposure to barium from different tissue sources (blood, nails, urine), as shown in Figure 6, we observed that indicators of chronic accumulation (such as hair and nails) provided more informative insights into the association with HL compared to indicators of daily exposure (urine). The pooled ORs were as follows: hair had an OR of 3.81 (2.05–7.06), nails had an OR of 2.26 (1.50–3.40), and urine had an OR of 1.22 (0.90–1.65).

### 3.2.3 | Metal concentrations

We grouped participants based on the blood concentrations of Pb and Cd, ranging from Q1 (normal group), Q2, Q3, Q4, to Q5. Figures 7 and 8 showed that as the concentration increased, the odds of HL also gradually increased. (1) Pb: the odds ratio (OR) and 95% CI for Q2, Q3, Q4, and Q5 were 1.07 (0.92–1.25), 1.14 (0.98–1.34), 1.26 (1.08–1.46), and 1.22 (1.04–1.42), respectively; (2) Cd: the OR and 95% CI for Q2, Q3, Q4, and Q5 were 1.07 (0.90–1.27), 1.07 (0.90–1.27), 1.17 (1.03–1.34), and 1.08 (0.80–1.46), respectively.

## 3.3 | Publication bias

We evaluated the presence of publication bias through funnel plots and Egger's test. Our meta-analysis's funnel plots generated for lead,

**TABLE 1** Characteristic of the studies.

| Year | Country | Heavy metal | Sample demographics | Gender (Male) | Hearing Loss evaluation and definition | Age | Metal levels (unit) | OR (95% CI) | Adjusted Model |
|---|---|---|---|---|---|---|---|---|---|
| 2022 | China | 10 trace metals elements (lead, barium, cadmium, cobalt, caesium, molybdenum, antimony, tin, thallium, and tungsten). | 8128 | 4035 (49.6%) | PTA > 25 dB | 14–57 Mean =34 | Lead 0.3 (0.16–0.53) (μg/L)<br>Barium 1.05 (0.51–2.09) (μg/L)<br>Cadmium 0.12 (0.05–0.29) (μg/L)<br>Cobalt 0.44 (0.25–0.71) (μg/L)<br>Caesium 4.40 (2.60–6.60) (μg/L)<br>Molybdenum 42.34 (21.4–74.93) (μg/L)<br>Antimony 0.05 (0.03–0.09) (μg/L)<br>Tin 0.52 (0.23–1.24) (μg/L)<br>Thallium 0.17 (0.10–0.26) (μg/L)<br>Tungsten 0.07 (0.03–0.15) (μg/L) | Lead 1.10 (0.81, 1.49)<br>Barium 1.22 (0.91, 1.64)<br>Cadmium 1.04 (0.68, 1.58)<br>Cobalt 1.32(0.97, 1.80)<br>Caesium 0.90 (0.67, 1.23)<br>Molybdenum 0.95 (0.70,1.30)<br>Antimony 1.17 (0.87, 1.58)<br>Tin 1.75 (1.28, 2.40)<br>Thallium 0.83 (0.61, 1.14)<br>Tungsten 0.95 (0.69,1.30) | Age, gender, race, hypertension, diabetes, hyperlipidaemia, noise exposure, triglyceride, total cholesterol, and low-density lipoprotein cholesterol. |
| 2019 | Korea | Cadmium | 3228 | 1610 (50%) | PTA > 25 dB | 54.2 ± 8.5 | 0.054 ± 0.360 (μg/L) | 1.13 (0.89, 1.45) Q2<br>1.08 (0.85, 1.38) Q3<br>1.43 (1.13, 1.81) Q4 | Age, sex, presence of diabetes mellitus and hypertension, smoking habit, alcohol intake, occupational and explosive noise exposure, and lead level. |
| 2019 | Japan | Arsenic (As) | 145 | 69 (34.9%) | PTA > 25 dB | 29.58 ± 10.96 | 2,367.6 ± 2,094.7 (μg/L) | 4 kHz (OR = 4.860; 95% CI: 1.257, 18.785; $P$ = 0.022), 8 kHz (OR = 8.301; 95% CI: 2.059, 33.457; $P$ = 0.003) 12 kHz (OR = 5.316; 95% CI: 1.376, 20.543; $P$ = 0.015) | Age, gender, smoking, and BMI, which have been reported to affect hearing. |
| 2018 | Japan | Manganese (Mn) | 145 | 69 (47.6%) | PTA > 25 dB | | | | |

(Continues)

**TABLE 1** (Continued)

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 29.6 ± 11.0 | Toenails 7.3 ± 7.6 (μg/g)<br>Hair 20.3 ± 19.9 (μg/g)<br>Urine 0.7 ± 2.1 (μg/g) | Toenails 4.19 (1.18, 14.82)<br>Hair 3.25 (0.83, 12.67)<br>Urine 1.15 (0.47, 2.84) | Age, sex, BMI, smoking and educational record. |
| 2018 | China | Lead (Pb)<br>Cadmium (Cd) | 234 | 46 (52.3%) | PTA > 25 dB | 4.73 ± 0.74 | Blood Pb 4.94 ± 0.20 (μg/dL)<br>Urinary Cd 2.49 ± 2.54 (μg/g) | Pb Q4 1.24 (1.029, 1.486)<br>Cd Q4 1.06 (0.970, 1.152) | Age, gender, weight, height, BMI, parent education level, family member smoking, family monthly income, residence distance to the road, residence nearby noise. |
| 2015 | Japan | Barium (Ba) | 145 | 69 (47.6%) | PTA > 25 dB | 29.58 ± 10.92 | Hair 7.08 ± 5.54 (μg/g)<br>Toenail 3.21 ± 2.87 (μg/g)<br>Urine 3.87 ± 4.85 (μg/g) | Hair 2.60 (0.85, 8.41)<br>Toenail 2.76 (1.15, 6.85)<br>Urine 1.16 (0.52, 2.56) | Models were adjusted for sex, 26 age, 43 body mass index 44 and smoking, 15 which were previously reported to affect hearing levels. |
| 2012 | USA | Lead (Pb)<br>Cadmium (Cd) | 3698 | 1,729 (48.6%) | PTA > 25 dB | 42.06 ± 0.28 | Pb 1.54 (1.49–1.60) (μg/dL)<br>Cd 0.40 (0.39–0.42) (μg/L) | Pb 1.54 (1.49, 1.60)<br>Cd 0.40 (0.39. 0.42) | Age, sex, race/ethnicity, education, BMI, ototoxic medication, pack-years of cigarette smoke, hypertension, and diabetes. |
| 2010 | USA | Lead (Pb) | 448 | 100 (44.8%) | PTA > 25 dB | 64.9 ± 7.3 | Tibia 22.5 ± 14.2 (μg/g)<br>Patella 32.5 ± 20.4 (μg/g) | Tibia 1.30 (1.03, 1.65)<br>Patella 1.59 (1.25, 2.02) | Age, education (>12 years of education or not), body mass index, pack-years of cigarettes, diabetes and hypertension, and diabetes. |
| 2011 | USA | Lead (Pb)<br>Mercury (Hg)<br>Cadmium (Cd) | 2535 | — | PTA > 25 dB | 12–19 | Pb > 2 (μg/dL) | Pb 2.22 (1.39,3.56)<br>Hg 1.95 (1.24,3.07)<br>Cd 3.08 (1.02,9.25) | Age, sex, race, poverty-income ratio, history of 3 or more ear infections, loud noise exposure, and smoking |
| 2017 | Korea | Lead (Pb)<br>Mercury (Hg)<br>Cadmium (Cd) | 5187 adults 853 adolescents | 2,548 (49.3%) | PTA > 25 dB in adults PTA > 15 dB in adolescents. | 46.2 | Pb 1.70 (1.25, 2.31) (μg/dL)<br>Hg 0.89 (0.68, 1.17) (μg/L) | Pb 1.26 (1.22, 1.30)<br>Hg 2.03 (1.96, 2.12)<br>Cd 0.36 (0.34, 0.38) | Age, sex, education, body mass index, cigarette smoke, current diagnosis of hypertension, current |

