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Revisión

The association of cadmium heavy metal with growth failure in children – A systematic review and meta-analysis

La asociación del metal pesado cadmio con el retraso del crecimiento en los niños: revisión sistemática y metaanálisis

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Abstract

Introduction: early exposure to cadmium toxic metal has been suggested to be associated with reduced infants/children growth; nevertheless, the available evidence is contradictory.

Objective: this meta-analysis aimed to examine the association of cadmium exposure through biological samples to growth measurements of infants/children, including body weight, height, body mass index (BMI), BMI-for-age (BMI Z-score), weight-for-age (WAZ), height-for-age (HAZ), and weight-for-height (WHZ) z-scores.

Methods: a systematic search in PubMed and Scopus was implemented to obtain the related studies. The standardized beta coefficients (β) and 95 % confidence intervals (95 % CI) were used as effect sizes to test the associations using the random effects analysis.

Results: a total of 15 studies with 6,181 participants were included in the meta-analysis. In the overall analysis, pooled analysis of available data revealed that cadmium exposure was inversely linked to height (β = -0.06, 95 % CI = -0.12 to -0.01) and WAZ (β = -0.01, 95 % CI = -0.02 to -0.003). These relationships were also supported by prospective cohort studies and urinary cadmium exposure. In the stratified analysis, cadmium exposure was negatively linked to the weight of children in prospective cohort studies, in studies that assessed urinary cadmium exposure. No significant association was detected between cadmium exposure and BMI, BMI Z-score, WHZ, and HAZ in the overall and subgroup analyses.

Conclusions: this meta-analysis emphasized the importance of cadmium exposure as a risk factor for growth failure in infants/children.

Keywords:

Infants. Children. Growth. Cadmium. Meta-analysis.

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Resumen

Introducción: se ha sugerido que la exposición temprana al metal tóxico cadmio se asocia a un crecimiento reducido de los bebés y niños; sin embargo, la evidencia disponible es contradictoria.

Objetivo: este metaanálisis tuvo como objetivo examinar la asociación de la exposición al cadmio a través de muestras biológicas con las mediciones de crecimiento de bebés/niños, incluidos el peso corporal, la altura, el índice de masa corporal (IMC), el IMC para la edad (puntuación Z del IMC) y las puntuaciones z de peso para la edad (WAZ), altura para la edad (HAZ) y peso para la altura (WHZ).

Métodos: se implementó una búsqueda sistemática en PubMed y Scopus para obtener los estudios relacionados. Los coeficientes beta estandarizados (β) y los intervalos de confianza del 95 % (IC 95 %) se utilizaron como tamaños del efecto para probar las asociaciones mediante el análisis de efectos aleatorios.

Resultados: se incluyeron en el metaanálisis un total de 15 estudios, con 6.181 participantes. En el análisis general, el análisis conjunto de los datos disponibles reveló que la exposición al cadmio estaba inversamente relacionada con la altura (β = -0,06, IC del 95 % = -0,12 a -0,01) y WAZ (β = -0,01, IC del 95 % = -0,02 a -0,003). Estas relaciones también fueron respaldadas por estudios de cohortes prospectivos y exposición al cadmio en orina. En el análisis estratificado, la exposición al cadmio se relacionó negativamente con el peso de los niños en estudios de cohortes prospectivos, en estudios que evaluaron la exposición al cadmio en la orina. No se detectó ninguna asociación significativa entre la exposición al cadmio y el IMC, la puntuación Z del IMC, el WHZ y el HAZ en los análisis generales y de subgrupos.

Conclusiones: este metaanálisis enfatizó la importancia de la exposición al cadmio como factor de riesgo del retraso del crecimiento en lactantes/niños.

Palabras clave:

Lactantes. Niños. Crecimiento. Cadmio. Metaanálisis.

INTRODUCTION

Growth failure in children, featured by stunting, underweight, and wasting (1), is a significant public health concern worldwide, with long-term implications on both physical and cognitive development (2-4). The growth and development of children are affected by several factors, such as genetics, recurrent infections, nutritional status, and socio-economic conditions (4-8). Environmental factors, such as exposure to heavy metals, have also been implicated as potential contributors to this problem (9). Among heavy metals, cadmium has attracted significant attention due to its high degree of toxicity, widespread presence in the environment, and the potential adverse effects it may have on children's growth (10).

