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ASSOCIATIONS OF GESTATIONAL EXPOSURE TO TOXIC METALS AND ALLERGIC OUTCOMES IN CHILDREN: A META-ANALYSIS

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Abstract

Objective: Because of their immunotoxic qualities and capacity to cross the placental barrier, exposure to toxic metals during pregnancy may have an impact on the development of allergy disorders in offspring. However, results from different research continue to be conflicting. The purpose of this meta-analysis was to determine the associations between gestational exposure to certain heavy metals and the risk of allergic outcomes to the child.

Methods: This systematic literature review was run through six databases, that is, Embase, PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar, up to February 2025. Included were observational studies on prenatal exposures to heavy metals and allergic conditions later in life. The pooled odds, risk, and hazard ratios, as well as standardized mean differences in body weight, were computed using the random-effects model. Systematic assessment was performed on heterogeneity, publication bias, and study quality.

Results: The meta-analysis that embodied 14 cohort studies with a composite sample of 292,057 participants from Korea, Taiwan, Japan, China, Mexico, France, Spain, and Sweden looked at the relationship between the prenatal exposure of distinct heavy metals most associated with lead (Pb), mercury (Hg), cadmium (Cd), chromium (Cr), and nickel (Ni), and allergic conditions during early childhood, such as asthma, atopic dermatitis, rhinitis, wheezing and food allergy. Across the metals investigated, none presented statistically significant evidence of relationship with any allergic outcome. The pooled odds ratio (ORs) for prenatal lead exposure and asthma, OR were 1.05 (95% CI: 0.85-1.24); for mercury exposure and atopic dermatitis, the OR of 1.00 (95% CI: 0.97-1.04); while for cadmium exposure and atopic dermatitis, it was 1.06 (95%CI: 0.87-1.25), respectively. Heterogeneity in studies was low to moderate, while funnel plot analyses did not reveal significant evidence for publication bias.

Conclusion: This meta-analysis found no definitive evidence for an association between prenatal exposure to selected toxic metals and allergic diseases in children. While biologically plausible mechanisms exist, current observational data do not substantiate a clear link. Future studies need to resolve these methodological limitations and investigate interactions between metals, timing of exposure, and genetic susceptibility.

Keywords: Prenatal Exposure, Heavy Metals, Allergic Diseases, Children, Meta-analysis, Lead, Mercury, Cadmium, Asthma, Dermatitis, Food Allergy.

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1 Introduction

Prenatal factors such as genetics, epigenetics, and environmental influences on the fetus play a significant role in the development of allergic disorders later in life [1, 2]. Asthma, allergic rhinitis (AR), and eczema are prevalent inflammatory conditions in children that have various risk factors [3]. Gestational exposure to particular environmental materials could lead to long-lasting and irreversible alterations and imbalances in the immune system, and resulting in a higher likelihood of developing allergic conditions [4].

Heavy metals such as lead (Pb), cadmium (Cd), zinc (Zn), selenium (Se), copper (Cu), mercury (Hg), arsenic (As), cesium (Cs), chromium (Cr), cobalt (Co), nickel (Ni), antimony (Sb), tin (Sn), vanadium (V), thallium (Tl), magnesium (Mg), and manganese (Mn) are widely found in food, soil, water, and air pollution. These materials have long-term persistence in the environment, and even low levels of them could induce toxicity [5, 6]. Heavy metals have immunotoxic effects, and some of them such as Pb, Hg, and Cd can cross the blood-placental barrier [4, 7-9]. Animal models have shown that inhaling lead raised levels of immunoglobulin E (IgE) and histamine levels [10]. Prenatal and early postnatal exposure to heavy metals, such as Pb, has been demonstrated to shift immune responses towards a Th2 bias and increase IgE production [2, 11]. Some studies have shown prenatal exposure to low amounts of Pb might contribute to heightened sensitization to common aeroallergens in early childhood [12]. Additionally, Chia-Yun Hsieh et al., investigated the effects of heavy metals during pregnancy and infancy on the development of asthma in a cohort that included 31,277 new asthma cases. Their results illustrated that exposure to Pb, particularly in combination with As, Cd, and Hg during both early and late pregnancy, is linked to a higher incidence of pediatric asthma [13]. In study by Ruan et al., 628 mother-infant pairs were investigated, and results showed that prenatal exposure to heavy metal, particularly As and Tl, was associated with the risk of allergic rhinitis [14]. Furthermore, Tsung-Lin Tsai and colleagues found that exposure to inorganic As, as well as the combined exposure to both inorganic As and Cd during pregnancy, was related to an increased risk of atopic dermatitis in young children [7]. In contrast, Dow and colleagues investigated the relationship between prenatal exposure to eleven heavy metals and the incidence of atopic diseases in children. They examined maternal urine, hair, and cord blood samples for the presence and amounts of heavy metals, and also monitored atopic conditions in their children up to 5.5 years old. Overall, their findings illustrated that exposure to certain heavy metals at delivery appeared to reduce the risk of atopic diseases, especially in boys [8]. Kampouri et al., evaluated the potential role of early-life exposure to toxic metals, including Cd, Pb, and Hg, in developing allergic diseases. They examined 482 pregnant women and their infants. Based on their findings, higher levels of gestational urinary Cd were related to increased odds of food allergy. However, higher levels of Pb in both gestational and infant erythrocytes were linked to lower odds of atopic eczema and food allergy, and the association of methylmercury with atopic eczema odds increased [11]. Miyazaki and colleagues examined 94,794 mother-infant pairs to evaluate the link between prenatal heavy

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metal element exposure and allergic diseases in early childhood. They did not find an association between prenatal exposure to Hg or Mn and the risk of allergic outcomes. However, prenatal exposure to Se illustrated a negative correlation with atopic dermatitis, food allergies, allergic rhinitis, and any allergic diseases, although it did not have the same effect on asthma [6]. Because of the inconsistencies between studies, we designed this meta-analysis to determine the role of gestational exposure to toxic metals and allergic outcomes in children.

2 Materials and methods

Search strategy

Two independent reviewers carried out a comprehensive search across multiple electronic databases, including Embase, PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar up to February 2025. Furthermore, the reviewers manually reviewed the reference lists of selected publications, as well as related review papers, to find any other potentially relevant publications. A combination of Medical Subject Headings (MeSH) terms and text-based keywords was used for the search strategy. The search terms included ((“heavy metals” OR “metallic element” OR lead OR Pb OR cadmium OR Cd OR zinc OR Zn OR selenium OR Se OR copper OR Cu OR mercury OR Hg OR arsenic OR As OR cesium OR Cs OR chromium OR Cr OR cobalt OR Co OR nickel OR Ni OR antimony OR Sb OR tin OR Sn OR vanadium OR V OR thallium OR Tl OR magnesium OR Mg OR manganese OR Mn OR “metal-rich pollutants” OR “ambient heavy metals” OR HMs) AND (“allergic diseases” OR asthma OR “allergic rhinitis” OR AR OR eczema OR conjunctivitis OR rhinitis OR “oral allergy syndrome” OR dermatitis OR “food allergy” OR wheezing OR “bronchial asthma” OR “hay fever” OR “atopic dermatitis” OR “atopic eczema” OR “coughing” OR “dyspnoea”) AND (“gestational exposure” OR pregnancy OR prenatal OR “prenatal exposure” OR “maternal exposure” OR “intrauterine exposure”)). This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines [15].

Inclusion and exclusion criteria

Publications that met the following criteria were included in this meta-analysis: 1) all observational study designs, such as cohort, cross-sectional, and case-control studies that examined the link between prenatal exposure to heavy metals and allergic outcomes in children, 2) written in English, 3) including mother-infant pairs, 4) including data about types of toxic metals to which mothers were exposed, 5) including data about allergic outcomes in infants and children. All in vitro or animal studies, comments, case reports, letters, ongoing trials, protocols, and reviews and studies lacking applicable data, and studies with duplicates or overlapping participants were excluded.

Study selection

Two independent reviewers eliminated duplicate publications and then screened the titles and abstracts of remaining articles to filter out irrelevant publications. After that, they reviewed the full texts of the remaining publications. Any uncertainties were addressed through discussion with a third reviewer.

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Data extraction

Two independent reviewers conducted data extraction. A data extraction sheet was developed specifically for this review. The extracted data included essential information such as the first author's name, publication year, study location, study design, participant demographics, sample size, types of heavy metals, gender of children, allergic outcomes (asthma, rhinitis, eczema, conjunctivitis, oral allergy syndrome, dermatitis, food allergy, wheezing, atopic dermatitis, atopic eczema, and coughing), and the measures of association including various metrics, including relative risk (RR), risk ratio (RR), hazard ratio (HR), odds ratio (OR), and standard mean differences (SMD). Any uncertainties were addressed through discussion with a third reviewer.

Quality assessment

The Newcastle-Ottawa Scale was used to evaluate the methodological quality of the included publications [16]. Two independent reviewers completed the quality assessment for all included publications. Additionally, the GRADE approach was employed to assess the quality of each outcome. Any uncertainties were addressed through discussion with a third reviewer.

Statistical analysis

In this meta-analysis the odds ratio (OR), hazard ratios (HR), risk ratio (RR), and standard mean differences (SMDs) with 95% confidence intervals (CIs) were employed to present estimates from individual publications. Furthermore, random-effects meta-analysis was used to pool the data. Heterogeneity was evaluated utilizing Cochran's Q-test and I2 test, and meta-regression and subgroup analysis were conducted to find potential sources of heterogeneity. The statistical significance was defined as $p < 0.05$. All statistical analyses were performed using STATA version 14.2 software (StataCorp, College Station, TX). The credibility of the evidence was assessed using GRADE profiler version 3.6 software (The Cochrane Collaboration, Oxford, UK), following GRADE recommendations [17, 18].