**TABLE 1** (Continued)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Cd 1.47 (1.05, 2.05) (μg/L) | | diagnosis of diabetes, occupational noise, reational noise, and firearm noise. |
| 2020 | China | Lead (Pb)<br>Cadmium (Cd) | 2016 | 1056 | PTA > 25 dB | 52.41 ± 11.58 | Pb 1.58 ± 0.17 (μg/dL)<br>Cd 0.34 ± 0.24 (μg/L) | Pb 1.016 (0.700,1.475)<br>Cd 1.495 (1.048,2.133) | Income level, education level, hypertension, diabetes, hyperlipidaemia, acute and chronic otitis media, migraine, anaemia, smoking, alcoholconsumption, and fruit and vegetable intake |
| 2018 | Korea | Lead (Pb)<br>Cadmium (Cd) | 6409 | 3185 | PTA > 25 dB | 47.1 ± 0.3 | Pb 2.82 ± 0.01 (μg/dL)<br>Cd 1.13 ± 0.01 (μg/L) | Pb 1.629 (1.161,2.287)<br>Cd 1.292 (0.896,1.865) | Age, body mass index, education, smoking, alcohol consumption, exercise, diagnosis of diabetes mellitus, hypertension, and noise exposure (occupational, loud, firearm noises) |
| 2018 | Korea | Lead (Pb)<br>Cadmium (Cd) | 2387 | — | PTA > 25 dB | 19–85 | Pb (0.515–26.507) (μg/dL)<br>Cd (0.098–5.170) (μg/L) | Pb 2.46 (2.41–2.52)<br>Cd 1.02(0.99–1.05) | Age, sex, monthly income, education level, smoking status, BMI, occupational noise, loud noise, firearm noise, hypertension, and diabetes. |
| 2019 | USA | Cadmium (Cd) | 2,065 | 880 (42.6%) | PTA > 25 dB | 47.9 | Pb (0.2–25.3) Mean value = 1.5 (μg/dL)<br>Cd (0.1–21.6) Mean value = 0.4 ( μg/L) | Pb 1.07 (0.80–1.44)<br>Cd 1.41 (1.05–1.90) | Age, sex, Years of education, occupation, smoking, alcohol use, exercise, and health history. |
| 2009 | China | Lead (Pb) | 412 | 411 (99.8%) | PTA > 25 dB | 36.0 ± 6.5 | Pb (55.9 ± 33.9) ( μg/dL) | Pb 3.54 (1.40–8.97) | Age, sex, education, cigarette smoking, alcohol drinking, and a detailed work history, including information about working conditions. |
| 2019 | China | Lead (Pb)<br>Cadmium (Cd) | 2016 | 1056 (52.4%) | PTA > 25 dB | 52.41 | Pb 1.58 ± 0.17 (μg/dL) | Pb 1.038(0.718–1.501)<br>Cd 1.491(1.049–2.119) | Age, body mass index, education, smoking, |

(Continues)

TABLE 1 (Continued)

| | |
|---|---|
| Cd 0.34 ± 0.2 (μg/L) | alcohol consumption, exercise, diagnosis of diabetes mellitus, hypertension, and noise exposure (occupational, loud, firearm noises). |

cadmium, and mercury exhibited reasonably symmetrical patterns. The results obtained from Egger's test were as follows: lead ($p = .604$), cadmium ($p = .293$), and mercury ($p = .844$). These results collectively indicate the absence of substantial publication bias for any of the metals analyzed. This suggests that the included studies were likely representative and not skewed toward particular result types.

## 4 | DISCUSSION

HL is a significant and prevalent global health issue affecting approximately 360 million individuals worldwide, according to the World Health Organization.[20] Clinically, HL is typically defined as an average pure-tone threshold exceeding 25 decibels.[5] This condition can be attributed to various factors, including congenital factors, infections, noise exposure, heavy metal exposure, and aging. One of the less explored contributors to HL is heavy metal exposure, which can occur through multiple routes in our daily lives, with food being the most common source of exposure. Existing literature suggests long-term exposure to heavy metals such as lead, cadmium, cobalt, arsenic, and mercury may lead to auditory dysfunction, with potential permanent consequences.[2,21]

Given the widespread ubiquity of heavy metal exposure, it is critical to investigate and recognize the relationship between environmental heavy metal exposure and the risk of HL. This meta-analysis and review aim to comprehensively examine the association between heavy metals, including lead, cadmium, mercury, arsenic, barium, and manganese, and the incidence of HL. By conducting this investigation, we can contribute vital evidence to inform strategies for preventing and diagnosing HL.

### 4.1 | Lead (Pb)

The association between environmental lead (Pb) exposure and HL has been supported by multiple studies. Population studies conducted by Shargorodsky, Huh, Choi and Park, Dalton, and Yin et al. have all found the correlation between lead exposure and the risk of HL.[4,14,17–19] Shargorodsky et al. suggested that heavy metal exposure is related to HL in American adolescents, particularly affecting high-frequency hearing (3, 4, 6, and 8 kHz).[18] Huh et al. analyzed data from a total of 7596 Korean individuals between 2010 and 2013 and found that blood lead concentrations ranging from 2.920 to 26.507 μg/dL were associated with HL.[14] Similarly, Choi and Park's study concluded that blood lead concentrations ranging from 2.823 to 26.507 μg/dL were associated with HL in adults.[3,4] Yin suggested that compared to the lowest lead concentrations, the highest levels of lead in the body increased the risk of HL by nearly 59%, including in adults, adolescents, and children.[16] Several possible mechanisms have been proposed to explain the association between blood lead concentrations and HL, including lead-induced neurotoxicity in the cochlea and auditory pathway. Bleecker suggests that lead exposure may impair the auditory pathway in the auditory nerve below the brainstem.[22]