Cadmium is released into the environment through various industrial processes, waste disposal methods, and agricultural practices (11). It can contaminate air, water, and soil, eventually accumulating in the human body mainly through food and drinking water (5,12). Once ingested, cadmium can cause multiple health issues, including renal dysfunction (13), skeletal damage (14), neurodevelopment impairment (15), immune dysfunction (16), and an increased risk of cancer (17). In humans, cadmium has a remarkably extensive biological half-life (> 15 years) with a very low excretion rate, and the total body contents of cadmium increases with age (18). Early exposure to cadmium could happen during prenatal and neonatal periods via transplacental transfer, breast milk, and complementary feeding (19,20). Thus, early childhood is considered a vital stage to decrease cadmium exposure and hinder its long-lasting outcomes.

Animal studies have established that the administration of cadmium is linked to decreased body weight and growth (21,22). In humans, prenatal cadmium has been negatively related to birth weight (23), but evidence of growth-associated impacts of cadmium exposure through various biological samples in infants/children is limited and inconclusive. The prospective cohort study by Gardner et al. (24) revealed that a higher urinary cadmium exposure during childhood is negatively linked to height, weight, and growth velocity at 5 years of age, while some studies failed to observe an association between cadmium in blood (25) and urine (26) with the growth indicators of children. The inconsistencies among the findings of the previous studies might be due to the difference in type of biological sample, sample size, study design, gender of participants, method used to assess cadmium, and the varieties in adjustment for covariates. Accordingly, the objective of this meta-analysis was to evaluate the association of cadmium exposure through biological samples to growth measurements of infants/children, including body weight, height, BMI, BMI-for-age Z-score, WAZ z-score, HAZ z-score, and WHZ z-score.

MATERIALS AND METHODS

This study was reported by following the PRISMA guidelines (27).

SEARCH STRATEGY

A comprehensive search of relevant literature from the beginning to September 2023 was conducted using PubMed and Scopus databases. Additionally, a manual search was conducted in the references of the related reviews and included studies to ensure no articles were missed. The search strategy was as follows: ("Cadmium"[Mesh] OR Cadmium[Title/Abstract]) AND ("Child"[Mesh] OR "Infant"[Mesh] OR child[Title/Abstract] OR Infant[Title/Abstract] OR children[Title/Abstract] OR infants[Title/Abstract] OR neonatal[Title/Abstract]) AND (growth[Title/Abstract] OR weight[Title/Abstract] OR length[Title/Abstract] OR height[Title/Abstract] OR anthropometry[Title/Abstract] OR length-for-age[Title/Abstract] OR height-for-age[Title/Abstract] OR weight-for-age[Title/Abstract] OR weight-for-length[Title/Abstract] OR weight-for-height[Title/Abstract] OR stunting[Title/Abstract] OR wasting[Title/Abstract] OR underweight[Title/Abstract] OR "Growth"[Mesh] OR Body Height"[Majr] OR "Child Development"[Mesh]). The search was restricted to articles published in English language. The retrieved studies were entered into the Endnote software, duplicates were removed, the titles/abstracts were reviewed by two independent authors, and then the full-text of the related articles were screened by two authors independently; any differences were resolved through a discussion among all researchers. Finally, studies meeting the inclusion criteria were included in the meta-analysis.

INCLUSION CRITERIA

The following inclusion criteria were considered: 1) observational studies (cohort, cross-sectional, or case-control) examining the relation of cadmium exposure to growth measurements (weight, height, BMI, BMI Z-score, WAZ, HAZ, or WHZ) in infants/children (under 12 years); 2) reported the standardized regression coefficient (β) and 95 % confidence interval (CI) for the associations or provided raw data to compute them; 3) the exposure was measured in biological samples, such as blood, urine, or hair. Animal studies, letters, book chapters, studies on adolescents/adults, editorials, review articles, studies that were on pregnant women, studies with irrelevant exposure/outcome, and studies that were not extractable were excluded.