Publication bias assessment

The existence of any publication bias in this meta-analysis was assessed using Egger's and Begg's tests. If significant publication bias was identified ($p < 0.05$), the Trim and Fill analysis was applied [19, 20].

Sensitivity analysis

The one-study-removed method was performed for sensitivity analysis to demonstrate the robustness of the findings [21].

3 Result

Literature search

This meta-analysis incorporated 14 cohort studies, encompassing data from 292,057 people, which included both mothers and children. The study was performed in several geographical regions, including Korea, Taiwan, Japan, China, Mexico, France, Spain, and Sweden. The metals most commonly evaluated were lead (Pb), featured in 11 research; cadmium (Cd) and mercury (Hg), each examined in 9 studies; and nickel (Ni) and arsenic (As), each documented in 4 investigations.

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Metals such as manganese (Mn), chromium (Cr), cobalt (Co), selenium (Se), vanadium (V), and titanium (Ti) were assessed with less frequency. The predominant allergic result described in the trials was atopic dermatitis, succeeded by asthma, allergic rhinitis, wheeze, food allergy, chest discomfort, and otitis. All research utilized a cohort design to evaluate prenatal or early-life exposure to heavy metals in connection with allergy outcomes in early childhood, with several studies integrating multipollutant models to more accurately represent real-world environmental exposures (Table 1).

Outcomes

Asthma

The exposure to heavy metals during the prenatal period and later development of asthma in the offspring was critically assessed for both lead (Pb) and mercury (Hg) sources (Figure 1 and 2).

Lead (Pb):

A combined analysis of studies on prenatal lead exposures yielded an odds ratio (OR) of 1.05 (95% CI: 0.85–1.24), suggesting no statistically significant relationship between maternal Pb exposure and the development of childhood asthma. With a Cochran-Q test of marginal significance (Q = 5.96, p = 0.11), there was moderate heterogeneity among the studies (I^2 = 56.87, \u03c4² = 0.02, H^2 = 2.32), thereby allowing us to assume that the source of variability was perhaps not substantial enough to influence the overall pooled estimate. Even though when taken together with the null value (1.00) falling within the computed statistical confidence interval cannot further justify the conclusion, the overall meta-analysis did provide us with a statistical z-value showing significant heterogeneity across the studies considered (z = 10.56, p < 0.001).

Mercury (Hg):

The mercury (Hg) meta-analysis reported a pooled odds ratio of 1.00 (95% CI: 0.98–1.02), reflecting the inconclusiveness of any relationship between prenatal Hg exposure and development of asthma in later childhood. The heterogeneity among studies was minimal (I^2 = 0.01%, τ^2 = 0.00, H^2 = 1.00), and the Q test corroborated the uniformity of results (Q = 2.04, p = 0.56). Notwithstanding the elevated z-score (z = 92.62, p < 0.001), the confidence interval closely centered around 1.00 corroborates the lack of a significant effect.

Atopic Dermatitis

The meta-analysis comparing prenatal exposure to several heavy metals and the incidence of atopic dermatitis in children found no significant correlations among the examined elements, including chromium (Cr), cadmium (Cd), mercury (Hg), nickel (Ni), and lead (Pb) (Figures 3, 4, 5, 6, and 7).

Chromium (Cr):

The analysis of the aggregated data revealed an odds ratio (OR) of 1.00 (95% CI: 0.97–1.03), signifying no significant correlation between prenatal Cr exposure and the incidence of atopic dermatitis. The heterogeneity across the included studies was minimal (I^2 = 0.00%, τ^2 = 0.00, H^2 = 1.00; Q = 1.39, p = 0.50), indicating uniformity in results. Despite the total effect attaining statistical significance (z =

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65.56, $p < 0.001$), the null effect size and narrow confidence interval underscore a conclusive absence of relationship.

Cadmium (Cd)

The aggregated odds ratio for cadmium exposure was 1.06 (95% CI: 0.87–1.25), indicating no statistically significant association with atopic dermatitis. The analysis revealed no heterogeneity ($I^2 = 0.00\%$, $\tau^2 = 0.00$; $p = 0.61$), suggesting a substantial consensus across the included studies.

Mercury (Hg):

The absence of association with atopic dermatitis was further supported by the odds ratio of 1.00 (95% CI 0.97–1.04) obtained from the meta-analysis on prenatal mercury exposure. With a low to moderate level of heterogeneity ($I2 = 34.14\%$, $\tau2 = 0.00$; $Q(6) = 7.41$, $p = 0.28$), the study outcomes showed moderate variability without statistically significant dispersion.

Nickel (Ni):

With a pooled odds ratio of 0.98 (95% CI: 0.94–1.03), prenatal nickel exposure did not appear to be significantly associated with the onset of atopic dermatitis. The Q-test revealed borderline significance ($Q(3) = 8.03$, $p = 0.05$) despite minimal heterogeneity ($I^2 = 0.01\%$, $\tau^2 = 0.00$). The reliability of the null finding is supported, nonetheless, by the consistency of impact predictions across investigations.

Lead (Pb):

The meta-analysis investigating prenatal Pb exposure revealed a pooled odds ratio of 0.99 (95% confidence interval: 0.84–1.14), suggesting no significant correlation with atopic dermatitis. Moderate heterogeneity was detected ($I^2 = 47.25\%$, $\tau^2 = 0.02$, $H^2 = 1.90$), although it lacked statistical significance ($Q = 10.04$, $p = 0.12$). Notwithstanding the substantial z-score ($z = 12.89$, $p < 0.001$), the presence of 1.00 within the confidence interval indicates a non-significant impact.

Wheezing

This meta-analysis encompassed three studies assessing the correlation between prenatal lead (Pb) exposure and the incidence of wheeze in children (Figure 8).

The pooled odds ratio (OR) was 1.05 (95% CI: 0.79, 1.32), signifying no substantial correlation between prenatal Pb exposure and the onset of wheeze in children.

The studies exhibited minimal heterogeneity ($I^2 = 19.04\%$, $\tau^2 = 0.02$, $H^2 = 1.24$; $Q = 2.84$, $p = 0.24$), indicating a significant degree of consistency. Despite the overall effect test being statistically significant ($z = 7.79$, $p = 0.00$), the confidence interval suggests an absence of a meaningful impact.

Rhinitis

This meta-analysis encompassed three studies investigating the correlation between prenatal lead exposure and the risk of rhinitis in children (Figure 9).

The pooled odds ratio was 1.04 (95% confidence interval: 0.77, 1.30), indicating no significant correlation between lead exposure during gestation and the onset of rhinitis.

Moderate to high heterogeneity was detected across the included studies ($I^2 =$

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66.82%, $\tau^2 = 0.04$, $H^2 = 3.01$; Q = 6.34, p = 0.04), signifying variability in the outcomes. The overall effect test was statistically significant (z = 7.71, p = 0.00); nevertheless, the confidence interval includes 1.00, indicating a null connection.

Food Allergy

Mercury (Hg):

This meta-analysis examined three research regarding the correlation between prenatal mercury (Hg) exposure and the incidence of food allergy in children (Figure 10 and 11).

The pooled odds ratio was 1.00 (95% confidence interval: 0.98, 1.02), indicating no statistically significant correlation between mercury exposure during gestation and the onset of food allergies.
The heterogeneity analysis indicated no variability across the studies included ($I^2 = 0.00\%$, $\tau^2 = 0.00$, $H^2 = 1.00$; p = 1.00), implying consistency in the results. Although the overall effect test demonstrates statistical significance (z = 85.07, p = 0.00), the narrow confidence interval indicates a null connection.
Lead (Pb):

This meta-analysis assessed four research regarding the correlation between prenatal Pb exposure and the likelihood of food allergies in children. The pooled odds ratio was 0.95 (95% confidence interval: 0.79, 1.11), suggesting no significant correlation between lead exposure during gestation and the onset of food allergies. The heterogeneity analysis revealed no variability ($I^2 = 0.00\%$, $\tau^2 = 0.00$, $H^2 = 1.00$; p = 0.22), indicating agreement among the trials. Despite the overall effect test being statistically significant (z = 11.78, p = 0.00), the confidence interval encompasses 1.00, indicating an absence of a conclusive risk or protective impact.

Publication Bias

The funnel plots from the meta-analyses demonstrated uniform and symmetrical distributions for the majority of exposures and outcomes, suggesting a generally minimal likelihood of publication bias. No significant asymmetry was seen in the plots regarding prenatal exposure to lead (Pb), mercury (Hg), chromium (Cr), cadmium (Cd), and nickel (Ni) in relation to several allergic disorders, including asthma, wheezing, atopic dermatitis, rhinitis, and food allergy. This indicates an absence of systematic bias in the reporting or inclusion of research. Specifically:

- Evidence-based funnel plots for Pb exposure with respect to asthma, wheeze, atopic dermatitis, and food allergy, were largely symmetrical, falling well within the very narrow fake 95% confidence interval, crowding around the average impact estimate. Rhinitis showed relatively little asymmetry in analysis, which speaks for potential publication bias or heterogeneity of study methodology.

- None of the funnel plots for mercury exposure as pertained to asthma, atopic dermatitis, or food allergy showed recognizable signs of publication bias because they were well symmetrically clustered around the common effect estimate and resided within the faux 95% confidence interval.

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- The funnel plot for Cr and Cd exposure in atopic dermatitis showed symmetrical distribution, with no significant deviations from the middle estimate, thus suggesting the absence of a publication bias.