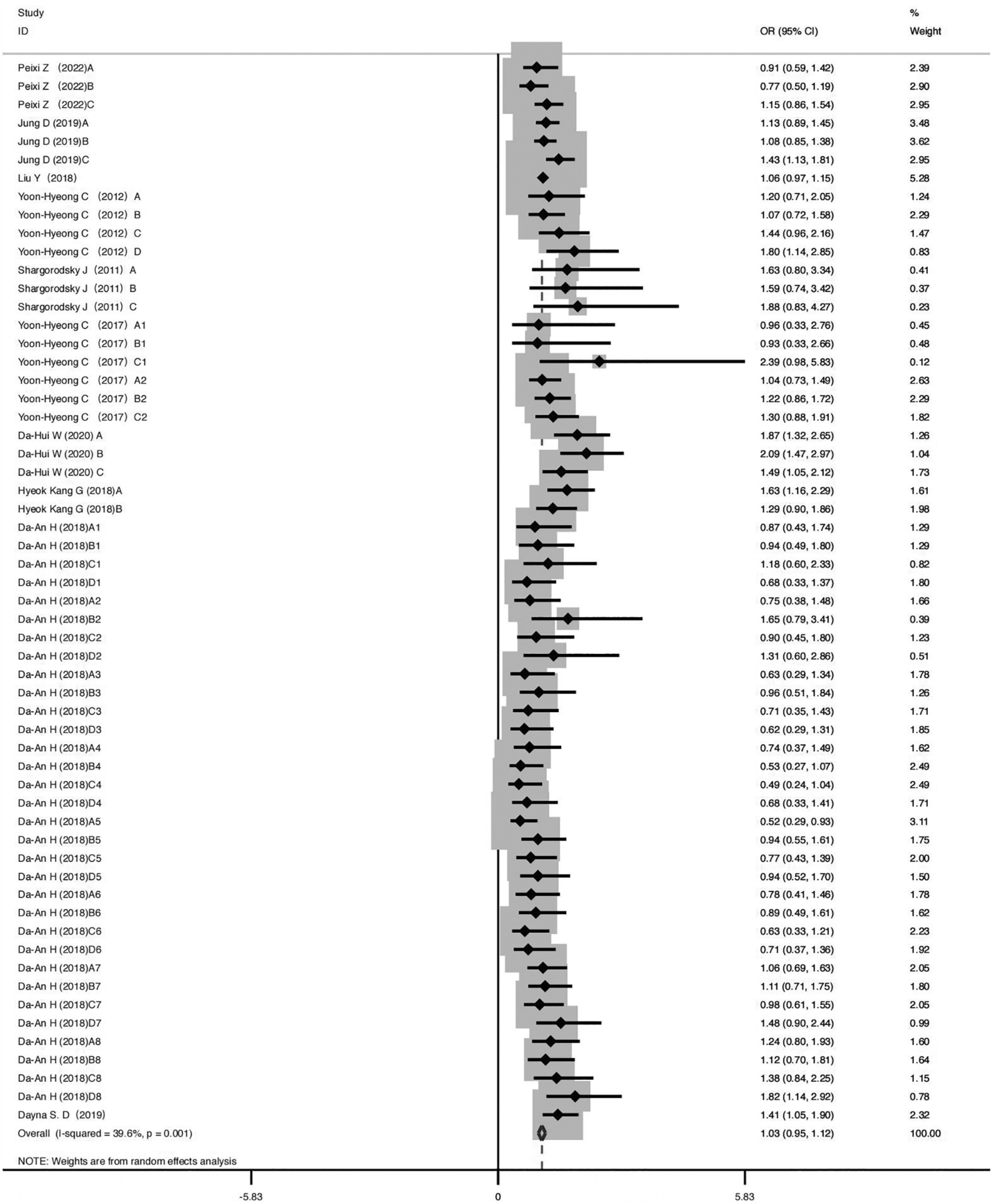


**FIGURE 2** Forest plot of the comparison of hearing loss with cadmium exposure. CI, confidence interval.

In order to determine the relationship between environmental lead exposure and HL, we conducted a meta-analysis of 10 studies that met the inclusion criteria. The results showed that the odds ratio (OR) for lead exposure and HL was 1.09 (95% CI 1.03–1.16), with no heterogeneity ($I^2 = 0.0\%$, $p = .293$) and a low likelihood of publication bias according to Egger's test. Therefore, we believe that an increase in lead levels is significantly associated with an increased risk of HL in the population. Furthermore, we performed subgroup analyses of lead exposure and hearing at different frequencies (0.5, 1, 2, 3, 4, 6 kHz). The results showed that at a frequency of 4 kHz, lead had a more significant impact on hearing compared to other frequencies, with an OR of 1.44 (95% CI 1.22–1.71) and no heterogeneity. This is consistent with previous research findings. In a cohort study by Park et al. conducted on a male community population, long-term cumulative lead exposure measured through bone K-x-ray fluorescence was significantly associated with hearing thresholds, particularly showing a noticeable reduction at the 4 kHz frequency.[17] Additionally, in subgroup analyses of blood lead concentrations, we found that as the