DATA EXTRACTION AND QUALITY ASSESSMENT

Two authors independently conducted the data extraction process for all included studies and disagreements were resolved through discussion. The following information was gathered from each publication: author's name, publication year, sample size, country, gender of participants, study design, outcomes assessed, mean age of participants, β and 95 % CI for the associations, method used for cadmium evaluation, type of exposure (sample), covariates used for adjustment in analyses, and statistical models applied for the analyzing of data. The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (28), on a scale ranging from 0 to 9 stars. For cross-sectional studies, we applied a modified version of NOS to assess the quality of studies. A score of 6 or higher indicates high quality, a score between 3 and 5 indicates medium quality, and a score below 3 indicates low quality (29).

STATISTICAL ANALYSIS

To evaluate the relationship between exposure to cadmium and growth indicators, the standardized regression coefficient (β) and its 95 % CI were applied. Since different statistical metrics (regression coefficient, correlation coefficient, or mean differences of outcomes in the low-exposed and high-exposed groups) were presented in the included publications, the β and its 95 % CI were used to synthesize the findings. The β and its 95 % CI were estimated with the use of the formulas presented in the supplementary figure 1 (https://www.nutricionhospitalaria.org/anexos/04965-01.pdf). Statistical heterogeneity among the included studies was assessed using the Q and I^2 statistics (30,31). Due to the anticipated heterogeneity, the DerSimonian and Laird random effects model was used for all pooled results (32). Subgroup analysis was performed based on the study design (prospective cohort vs. cross-sectional), method of cadmium measurement (inductively coupled plasma mass spectrometry (ICP-MS), graphite furnace atomic absorption spectrometry (GFAAS), and flame atomic absorption spectrometry [FAAS]), adjustment for covariates (yes vs. no), gender of participants (boy, girl, and both) and type of sample (blood, urine, and hair) to explore possible sources of heterogeneity. Publication bias was evaluated using the Egger's test (33). Statistical calculations were performed using STATA software (version 14.0; Stata Corporation, College Station, TX, USA), and *p*-values < 0.05 were considered statistically significant.

RESULTS

STUDY CHARACTERISTICS

The systematic search yielded a total of 1,160 publications, out of which 302 were identified as duplicates. After excluding 808 articles based on their titles and abstracts, 50 studies remained for full-text evaluation. Ultimately, 15 publications (5,9,18,24-26,34-42), published between 2001 and 2022 with a combined sample size of 6,181 subjects, were included in the meta-analysis. The screening process of the studies is depicted in figure 1. These studies originated from four continents, with 5 from Europe (25,26,35,36,41), 3 from Africa (18,39,40), 1 from America (34), and 6 from Asia (5,9,24,37,38,42). Among them, 5 records were prospective cohort studies (5,24,34,38,41) and 10 records were cross-sectional studies (9,18,25,26,35-37,39,40,42). The sample sizes of the analyzed publications ranged from 32 to 1,505 participants. The man age of participants ranged from ≤ 4 weeks to 11 ± 0.4 years. The frequency of participants with male sex among the included studies varied from 49 % to 52 %. Type of exposure (sample) was hair in 2 studies (35,41), urine in 5 studies (5,24,26,37,38), and blood in 8 studies (9,18,25,34,36,39,40,42). Cadmium levels were determined using inductively coupled plasma mass spectrometry (ICP-MS) in 10 studies (5,24,26,34,35,37-41), graphite furnace atomic absorption spectrometry (GFAAS) in 4 studies (9,25,36,42), and flame atomic absorption spectrometry (FAAS) in 1 study (18). Most studies adjusted their results for potential covariates, although 6 publications (18,25,36,37,39,41) reported unadjusted results without accounting for confounders. Data on height, weight, BMI, BMI Z-score, WAZ, WHZ, and HAZ were available in 4 studies (9,24,36,42), 6 studies (9,18,24,25,36,37), 3 studies (26,36,42), 8 studies (5,24,34,35,37-39,41), 2 studies (39,41), and 8 studies (5,24,34,35,38-41), respectively. The quality of the included publications ranged from medium to high, with scores between 3 and 9 (median score: 6.73). Table I provides an overview of the characteristics of the included papers.