- Notably, asymmetries were found in 95% of the studies, with many studies concentrating on the middle estimate; only very few fell outside a projection-confined 95 percent confidence interval. The fact that such close relationship with the common effect estimate might, however, lack the power to detect possible imbalance with a restricted number of studies.

4 Discussion

This comprehensive meta-analysis examined the associations between prenatal exposure to various toxic metals—specifically lead (Pb), mercury (Hg), cadmium (Cd), chromium (Cr), and nickel (Ni)—and the subsequent development of allergic diseases in children, including asthma, atopic dermatitis, rhinitis, wheezing, and food allergies. The aggregated data from many observational studies indicated no statistically significant associations between prenatal exposure to these metals and the incidence of allergic disorders in offspring. The results suggest that, given the exposure levels and conditions analyzed, prenatal exposure to these specific heavy metals is unlikely to be a significant contributor to the development of allergic diseases in children.

Our findings align with other previous studies indicating minimal or inconsistent associations between prenatal heavy metal exposure and allergic outcomes in children. Miyazaki et al. [22] conducted a comprehensive study including around 95,000 mother-infant pairs within the Japan Environment and Children's research cohort. No significant associations were identified between allergy outcomes in early infancy and prenatal exposure to mercury or manganese. They discovered a negative correlation between prenatal selenium (Se) exposure and the incidence of atopic dermatitis, food allergies, and allergic rhinitis, suggesting a potential protective effect of some essential trace elements[22].

A comprehensive review and meta-analysis conducted by Chen et al. [23] included 16 studies including over 120,000 mother-child dyads. Their investigation found no significant associations between the onset of asthma, allergic rhinitis, or atopic dermatitis in children with prenatal exposure to lead, cadmium, or mercury. This comprehensive investigation indicates that, at typical ambient exposure levels, these metals are unlikely to substantially influence the incidence of allergic diseases in children[23].

Conversely, several investigations have identified associations between allergic diseases and prenatal exposure to heavy metals. Ruan et al. [24] found that the risk of allergic rhinitis in children increased with prenatal exposure to arsenic (As) and thallium (Tl). Their investigation shown that As and Tl significantly elevated the overall risk, hence emphasizing the potential immunotoxic effects of these metals [24].

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Dow et al. [8] focused on a sample of children in the ELFE French longitudinal birth cohort and examined the relationship between childhood atopic diseases and prenatal exposures to eleven different heavy metals. They suggested that prenatal exposure to certain metals in utero-thus the inverse association with some allergic outcomes, such as rhinitis, eczema, and clusters of multimorbidities-seriously affected boys; cobalt and cesium were implicated as heavy metals. In girls, on the other hand, a direct association was made between cadmium and cesium and rhinitis. Moreover, associations between prenatal lead and allergic outcomes appeared absent, thus confirming the results of this meta-analysis. These observations denote that the relationship between prenatal metal exposure and allergic disease appears to depend on the particular metal being studied, the biological environment used for exposure assessment, sex of the child, and definitions of the outcomes being examined. Future investigations will also need to account for various effect modifiers, such as sex, and apply advanced modeling strategies to jointly investigate mixed exposures with multimorbidity patterns[8]. Additionally, study conducted by Lee et al.[25] indicated that prenatal exposure to a mixture of heavy metals, including cadmium and nickel, was associated with an increased incidence of atopic dermatitis in neonates. This outcome underscores the necessity of considering cumulative exposures to many metals, since their synergistic effects may differ from those of individual exposures[25]. Kampouri et al. [26] discovered that elevated urinary cadmium levels during pregnancy were associated with an increased likelihood of food allergies, but higher lead levels in both gestational and neonatal erythrocytes were correlated with a reduced risk of atopic dermatitis and food allergies. These findings suggest that several factors, such as the specific metal, levels of exposure, and time, may influence the relationship between prenatal heavy metal exposure and allergic outcomes[26].

Variations across these studies may be attributed to differences in research design, demographic characteristics, exposure assessment methodologies, and the specific metals examined. The impact of heavy metals on the developing immune system may be influenced by variations in genetic vulnerability, nutritional status, and concurrent exposure to other environmental pollutants.

The immunotoxic potential of heavy metals has been well recognized [27]. Metals such as Pb, Cd, and Hg can traverse the placental barrier and may disrupt the development of the embryonic immune system [28]. All of these metals are associated with the onset of allergic diseases by modifying immunological responses to a Th2 phenotype, enhancing IgE production, and impairing regulatory T-cell function [29-31]. Research on animals has demonstrated that prenatal exposure to lead (Pb) can elevate IgE levels and histamine release, so substantiating the hypothesis of metal-induced allergy sensitization [32, 33]. Moreover, epigenetic alterations induced by heavy metals during critical stages of immune system development may influence gene expression and immunological functionality throughout life [34-36]. Alterations in DNA methylation patterns and histone changes may influence the formation and functionality of immune cells,

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thereby predisposing individuals to allergic diseases [35]. The absence of significant associations in our meta-analysis may suggest deficiencies in exposure assessment, variability in exposure levels, or the influence of confounding factors.

Besides creating an imbalance in immunological profiles through epigenetic regulation, oxidative stress provides a pathway through which heavy metals perform their toxic effects on the immune system as it develops [37, 38]. Reactive oxygen species (ROS) damage macromolecules of cells, injures redox homeostasis disturbed with heavy metals, cadmium, lead, and mercury, all contributing to its formation [37-39]. During the course of the gestation-old, oxidative imbalance can impair placental function, fetal growth, and immune cell maturation. Increased oxidative stress activates pro-inflammatory signaling cascades, such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which otherwise might be involved in the transcription of genes associated with inflammation and allergic sensitization [40, 41]. Continuous oxidative injury may also favor dendritic cell maturation and improve antigen presentation, resulting in Th2 polarization later in life and subsequent allergic responses [42, 43].

Disruption of the maternal-fetal microbiome and gut-immune axis forms another plausible cause-effect relationship between metal exposure in the prenatal period and allergic outcomes [44]. New insights propose that the exposure of the fetal gut to heavy metals and other dangerous chemicals during pregnancy is associated with an increased change in the profile of maternal microbiota and also with the change in the process of neonate gut colonization [45, 46]. Because early exposure to microbes is central to developing immune tolerance, then a loss of diversity of microbes may compromise the induction of regulatory T cells and mucosal immunity-essential to preventing allergic sensitization [47]. For example, it has been shown that growth-hindering mercury and cadmium are beneficial for inhibiting Bifidobacteria, Lactobacilli, and others, thus increasing gut leakage and inflammation at the systemic level. Such excessive microbial disbiosis and an immature or misregulated immune system may result in an increase in allergic reactivity later after birth [48, 49].

The comprehensive search strategy including many databases and a broad range of heavy metals and allergic outcomes is a significant strength of this meta-analysis. The use of several research methodologies and comprehensive quality assessments significantly enhances our outcomes. Utilizing consistent effect measurements and random-effects models elucidates inter-study variability and provides more generalizable forecasts.

Nevertheless, certain constraints necessitate contemplation. The observational nature of the included research precludes causal inferences. Variations in exposure assessment methodologies, timing of exposure evaluation, and definitions of allergic outcomes might lead to discrepancies and affect the comparability of results. The statistical power to detect connections is further reduced by the limited number of studies on specific metal-outcome pairs. Identified associations may be influenced by confounding variables like as socioeconomic status, maternal nutrition, and simultaneous exposure to other environmental pollutants.

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Furthermore, the majority of studies relied on single-time-point evaluations of metal concentrations, which failed to accurately reflect cumulative exposure or critical periods of susceptibility. The absence of standardized methods for exposure assessment and outcome definition across studies complicates meta-analytical synthesis and interpretation.

While our findings do not establish a definitive correlation between prenatal exposure to the analyzed heavy metals and allergic diseases in progeny, the potential for nuanced or enduring effects remains plausible. Given the acknowledged immunotoxic properties of many metals, particularly in pregnant women, efforts to mitigate environmental exposure remain prudent.

Future studies should give longitudinal studies with exact exposure assessment including timing and dosage top priority as well as the cumulative consequences of many metals. Examining the basic biological pathways such as epigenetic changes and immune system development might clarify the intricate link between prenatal environmental exposures and the likelihood of allergy disorders. Gene-environment interactions and the influence of dietary variables on vulnerability to metal-induced immunotoxicity merit further investigation.

Uniformity of exposure assessment techniques and outcome criteria across research would improve comparability and enable meta-analytical synthesis. Including exposure and impact biomarkers would strengthen the evidence base and guide focused treatments by using sophisticated statistical methods to consider co-exposures and confounding variables.

5 Conclusion

Using meta-analytical methods, available observational evidence summarised the relationships between prenatal exposure to selected toxic metals and allergic outcomes in childhood, including asthma, atopic dermatitis, rhinitis, wheezing, and food allergens. Such findings established a sounding no significant relationship results vis-a-vis exposure during gestation on metals such as Pb, Hg, Cd, Cr, and Ni, towards developing allergic conditions across diverse kinds of studies populations.

Although there is some biological plausibility and mechanism evidence regarding the immunotoxic potential of specific heavy metals. our evidence suggests that, at the levels studied here, gestational exposure to these metals is probably not very important in the risk of allergic diseases in offspring.

Inconsistencies such as these, along with methodological differences, underreporting or absence of data available on some metal-outcome pairings, and limitations inherent to observational research, also show how further inquiry is needed. Long-term cohort designs within future research emphasizing repeated, standardized exposure measurements, mechanistic exploration into immunological and epigenetic effects, and synergistic effects of multiple metal exposures of careful consideration should be included.