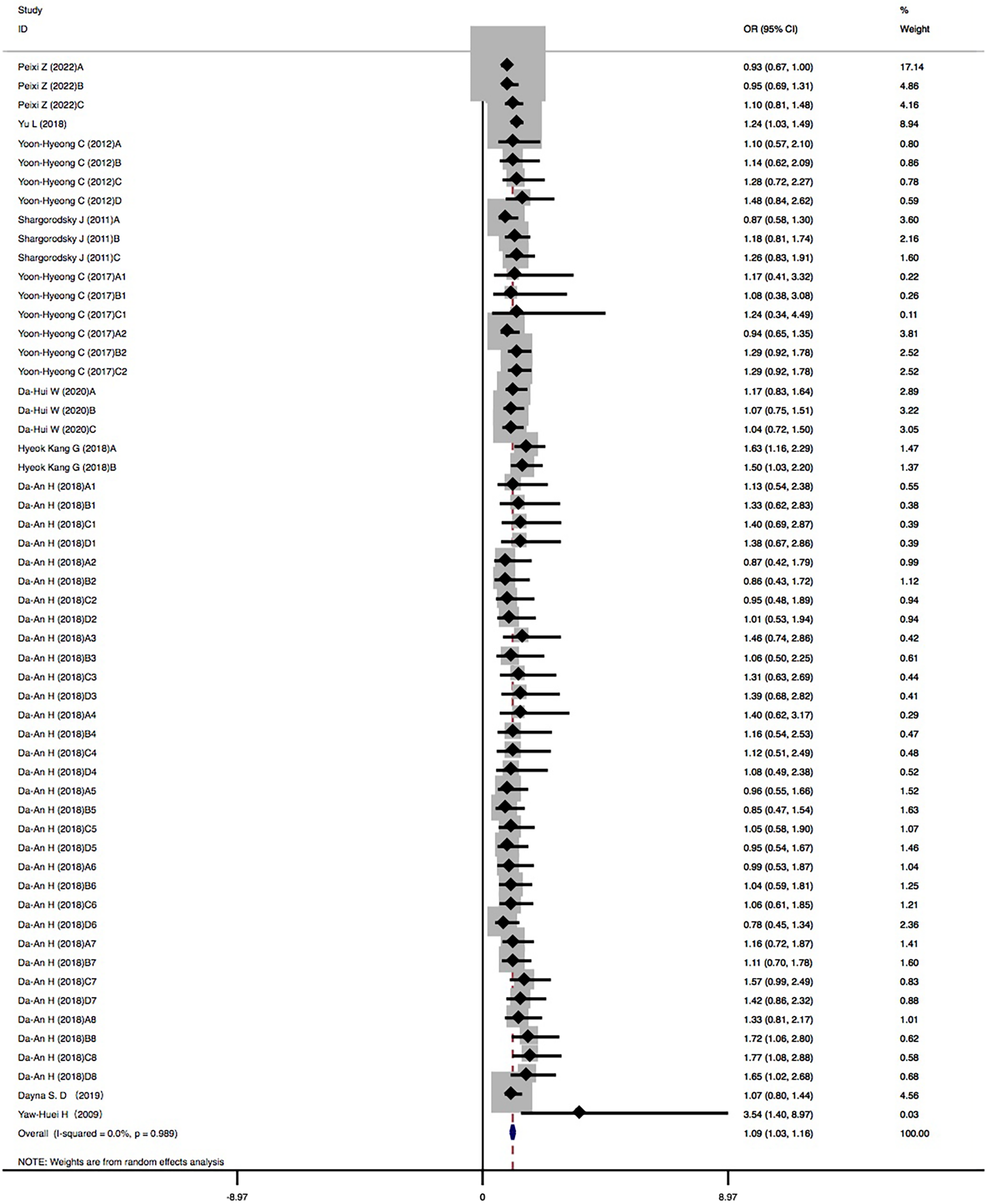


**FIGURE 3** Forest plot of the comparison of hearing loss with lead exposure. CI, confidence interval.

metal blood concentration increased, the likelihood of HL also increased. Compared to the low concentration group (Q2, 0.90–1.30 μg/dL), the high concentration group (Q5, 2.80–54.00 μg/dL) showed a more pronounced relationship with HL.

In conclusion, this meta-analysis demonstrates that increased lead exposure is significantly associated with an increased risk of HL in adults and adolescents, with a greater impact on high-frequency hearing (4 kHz). Reducing lead exposure may contribute to the prevention

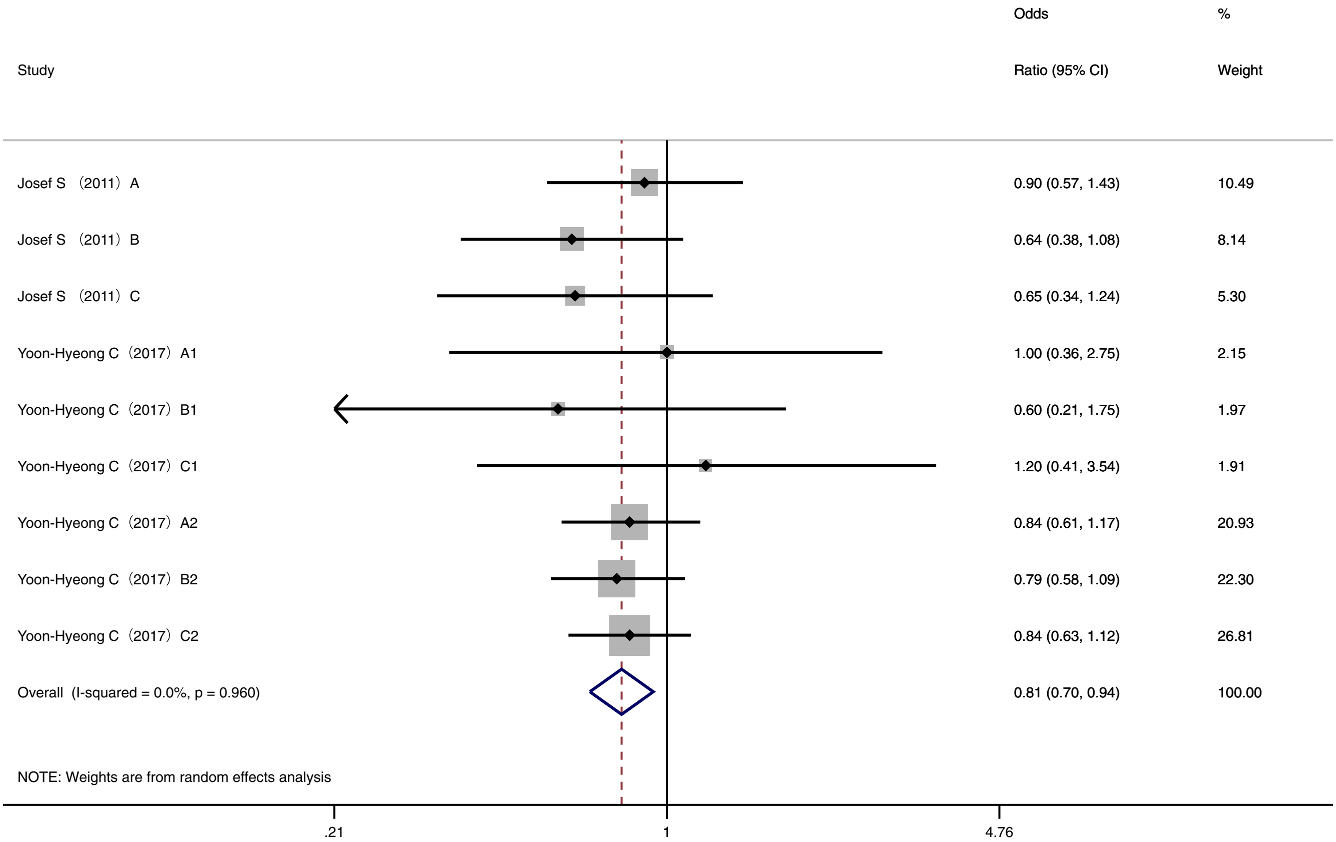


**FIGURE 4** Forest plot of the comparison of hearing loss with mercury exposure. CI, confidence interval.

or delay of HL development, and using the 4 kHz frequency can provide better assessment of this type of HL.

## 4.2 | Cadmium (Cd)

Some studies have indicated the detrimental effects of cadmium on auditory function. Cadmium can induce damage to the auditory system through the generation of reactive oxygen species, leading to mitochondrial depolarization, cell apoptosis, and increased activation of extracellular signal-regulated kinases, ultimately causing irreversible damage.[23] Choi et al. analyzed the impact of lead and cadmium exposure on HL in 3698 American adults using the National Health and Nutrition Examination Survey from 1999 to 2004.[4] They found that low levels of cadmium and lead exposure can result in HL. Shargorodsky et al. also observed a significant correlation between high urinary cadmium levels and low-frequency HL, with a higher odds ratio.[18] In a case–control study conducted by Da-Hui et al. involving 1008 participants in Zhejiang Province, China, it was found that compared to the first quartile of blood cadmium level, the second and third quartiles had an increased risk of HL, while the fourth quartile showed a decreased risk, following a reverse U-shaped pattern.[14] However, due to the retrospective cross-sectional design commonly used in existing studies on cadmium exposure, causality between cadmium levels and HL cannot be determined.