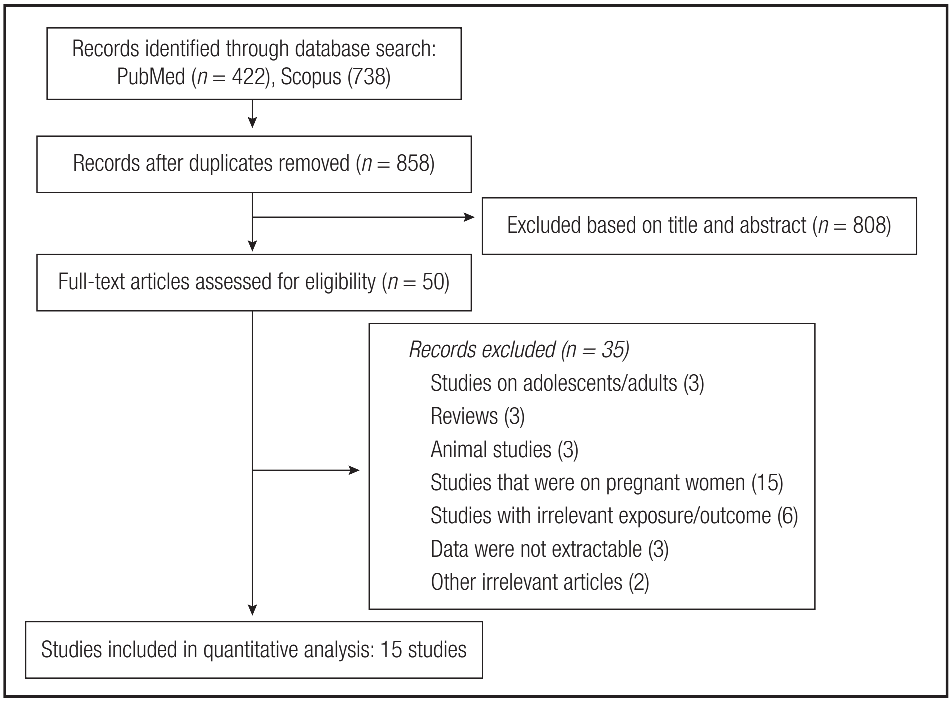

Figure 1.

Flow chart of study selection.

CADMIUM EXPOSURE AND GROWTH MEASUREMENTS

The results of the overall and subgroup analyses by study design, method used to assess cadmium, gender of participants, adjustment for covariates (yes vs. no), and type of sample is presented in table II. In the overall analysis, when all effect sizes were pooled using the random effects model, a significant inverse relationship was found between higher cadmium exposure and height (β = -0.06, 95 % CI = -0.12 to -0.01; Fig. 2) and WAZ (β = -0.01, 95 % CI = -0.02 to -0.003; Fig. 3) in children. In the subgroup analyses, the negative correlation of cadmium to height and WAZ was also supported by prospective cohort studies (height: β = -0.11, 95 % CI = -0.17 to -0.05; WAZ: β = -0.01, 95 % CI = -0.02 to -0.002) and urinary cadmium exposure (height: β = -0.11, 95 % CI = -0.17 to -0.05 [Fig. 2]; WAZ: β = -0.01, 95 % CI = -0.02 to -0.004 [Fig. 3]) (Table II). Moreover, in the stratified analysis, cadmium exposure was negatively linked to the weight of children in prospective cohort publications, in studies that assessed urinary cadmium exposure, and in studies that used ICP-MS or FAAS to assess cadmium levels (Table II). No significant association was detected between cadmium exposure and BMI (Fig. 2), BMI Z-score (Fig. 3), WHZ (Fig. 3), and HAZ (Fig. 3) in the overall and subgroup analyses (Table II).

HETEROGENEITY AND PUBLICATION BIAS

A significant heterogeneity was observed across the studies on weight (I^2 = 76.5 %, p = 0.001), BMI Z-score (I^2 = 66.5 %, p = 0.01), WAZ (I^2 = 48.9 %, p = 0.02), WHZ (I^2 = 69.9 %, p = 0.03), and HAZ (I^2 = 62.3 %, p = 0.002). There was no publication bias for all growth indicators (Table II, Supplementary figures 2-8).