Apart from the lack of well-established evidence linking heavy metal exposure during pregnancy to allergic outcomes, reducing maternal exposure to heavy metals during pregnancy has been one of the most justified preventive public

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health measures against such exposure. In the end, ongoing initiatives to lower environmental contaminants and enhance maternal-fetal health monitoring might help lower the prevalence of allergic and non-allergic disorders in subsequent generations.

Declarations

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Ethical statement: Not applicable

Availability of data and material:

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Authors' contributions:

Original Draft, Resources, Visualization, Formal Analysis, Software, Writing – Review & Editing: NG, NT, and SMH.

Original Draft, Resources, Writing – Review & Editing: NG, NT, SMH, EY, AM, AA, MA

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ТАБЛИЦЫ

Table 1. Summary of included studies.

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Author (ref)	Year	Country	Design	Participants	Heavy metals	Outcomes assessed
Lee et al. [25]	2021	Korea	Cohort	738 mother–children pairs	Pb, Hg, Cd	Atopic Dermatitis
Ho et al.[50]	2022	Taiwan	Cohort	140 mother–children pairs	Ni	Atopic Dermatitis
Kim et al. [51]	2013	Korea	Cohort	637 mother–children pairs	Pb, Cd	Atopic Dermatitis
Kim et al. [52]	2019	Korea	Cohort	331 children	Pb, Cr, Hg, Cd	Atopic Dermatitis
McRae et al. [53]	2022	Mexico	Cohort	633 mother-children pairs	Mn, Pb	Asthma, Wheeze
Pesce et al. [54]	2020	France	Cohort	651 mother-children pairs	Pb, Cd, Mn	Asthma, Atopic Dermatitis, Food Allergy, Allergic Rhinitis
Hsieh et al. [55]	2021	Taiwan	Cohort	171,281 children	As, Cd, Hg, Pb	Asthma, Allergic Rhinitis
Tsai et al. [56]	2021	Taiwan	Cohort	586 mother-children pairs	Cd, Ni, Pb, Co, Cu, Cd	Atopic Dermatitis
Miyazaki et al. [22]	2023	Japan	Cohort	94,794 mother-infant pairs	Hg, Mn, Se	Asthma, Atopic Dermatitis, Food Allergy, Allergic Rhinitis
Ruan et al. [24]	2022	China	Cohort	628 mother-infant pairs	V, Cr, Ni, As, Cd, Ti, Pb	Atopic Dermatitis, Wheeze, Allergic Rhinitis
Shin et al. [57]	2019	Korea	Cohort	1,061 mother-	Hg	Atopic Dermatitis

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				children pairs		
Dow et al. [8]	2025	France	Cohort	18,040 mothers and 18,329 infants	As, Ca, Cs, Cr, Co, Ni, Sb, Sn, V, Hg, Pb	Asthma, Atopic Dermatitis, Food Allergy, Wheeze Allergic Rhinitis
Carrasco et al. [58]	2021	Spain	Cohort	1868 children	Hg	Wheezing, Asthma, Chestiness, Atopic Dermatitis, Otitis
Kampouri et al. [26]	2023	Sweden	Cohort	482 mother-infant pairs	Cd, Hg, Pb,	Atopic Dermatitis, Food Allergy

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РИСУНКИ

Figure 1. Forest and Funnel Plot of Lead (Pb) Exposure and Asthma Risk.

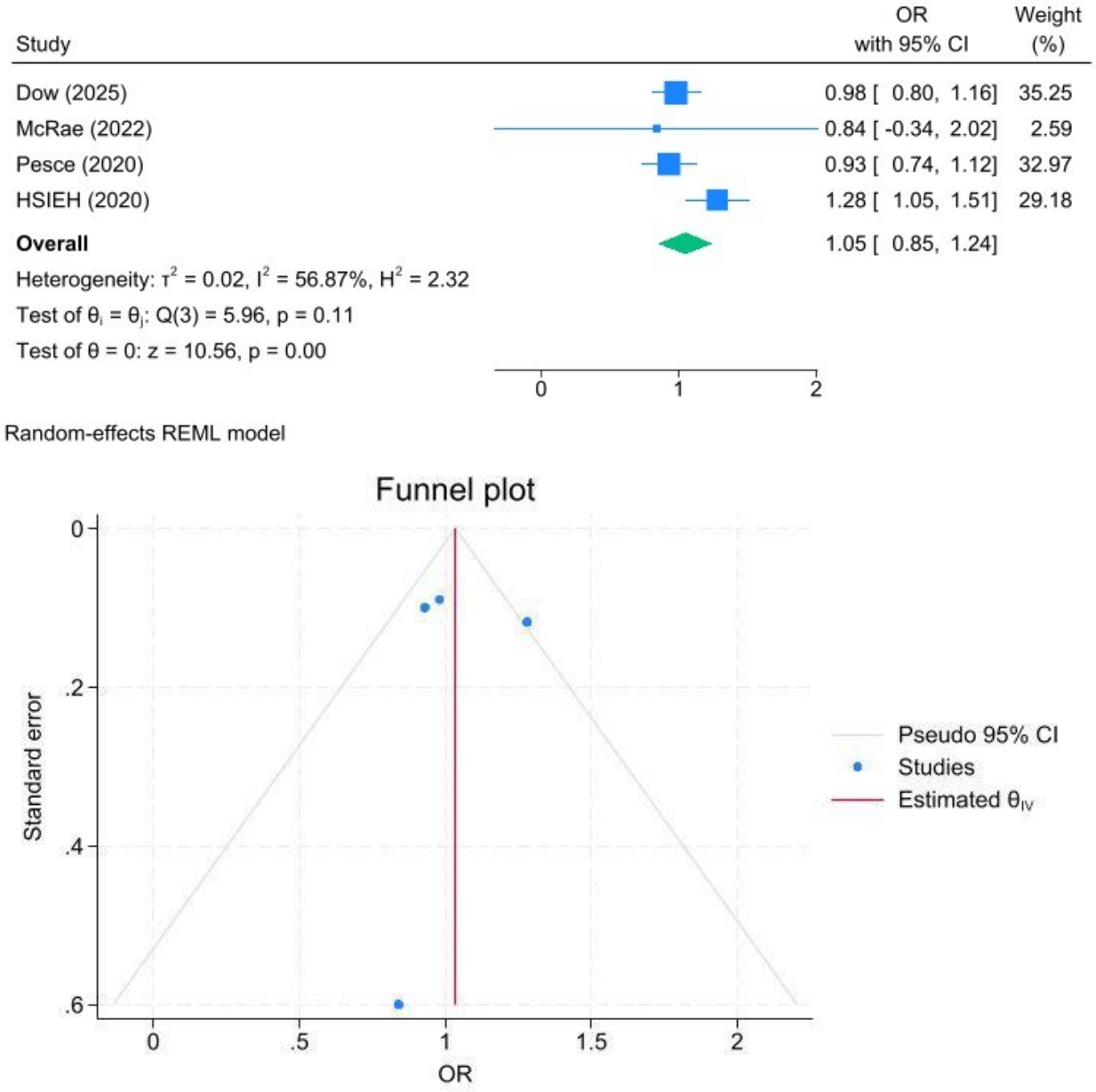

Figure 2. Forest and Funnel Plot of Mercury (Hg) Exposure and Asthma Risk

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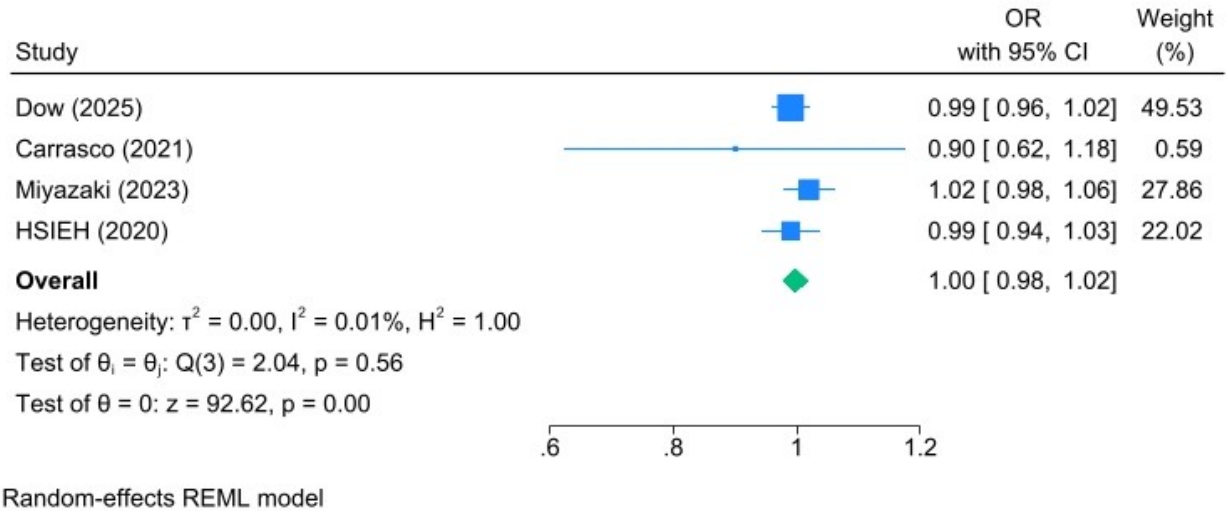