We conducted a systematic review and meta-analysis of 10 studies meeting the inclusion criteria on cadmium-induced HL. The results of our study showed that elevated blood cadmium levels increased the risk of HL, with an odds ratio (OR) of 1.03 (95%CI 0.95, 1.12). The meta-analysis revealed an $I^2$ value of 39.6%, indicating moderate heterogeneity, and demonstrated no significant publication bias. Additionally, we categorized the subjects based on their blood cadmium concentrations from low to high, into groups ranging from Q1 (normal group: 0.515–1.780 μg/L) to Q5 (high concentration group: 1.599–5.170 μg/L). The pooled analysis indicated a significant relationship between the Q4 group (1.187–1.599 μg/L) and HL, suggesting a positive association between increasing blood cadmium levels and HL. However, a decreasing trend was observed in the Q5 group. We speculate that this discrepancy may be due to the limited number of studies available for the Q5 group (only two studies).[3,14] Further research is needed to explain this observation.

## 4.3 | Barium (Ba)

In our daily lives, barium is a common element that we constantly intake through drinking water and food. It has been established that high-dose exposure to barium (100 mg/kg/day) can cause physiological damage.[12,24] However, there is limited literature and research on the relationship between barium and HL, with only two studies

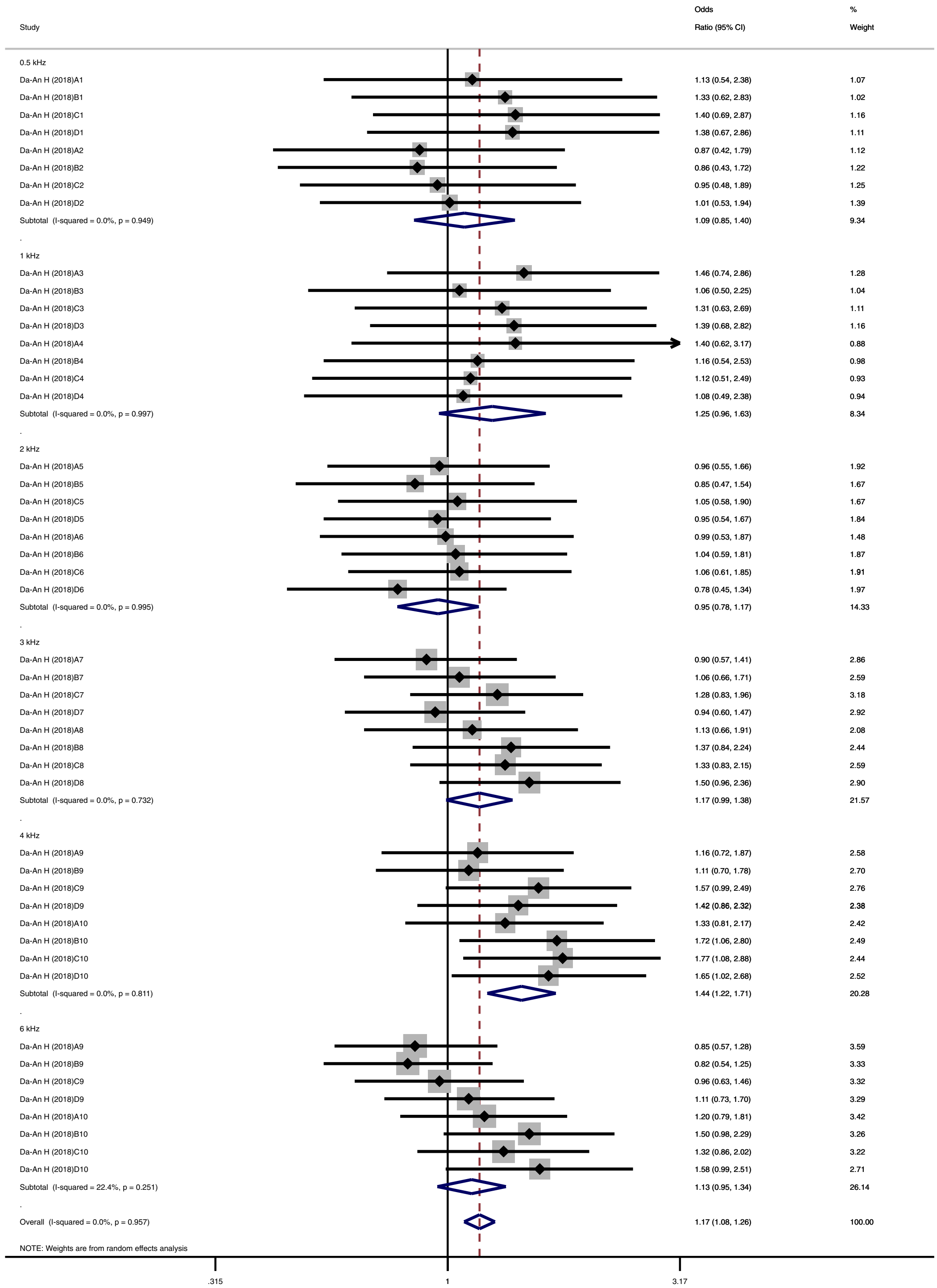


**FIGURE 5** The magnitude of hearing loss at different frequencies when measuring hearing loss caused by heavy metal exposure using pure-tone audiometry (PTA).

meeting our inclusion criteria. In 2012, Ohgami et al. injected mice with low-dose barium in drinking water and found specific distribution of barium in the inner ear, resulting in severe ototoxicity and inner ear degeneration.[25] In 2016, they investigated the ototoxicity of barium in humans and found a significant correlation between HL and barium levels in hair and toenails, particularly at high frequencies of 8 and 12 kHz.[12]

We conducted a subgroup analysis of human biological samples for barium (Ba) and found a significant correlation between Ba levels in hair and toenails and HL. The combined odds ratios (OR) were as follows: OR for hair was 3.81 (2.05–7.06), OR for toenails was 2.26 (1.50–3.40), and OR for urine was 1.22 (0.90–1.65). This suggests that chronic accumulation indicators such as hair and toenails increase the risk of HL compared to the daily exposure indicator (urine). We