DISCUSSION

With a comprehensive analysis of 15 studies encompassing a total sample size of 6,181 participants, this study assesses the relationship between cadmium exposure in different biological samples and various growth measurements, including weight, height, BMI, BMI Z-score, HAZ, WAZ, and WHZ. By synthesizing the available studies, we disclosed that cadmium exposure may negatively affects the growth indicators of infants/children, including height, weight, and WAZ.

Worldwide, several millions of individuals are exposed to cadmium because of anthropogenic and natural activities that result in a widespread distribution of cadmium in the environment, contributing to potential adverse effects on health outcomes (43). Recently, animal and human studies have proposed that In utero exposure to cadmium can have serious negative effects on the growth of neonates (44). Nevertheless, the association of postnatal exposure to cadmium with growth of infants/children has been contradictory. In contrast to the present analysis, the cross-sectional study by Olszowski et al. (25) on 71 subjects in Poland did not find a relationship between blood cadmium and body weight of infants. Moreover, in the study by Wang et al. (26) in Belgium on 249 children (aged 5.83 ± 0.37 years), urinary cadmium was not relates to BMI of children. However, a longitudinal cohort in rural Bangladesh reported that children's urinary cadmium, reflecting long-term exposure, was negatively linked to WAZ, and possibly HAZ at 10 years of age (5).

Table I. Characteristics of studies

Reference	Year	Country	Study design	Age (range or mean ± sd)	Type of sample	Exposure assessment	Sex	No. of participants	Outcomes	Statistical models	Adjustment	Quality score
Orun (41)	2022	Turkey	Prospective cohort	8 months of age	Hair	ICP-MS	Boy	24	WAZ, WHZ, HAZ, BMI Z-score	Spearman's correlation	Crude	6
							Girl	22				
Igra (38)	2019	Bangladesh	Prospective cohort	8.9 ± 0.15 years	Urine	ICP-MS	Boy	248	WAZ, HAZ	Multivariable linear regression	Adjusted for sex, maternal education, family's socio-economic status, children's hemoglobin, osteocalcin, vitamin D3, IGF-1, urinary arsenic, and urinary deoxy-pyridinoline at 9 y of age	8
							Girl	256				
Ashley-Martin (34)	2019	Canada	rospective cohort	2-5 years	Blood	ICP-MS	Boy	236	WAZ, HAZ, BMI Z-score	Multivariable linear regression	Adjusted for maternal education, country of birth, maternal age, maternal postnatal BMI, prenatal smoking, paternal BMI, and spline of concurrent metals and elements (As, Cd, Hg, Se; Mo, Zn), and maternal exposures to metals	9
							Girl	213				
Yang (42)	2012	China	Cross-sectional	3-8 years	Blood	GFAAS	Both	246	BMI, Height	Multiple linear regression	Adjusted for age and sex	8
Wang (26)	2017	Belgium	Cross-sectional	5.83 ± 0.37 years	Urine	ICP-MS	Both	249	BMI	Pearson's correlation	Adjusted for creatinine levels	7
Olszowski (25)	2016	Poland	Cross-sectional	NR	Blood	GFAAS	Both	71	Weight	Pearson's correlation	Crude	6
Moody (40)	2020	Uganda	Cross-sectional	6-59 months	Blood	ICP-MS	Both	97	HAZ	Multivariable linear regression	Adjusted for level of educational attainment of mothers and a history of child hospitalization	7
Mbunga (39)	2022	Congo	Cross-sectional	32 ± 15.18 months	Blood	ICP-MS	Both	412	WAZ, WHZ, HAZ	Mean difference of outcomes in high vs. low exposure to cadmium	Crude	5

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Table I (cont.). Characteristics of studies