Random-effects REML model

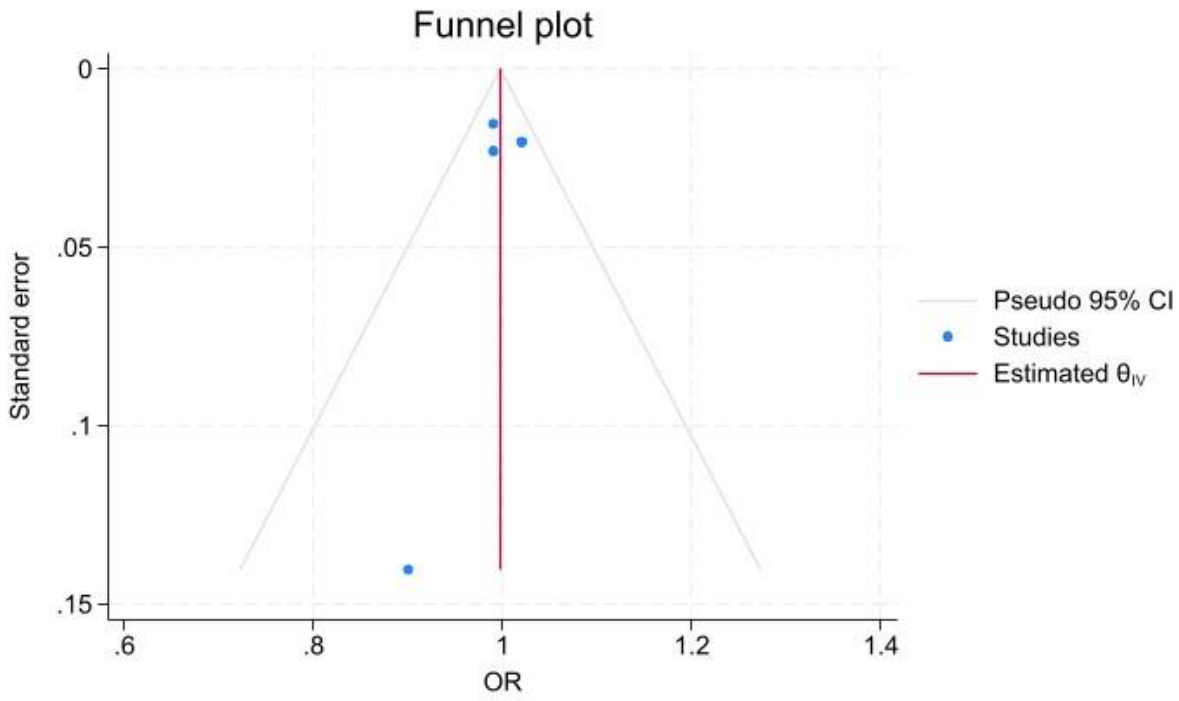

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Figure 3. Forest and Funnel Plot of Chromium (Cr) Exposure and Atopic Dermatitis Risk

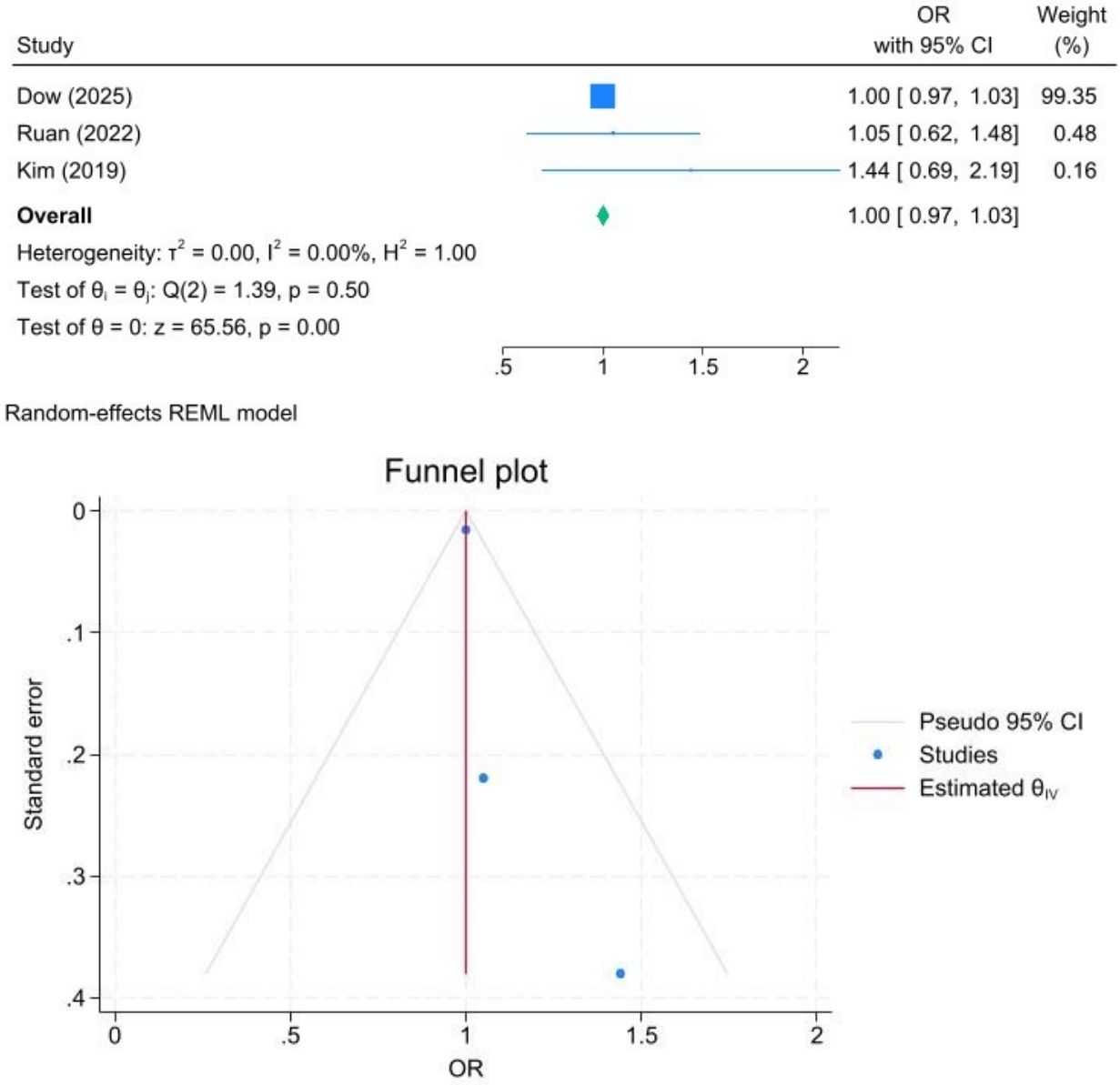

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Figure 4. Forest and Funnel Plot of Cadmium (Cd) Exposure and Atopic Dermatitis Risk

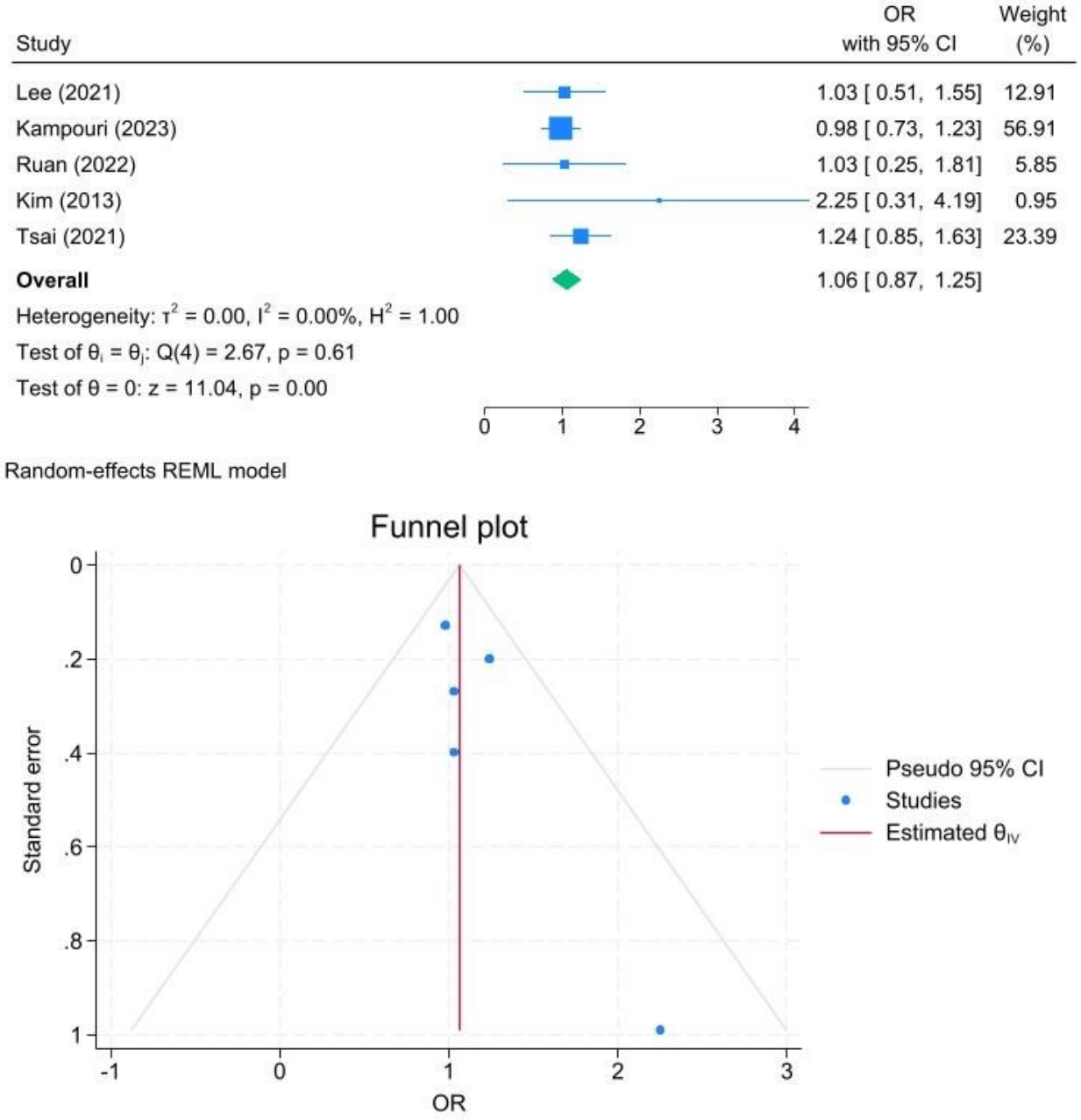

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Figure 5. Forest and Funnel Plot of Mercury (Hg) Exposure and Atopic Dermatitis Risk