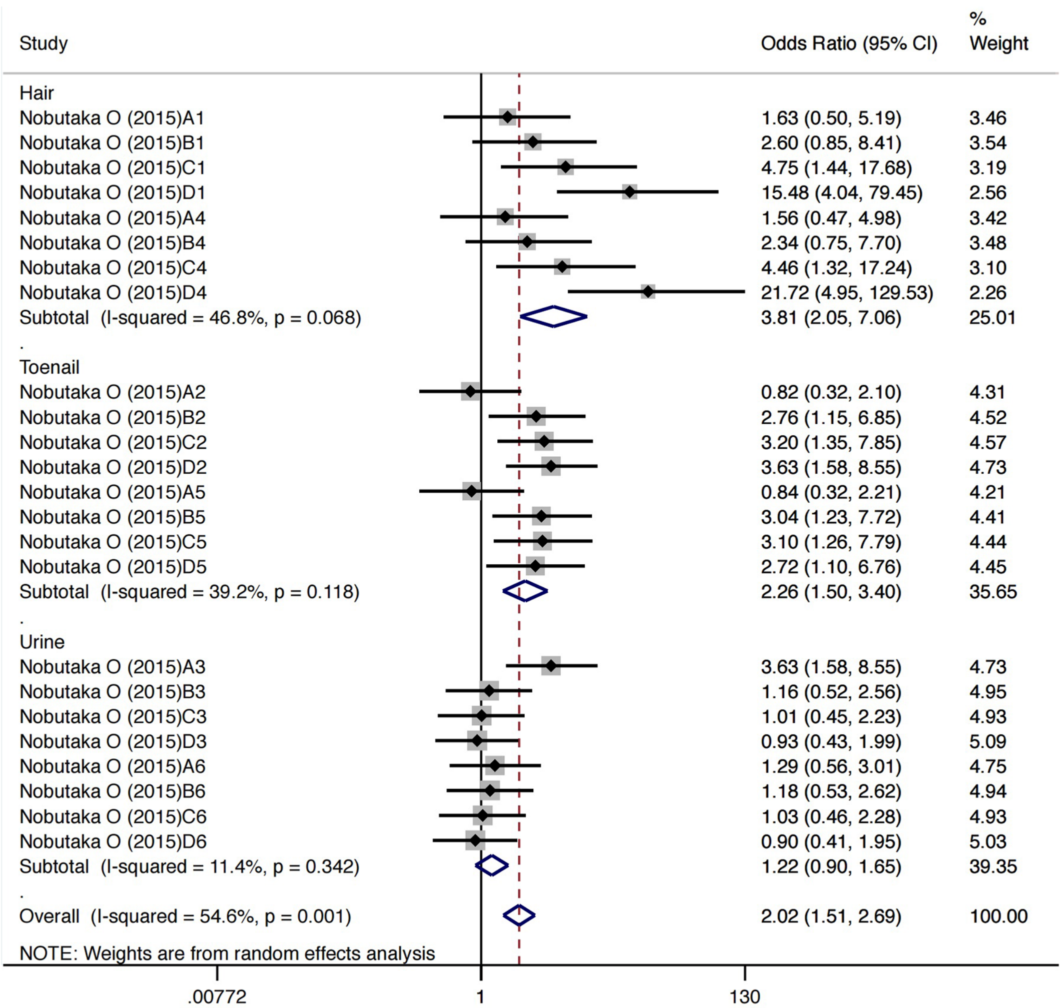


**FIGURE 6** Barium concentration in different tissue sources (blood, nails, urine) and degree of hearing loss.

believe this is due to the long-term accumulation of heavy metals, leading to severe HL and degeneration of the Corti organ, which is irreversible. Therefore, monitoring the levels of heavy metals in the environment is an important measure to reduce the risk of HL associated with long-term exposure to heavy metal environments.

### 4.4 | Arsenic (As)

As is a toxic metalloid that is found in soil, air, water and rocks, contamination of groundwater with As is a widespread issue worldwide.[6,26] Shargorodsky et al. conducted a study on 2535 American adolescents, analyzing the relationship between urinary arsenic levels and HL.[18] However, the research indicated that there was no definitive overall association between the quartiles of urinary arsenic levels and HL. Kesici (2015) investigated the relationship between arsenic exposure and HL by measuring blood arsenic levels and assessing hearing in miners.[27] The study confirmed the ototoxic effects of arsenic. However, no dose–response relationship was found between blood arsenic levels and hearing thresholds. This could be due to blood arsenic levels not reflecting cumulative or long-term exposure. In response to this, Li and Ohgami (2018) conducted an epidemiological survey of 145 Bangladeshis aged 12–55 years in 2014.[12] They looked at the relationship between arsenic levels in toenails and hair, an indicator of chronic exposure, and hearing. They concluded that levels of arsenic in toenails were significantly associated with hearing loss at the frequencies of 4kHz, 8kHz, and 12kHz. The ORs for these associations were 4.27, 3.91, and 4.15, respectively, with 95% CIs of (1.51-12.05), (1.47-10.38), and (1.55-11.09). However, the significant association between hair arsenic levels and HL was limited to 12 kHz. Furthermore, Saunders et al. found in their study that there was a significant relationship between arsenic concentration and DPOAE amplitude at 2 kHz in 59 gold miners.[28]

These studies suggest that exposure to the heavy metal arsenic may be associated with HL, but the specific correlations and impacts still require further research and exploration.

### 4.5 | Mercury (Hg)

It is estimated that about half of the total mercury in the atmosphere is associated with various industrial applications such as burning fossil fuels