Reference	Year	Country	Study design	Age (range or mean ± sd)	Type of sample	Exposure assessment	Sex	No. of participants	Outcomes	Statistical models	Adjustment	Quality score
Kippler (37)	2011	Bangladesh	Cross-sectional	11-17 weeks	Urine	ICP-MS	Both	92	Weight, WAZ	Spearman's correlation	Crude	6
Hossny (18)	2001	Egypt	Cross-sectional	Birth to 4 weeks	Blood	FAAS	Both	32	Weight	Pearson's correlation	Crude	5
Fabelova (35)	2018	France	Cross-sectional	Aged < 6 years	Hair	ICP-MS	Both	211	WAZ, HAZ, BMI Z-score	Multivariable linear regression	Adjusted for maternal height and BMI, age at pregnancy, income, education, smoking, origin of mother, time in France, children food insecurity, breastfeeding, and homelessness duration	7
Zeng (9)	2018	China	Cross-sectional	4.66 ± 1.25 years	Blood	GFAAS	Both	470	Weight, Height	Multivariable linear regression	Adjusted by age, gender, family members smoking, parental education level and family income level	8
Igra (5)	2021	Bangladesh	Prospective cohort	9.5 ± 0.18 years	Urine	ICP-MS	Boy	803	WAZ, HAZ	Multivariable linear regression	Adjusted for child gender, age, maternal parity (number of children), maternal education, the family's socioeconomic status, maternal height, and maternal weight	8
							Girl	727				
Huzior-balajewicz (36)	2001	Poland	Cross-sectional	11 ± 0.4 years	Blood	GFAAS	Both	267	BMI, Weight, Height	Mean difference of outcomes in high vs. low exposure to cadmium	Crude	3
Gardner (24)	2013	Bangladesh	Prospective cohort	1.5 and 5 years	Urine	ICP-MS	Both	1505	Weight, Height, WAZ, HAZ	Multivariable linear regression	Adjusted for child's sex, family socioeconomic status, season of birth, gestational age at birth, maternal education, maternal height or body mass index , maternal tobacco-chewing, indoor cooking without ventilation, and birth order	8

ICP-MS: inductively coupled plasma mass spectrometry; GFAAS: Graphite furnace atomic absorption spectrometry; FAAS: Flame atomic absorption spectrometry; BMI: body mass index; IGF-1: insulin-like growth factor 1; WHZ: weight-for-height z score; WAZ: weight-for-age z-score; HAZ: height-for-age z-scores; NR: not reported.