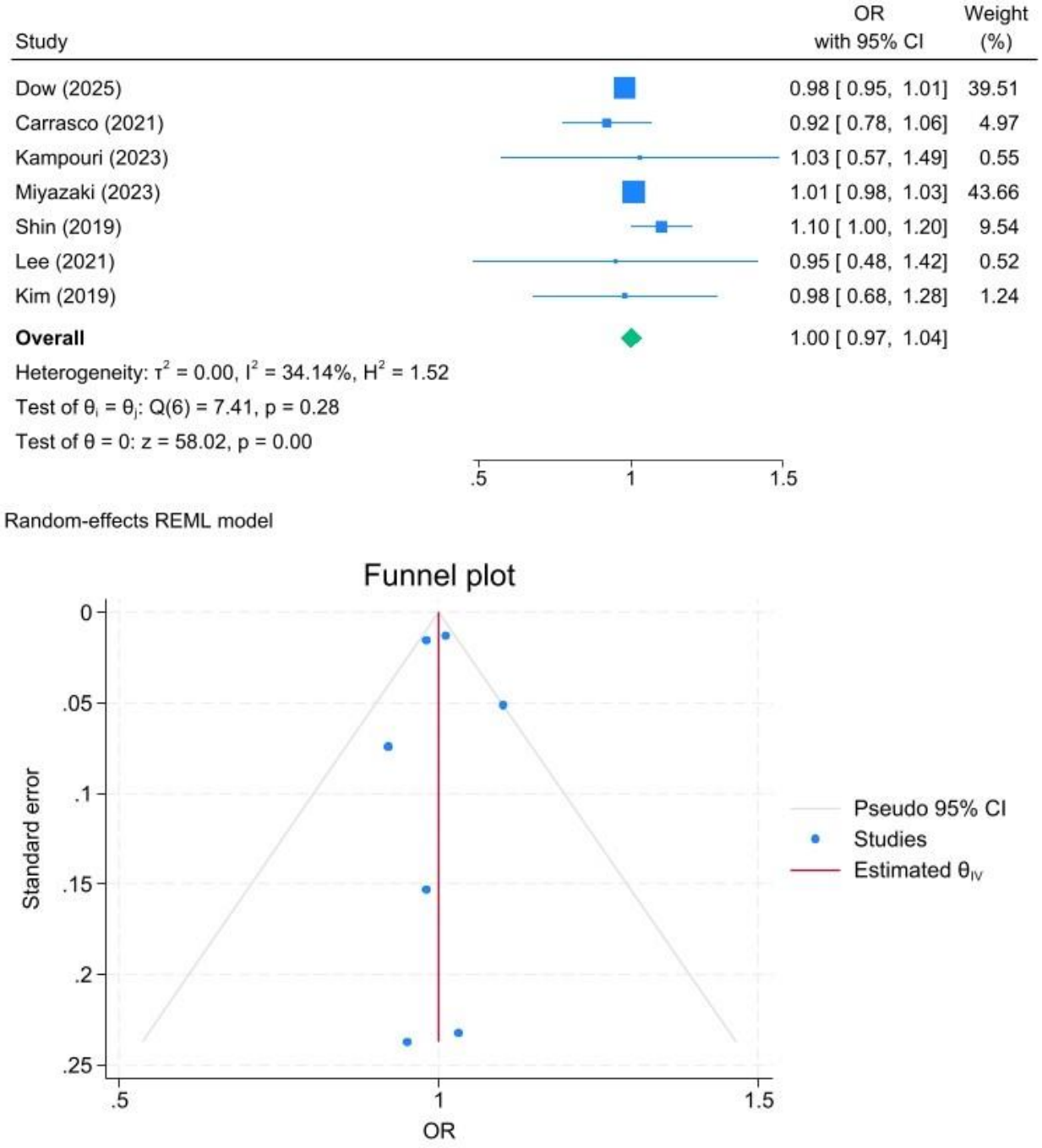

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Figure 6. Forest and Funnel Plot of Nickel (Ni) Exposure and Atopic Dermatitis Risk

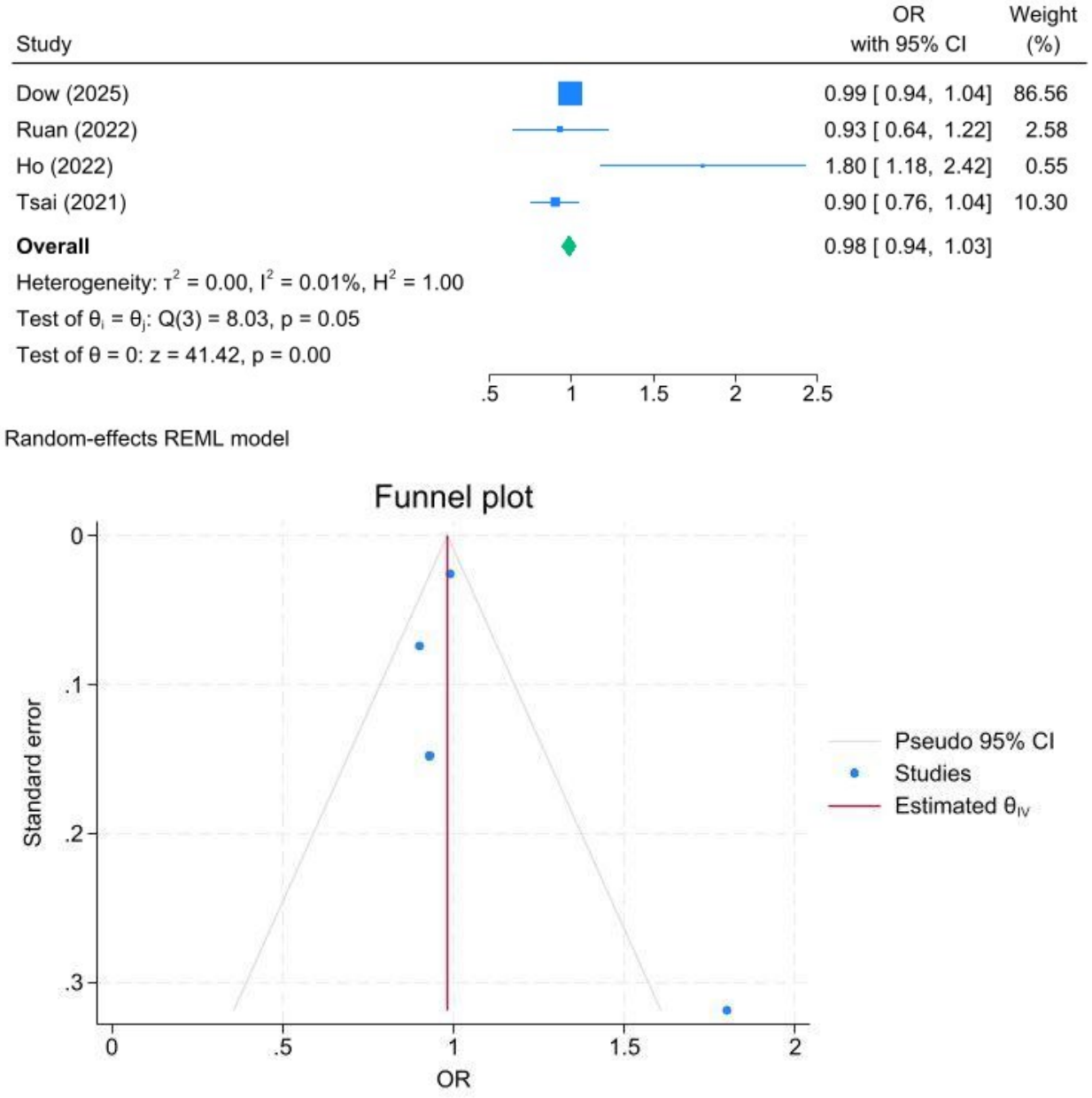

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Figure 7. Forest and Funnel Plot of Lead (Pb) Exposure and Atopic Dermatitis Risk