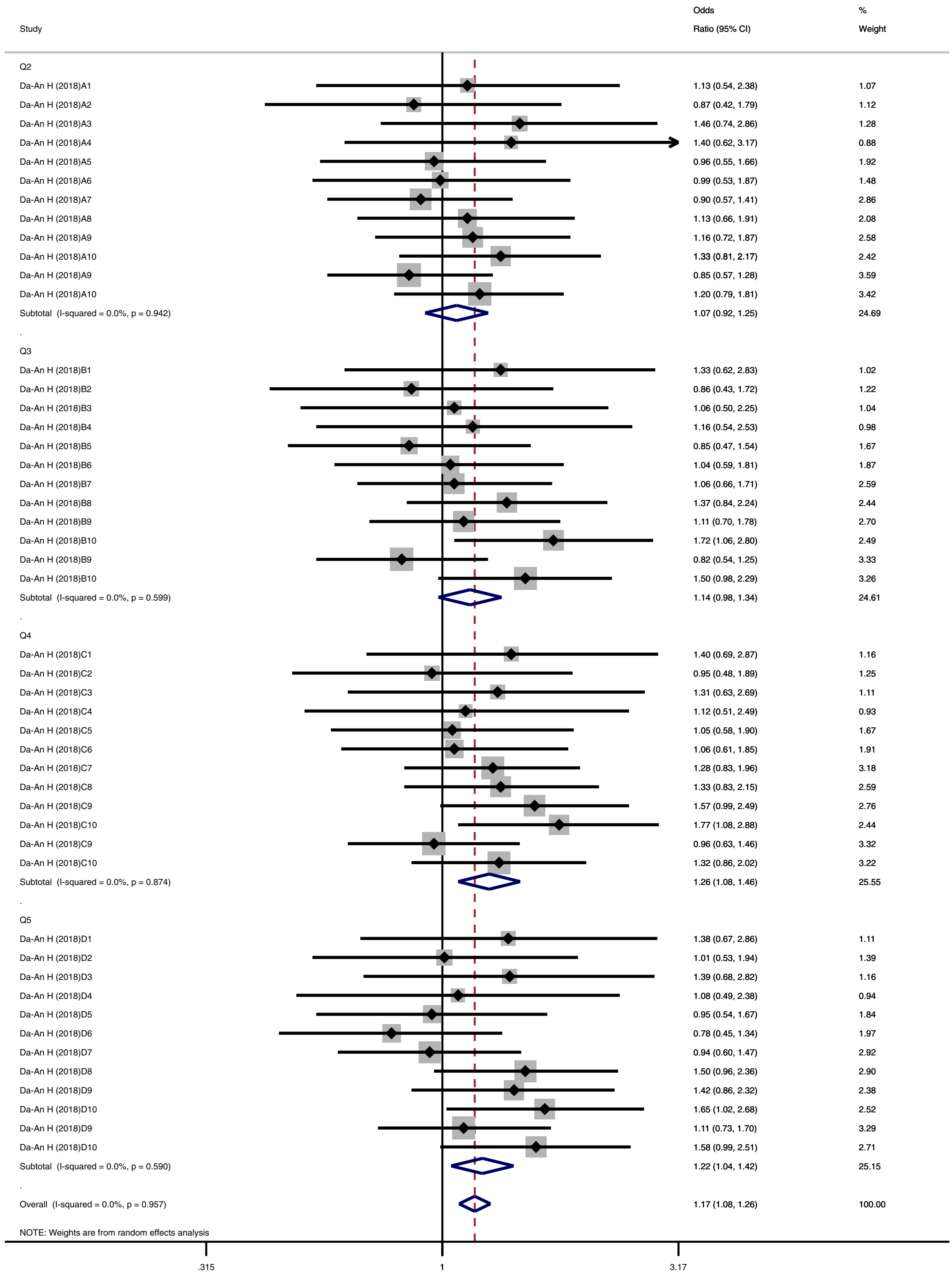


**FIGURE 7** The relationship between different concentrations of blood lead and the degree of hearing loss. CI, confidence interval.

and metal smelting. The relationship between mercury exposure and HL remains uncertain. Five studies have found no significant association between mercury exposure and HL.[3,18,29–31] Murata et al. found an association between prolonged latency of the III peak of BERA at 40 Hz and high mercury exposure (more than 10 mg/g).[32] However, this association may depend on the specific threshold of exposure levels.

In this article, only two studies met the inclusion criteria for the meta-analysis regarding Hg, and neither did not find an association between blood Hg and HL.[3,18] One of the studies, conducted by Shargorodsky et al. assessed the relationship between blood lead, blood mercury, urine cadmium, arsenic levels, and HL in participants aged 12–19 years from the 2005 to 2008 National Health and Nutrition Examination Survey in the United States. The results showed no significant association between the quartiles of blood levels and HL. The researchers suggested that this may be due to blood mercury levels reflecting only short-term exposure and not reflecting historical, long-

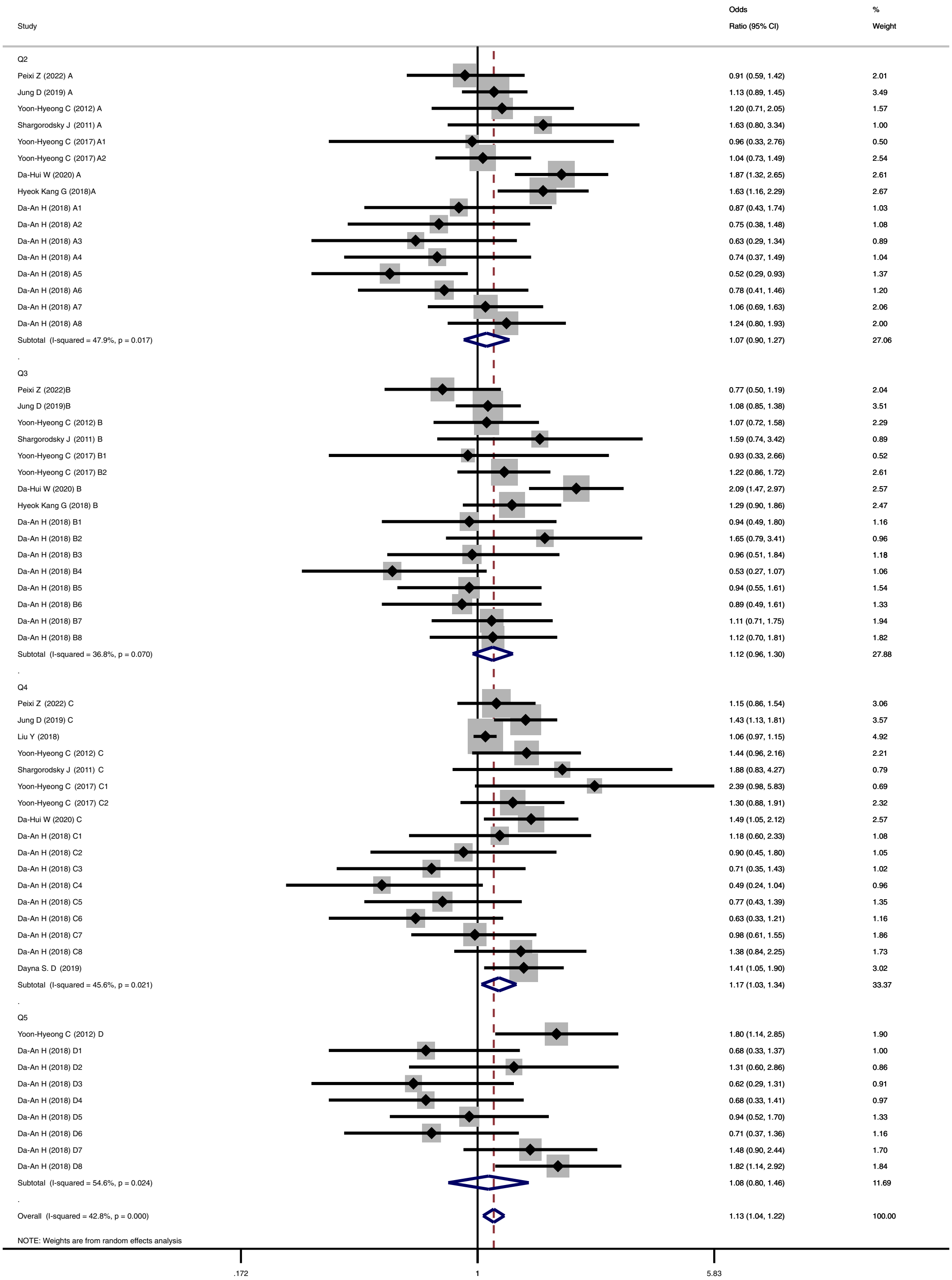


**FIGURE 8** The relationship between different concentrations of blood cadmium and the degree of hearing loss. CI, confidence interval.

term, or low-level doses of mercury exposure. Another study by Choi et al. analyzed data from adult and adolescent participants in the 2010–2012 Korean National Health and Nutrition Examination Survey. They also found no significant association between blood mercury levels and HL in both populations.