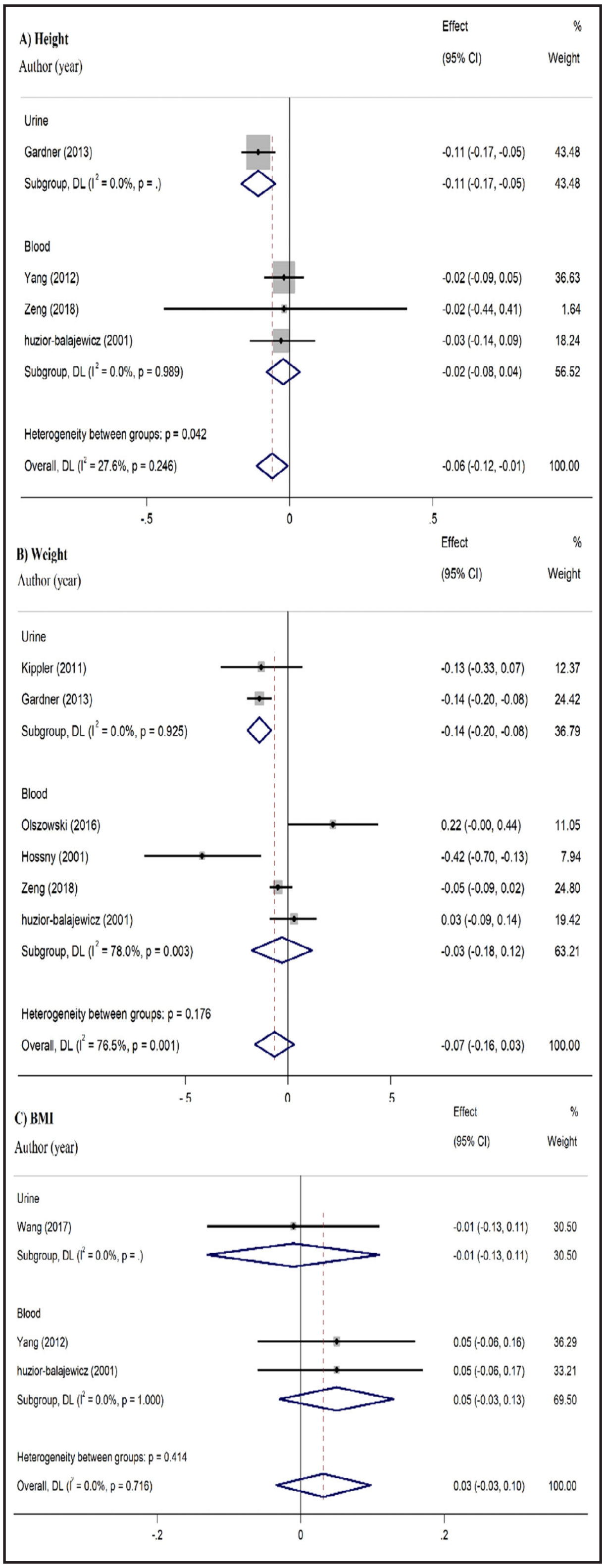

Figure 2.

Meta-analysis of the association between exposure to cadmium and height (A), weight (B), and body mass index (BMI) (C) of children stratified by sample type (β coefficient and 95 % confidence interval (CI) (DL: The DerSimonian and Laird random effects analysis; CI: confidence interval).

In line with the present meta-analysis, the prospective cohort study by Gardner et al. (24) on 1505 children aged 1.5 to 5 years revealed that a higher urinary cadmium exposure is negatively linked to height and weight at 5 years of age. The contradictions among the results of the available studies might result from the differences in study design, duration of exposure, adjustment for confounders, and the characteristics of participants such as age and gender. Our meta-analysis supported the negative relation of cadmium exposure to growth indicators of children. Chronic exposure to low levels of cadmium in infants/children can occur through polluted water as well as breast milk, cereals, seafood, and vegetables, which are common complementary foods for infants in low-income countries (43). Overall, our results propose that reducing exposure to cadmium could be an essential preventive approach to reduce the burden of growth failure in children/infants, especially in polluted regions. To reduce exposure to cadmium in children and infants, several measures can be taken based on the identified sources of exposure. Cadmium exposure can occur through various pathways, including consumption of contaminated food, air pollution, and consumer products like cheap jewelry and some plastics (45,46). Some preventive measures based on the identified sources of exposure include: 1) encouraging pregnant women and children to limit the consumption of certain types of food known to contain high levels of cadmium, such as contaminated rice, leafy vegetables, and shellfish (46); 2) implementing measures to reduce air pollution, such as promoting the use of clean energy sources and reducing emissions from industrial activities (45); and 3) increasing awareness about the potential risks associated with the use of cadmium-containing consumer products, and promote the use of safer alternatives (46).

The biological mechanisms for the association between cadmium exposure and growth failure in children are not well-known, but can be explained by several mechanisms, including disruption of the endocrine system, impairment of nutrient absorption and utilization, oxidative stress and cellular damage, disruption of bone and calcium homeostasis, and immune system dysfunction (47-50). Cadmium can interfere with the normal functioning of the endocrine system, which plays a critical role in growth regulation. It can disrupt hormone production and signaling, particularly affecting the growth hormone (GH) axis (51). Cadmium exposure has been shown to decrease GH secretion, impair insulin-like growth factor 1 (IGF-1) production, and alter thyroid hormone levels (47,52). These disruptions in hormone balance can potentially lead to reduced weight and height of children. Cadmium can affect the absorption and utilization of essential nutrients necessary for growth and development. It can interfere with the absorption of calcium, zinc, and iron, resulting in deficiencies of these vital nutrients (53). Calcium and zinc are essential for bone growth and development, while iron is crucial for red blood cell production and oxygen delivery (54,55). Deficiencies in these nutrients can directly impact growth and contribute to growth failure (55). Cadmium exposure can induce oxidative stress, a condition characterized by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them (48). ROS can cause damage to cells, tissues, and organs, including those involved in growth and development (56). Oxidative stress can lead to inflammation, im-