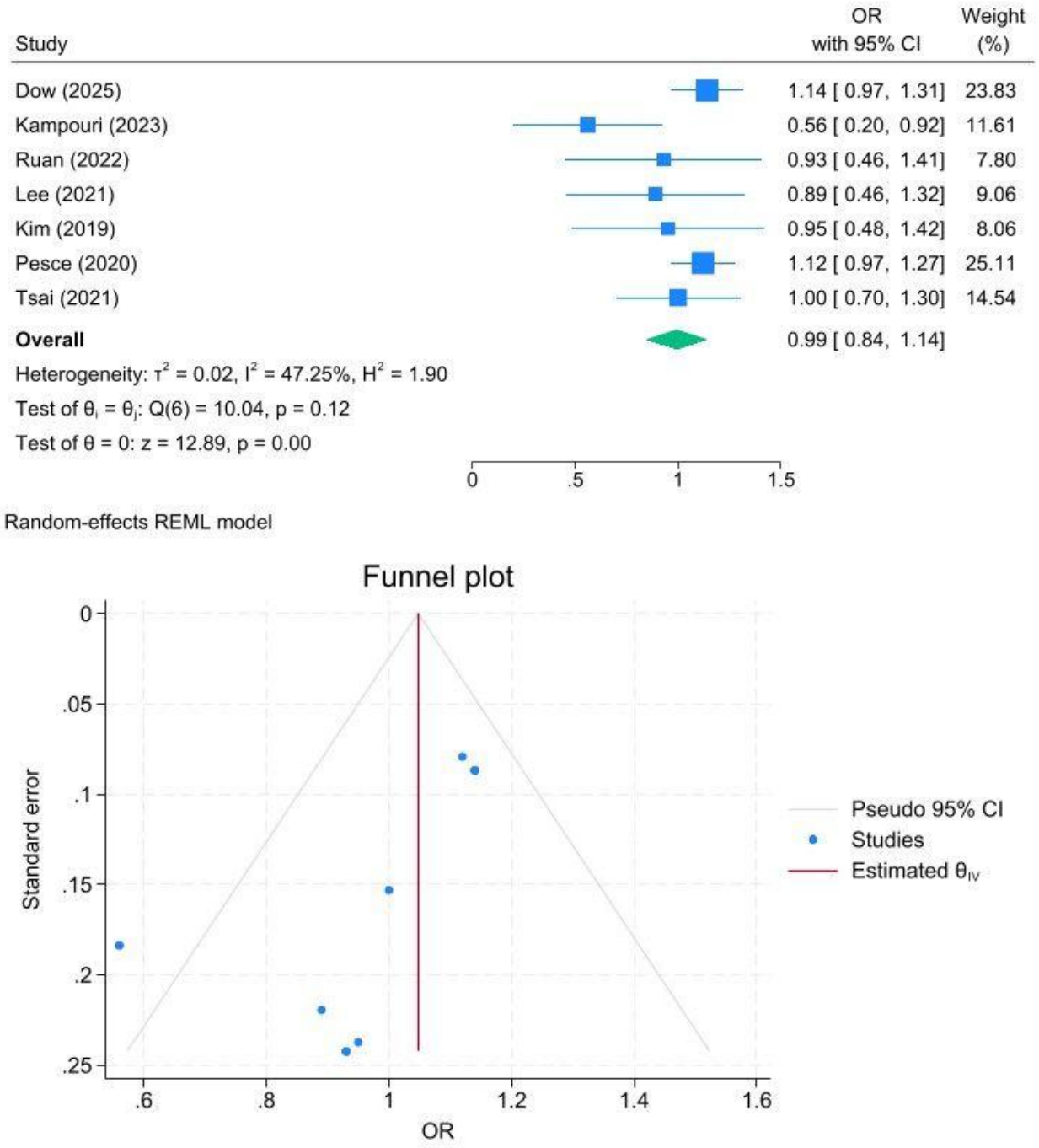

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Figure 8. Forest and Funnel Plot of Lead (Pb) Exposure and Wheezing Risk

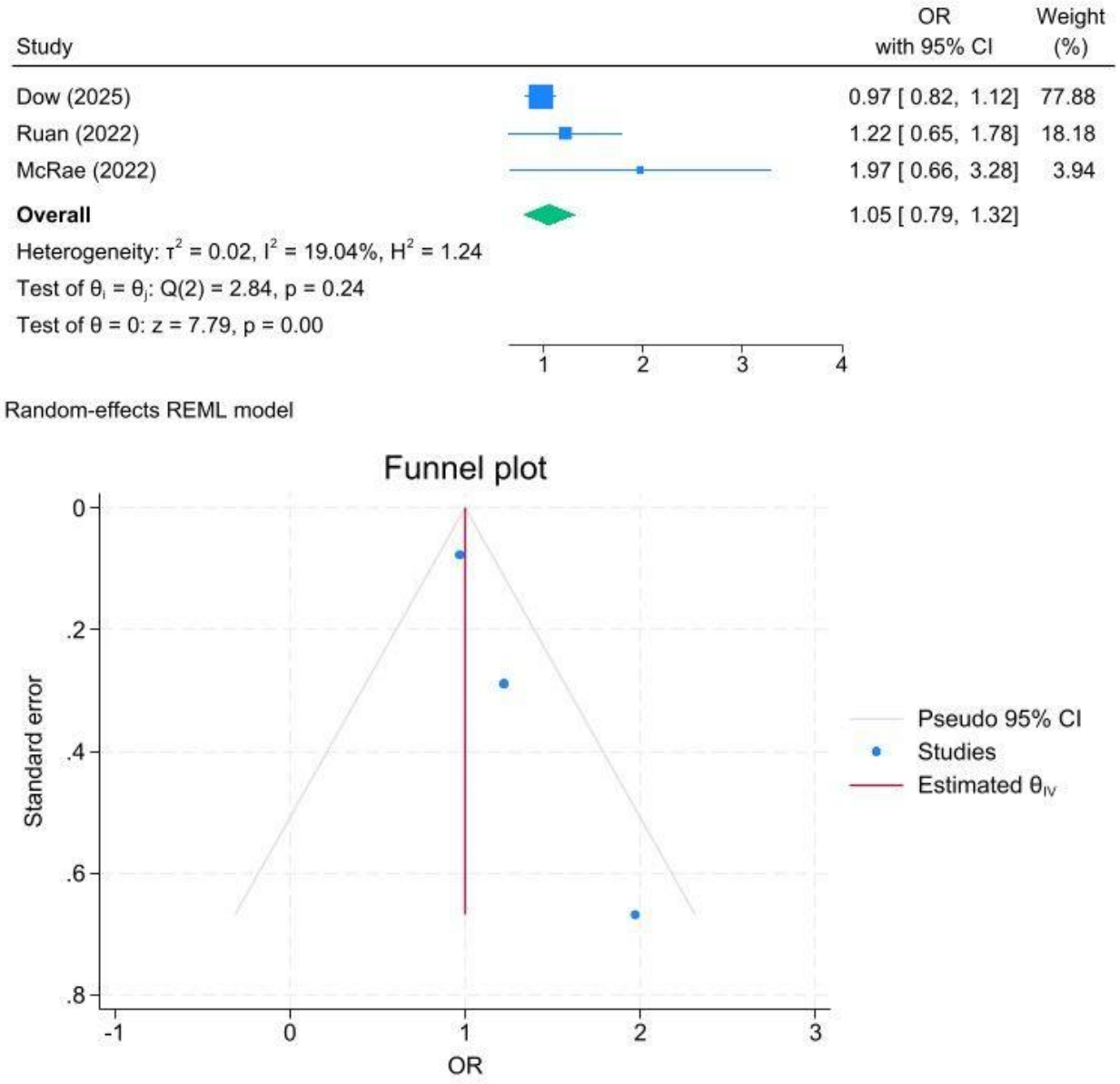

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Figure 9. Forest and Funnel Plot of Lead (Pb) Exposure and Rhinitis Risk

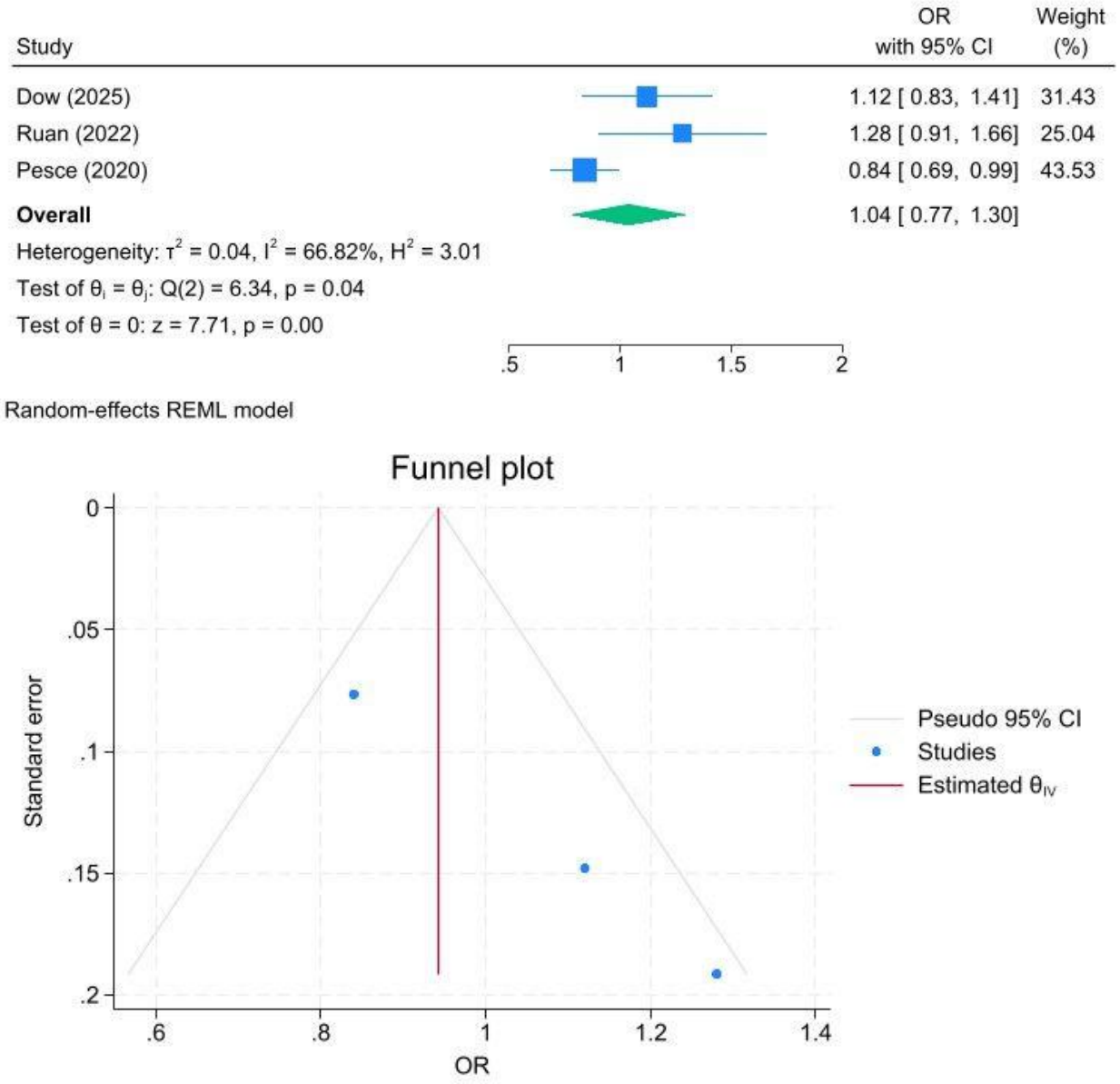

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Figure 10. Forest and Funnel Plot of Mercury (Hg) Exposure and Food Allergic Risk