However, our meta-analysis showed that mercury has a protective effect on hearing, with an odds ratio of 0.81 (0.70–0.94) with no heterogeneity. There are several possible explanations for these results: (1) It could be due to differences in data sources, as they may have different study designs, sample sizes, and data quality, which can influence the results. (2) It could be due to differences in research methods and analysis techniques, which can also lead to variations in results. (3) Potential biases, such as publication bias, selection bias, or reporting bias, could contribute to the discrepancy between the literature findings and the meta-analysis results. We need further research and analysis to determine the reasons for these differences. Future studies may require stricter methodological controls and assessments of data quality to obtain more reliable conclusions.

### 4.6 | Manganese (Mn)

Manganese is a neurotoxic element associated with age-related diseases. Previous studies have shown hearing impairment in welders exposed to high concentrations of manganese in welding fumes and in workers exposed to both noise and manganese.[11,33] Unfortunately, these clinical findings are limited and largely inconclusive regarding the role of manganese, as multiple confounding factors such as noise, aging, and smoking are simultaneously present. Laboratory studies by Ma et al. have demonstrated that manganese accumulation in the inner ear of rats can cause damage to hair cells, neurons, or supporting cells in the cochlea.[34] Ding et al. found in their study using organotypic cultures of postnatal day 3 rat cochlea that manganese damages sensory hair cells, peripheral auditory nerve fibers, and spiral ganglion neurons (SGNs) in a dose- and time-dependent manner.[35] Ohgami et al. found that WT mice exposed to manganese showed accelerated age-related HL, providing new evidence for Mn-mediated ototoxicity.[36] Nobutaka utilized inductively coupled plasma mass spectrometer (ICP-MS) to determine the levels of Mn in toenails, hair, and urine, as well as the hearing levels (1, 4, 8, and 12 kHz) in a cohort of 145 healthy participants in Bangladesh.[11] Multivariate analysis revealed a significant association between HL and manganese levels in toenails at 8 and 12 kHz, but they did not find association between HL and manganese levels in hair.

Based on these in vivo and in vitro findings, excessive exposure to manganese may lead to HL in both humans and experimental animals. However, further research is still needed to determine the exact relationship between manganese and HL. Additionally, more population studies and long-term follow-up observations are required to fully assess the potential risks of manganese to human hearing.

### 4.7 | Regional and population variations

We conducted a preliminary analysis of the relationship between heavy metal exposure and HL in different countries. The dataset covers studies from various countries, including China, South Korea, Japan, and the United States, with a focus on heavy metals such as lead (Pb), cadmium (Cd), arsenic (As), and manganese (Mn). These studies reported varying levels of different heavy metals, reflecting the influence of geographical location and environmental factors on heavy metal exposure. HL was primarily assessed using the pure-tone average hearing threshold (PTA > 25 dB), and adjusted models considered factors such as age, gender, BMI, smoking habits, and more.

Further analysis of the data revealed variations in the correlation between heavy metal exposure and HL in different countries. For example, studies in China and Japan encompassed multiple heavy metals, including lead, barium, cadmium, cobalt, cesium, molybdenum, antimony, tin, thallium, and tungsten. While the combinations of elements and results varied across studies, the overall trend suggests a potential association between heavy metal exposure and HL. In South Korea, the research primarily focused on the relationship between Cd exposure and HL. Their findings indicated an association between different Cd concentrations and HL, with an increasing risk as Cd levels rose. In the United States, the studies primarily concentrated on lead and cadmium, with results indicating an association between these two heavy metals and HL. It is evident that different heavy metals have varying impacts on HL, potentially related to their toxicological properties and exposure levels. Population characteristics such as age, gender, and regional distribution also play a role in the relationship between heavy metal exposure and HL. This suggests that future research should further consider the influence of these variables in the analysis.

### 4.8 | Strengths and limitations

This meta-analysis has several notable strengths: (1) It is the first study to conduct a meta-analysis on the relationship between exposure to multiple heavy metals and HL. Compared to previous research, our study covers a wide range of heavy metal elements and systematically reviews and summarizes the research findings on the association between heavy metals and HL. (2) We conducted subgroup analyses based on the frequency of PTA to explore the potential influence of measurement frequency on estimating HL caused by environmental lead exposure. Our results highlight that lead exhibits its most substantial impact on hearing at the 4 kHz frequency compared to lower frequencies. (3) We carried out subgroup analyses differentiating between short-term and long-term exposure to heavy metals, which revealed a significant correlation between barium levels in hair and toenails and hearing levels. Hence, the chronic accumulation of heavy metals could be a significant high-risk factor leading to severe HL. (4) Our subgroup analyses involving blood concentrations of lead and cadmium demonstrated a proportional increase in the risk of HL with rising blood concentrations of these heavy metals.

However, our study needs to consider several potential limitations: (1) The cross-sectional study design restricts us from inferring correlations and does not allow for establishing causal relationships. (2) Although the studies attempted to adjust for confounding factors associated with hearing, controlling or considering all variables that might influence the study results remains challenging. Unmeasured or unknown covariates could impact the validity of our conclusions. (3) The underlying mechanisms linking HL and trace metals still need to be understood. (4) The current body of research predominantly focuses on the effects of lead and cadmium exposure on hearing, underscoring the need for further epidemiological analysis to explore the effects of other heavy metal elements.

## 5 | CONCLUSION

This study demonstrates a significant association between human HL and exposure to heavy metals such as lead, cadmium, and barium. These findings not only emphasize the potential threat of heavy metals in auditory health but also highlight the importance of using blood concentrations of heavy metals as predictive indicators for HL. Notably, our research further underscores that the levels of heavy metals in nails and hair, as indicators of long-term exposure, have a higher predictive value than those in urine, reflecting short-term exposure. This provides robust support for future assessments of exposure. We also recommend the inclusion of high-frequency measurements at 4 kHz in the evaluation of HL. It enhances the accuracy of detecting and assessing HL induced by heavy metal exposure.

In the future, we plan to employ longitudinal study designs and advanced statistical methods to control confounding factors better and enhance the reliability of our findings. Moreover, incorporating genetic research and applying more precise biomarkers are expected to deepen our understanding of the mechanisms behind heavy metal-induced HL. These approaches promise to provide more refined tools for risk assessment.

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## CONFLICT OF INTEREST STATEMENT

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## ORCID

*Fang Wang* https://orcid.org/0000-0001-5918-3487
*Frank Böhnke* https://orcid.org/0000-0002-0483-7081
*Markus Wirth* https://orcid.org/0000-0001-7240-5363

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