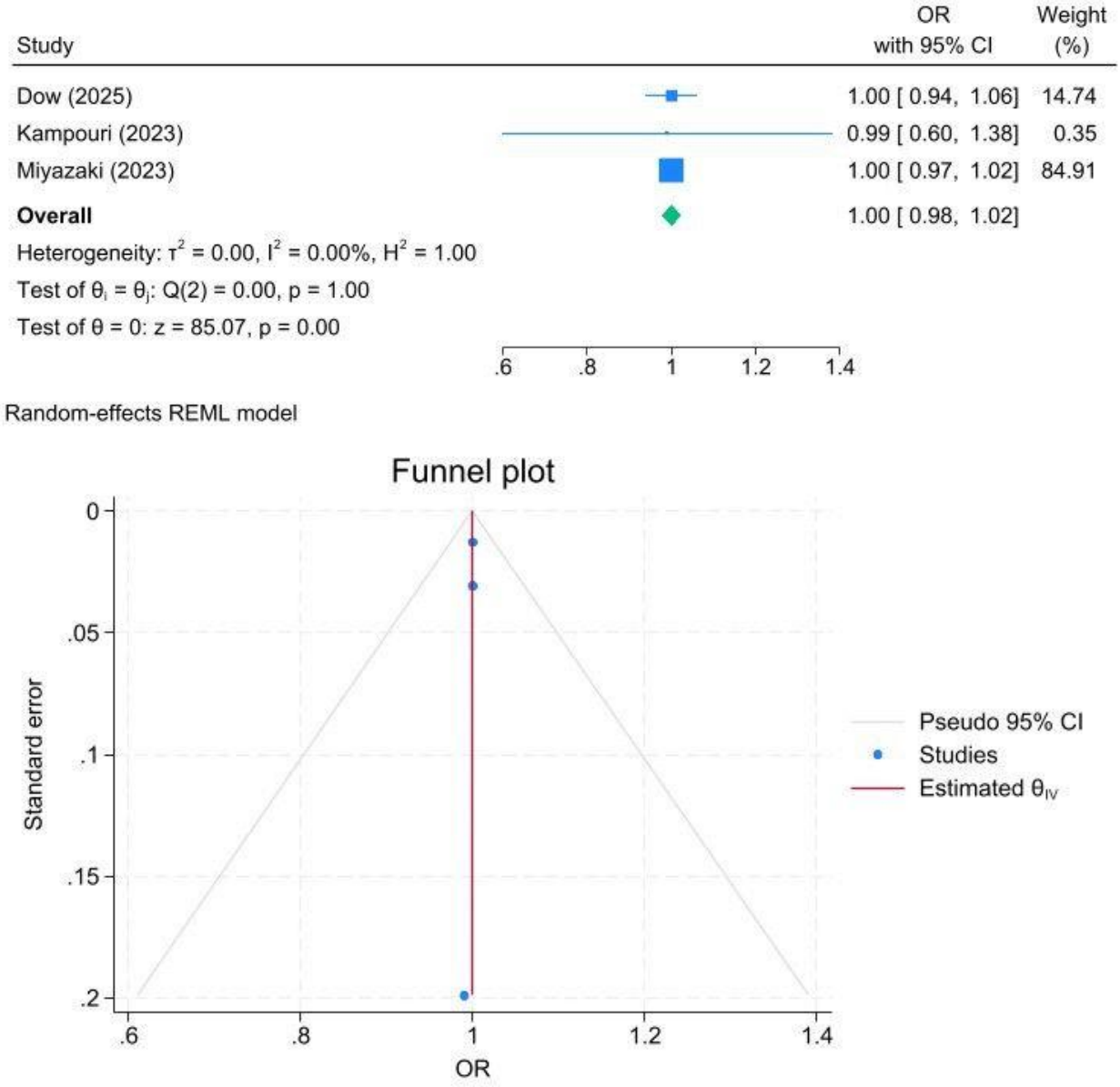

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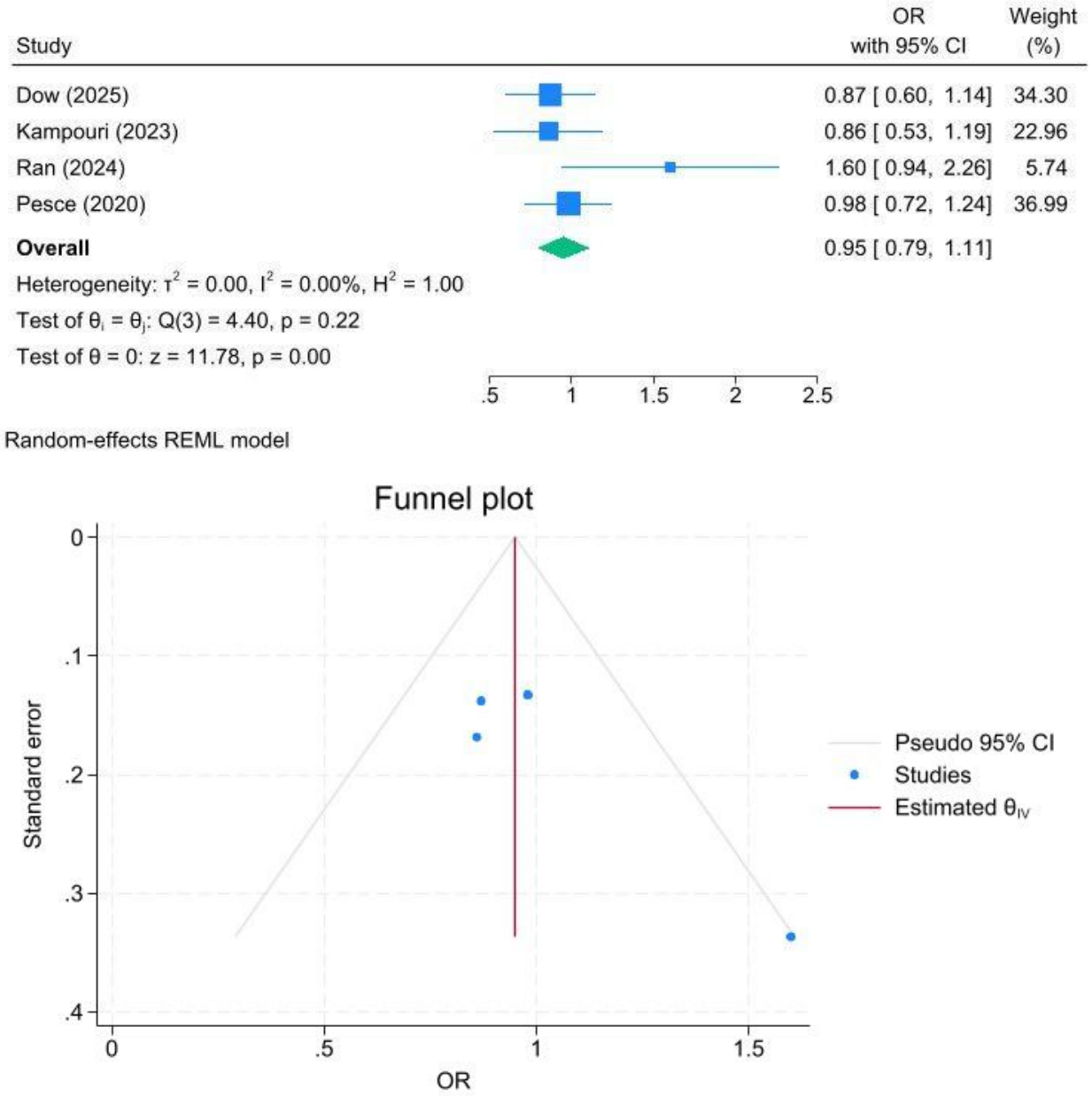
Figure 11. Forest and Funnel Plot of Lead (Pb) Exposure and Food Allergic Risk



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Блок 3. Метаданные статьи

ASSOCIATIONS OF GESTATIONAL EXPOSURE TO TOXIC METALS AND ALLERGIC OUTCOMES IN CHILDREN: A META-ANALYSIS

Сокращенное название статьи для верхнего колонтитула:

GESTATIONAL EXPOSURE TO TOXIC METALS AND ALLERGIC OUTCOMES IN CHILDREN

Keywords: Prenatal Exposure, Heavy Metals, Allergic Diseases, Children, Meta-analysis, Lead, Mercury, Cadmium, Asthma, Dermatitis, Food Allergy.

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