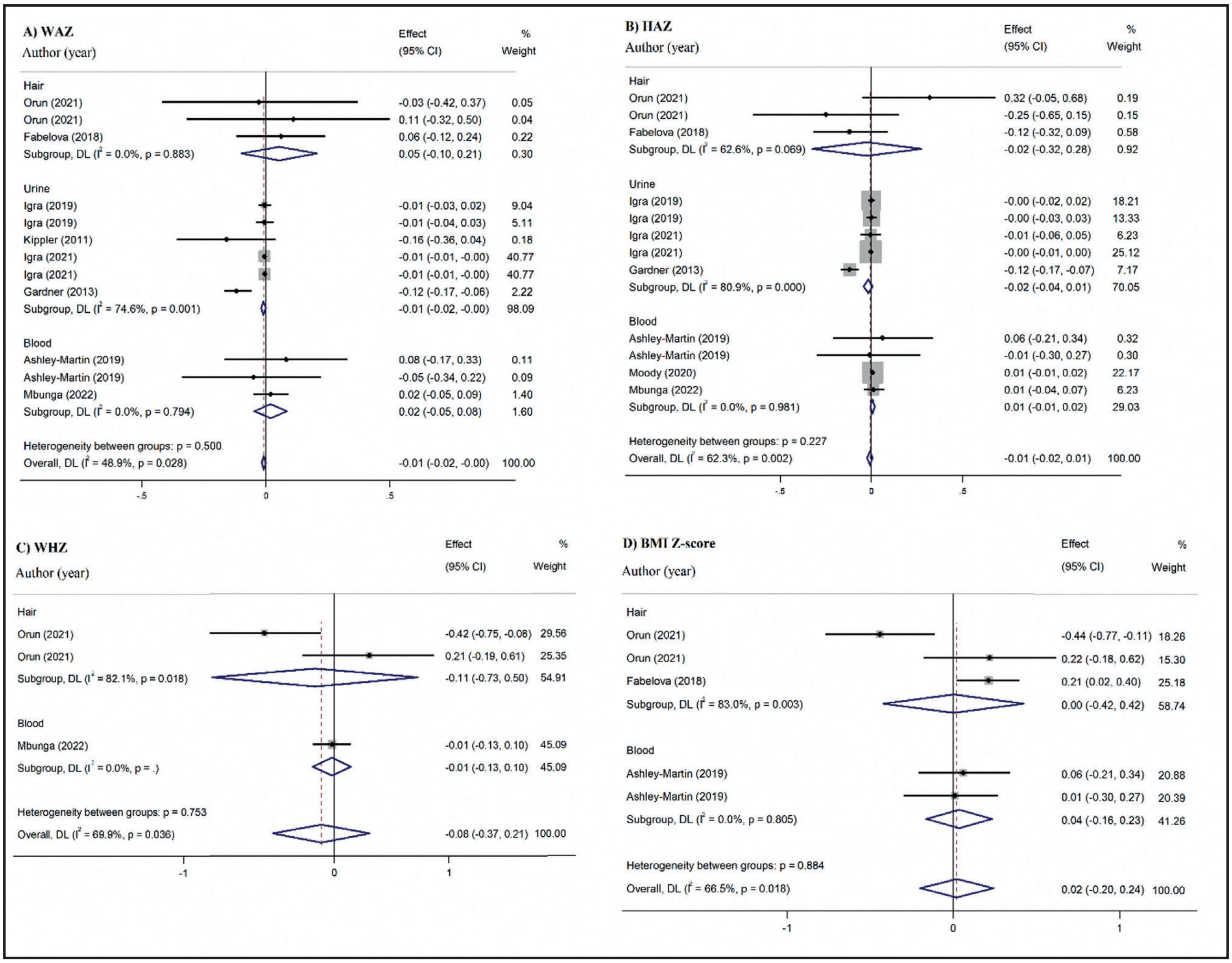

Figure 3.

Meta-analysis of the association of exposure to cadmium with weight-for-age z score (WAZ) (A), height-for-age z-score (HAZ) (B), weight-for-height z score (WHZ) (C), and body mass index (BMI)-for-age z score (D) stratified by sample type (β coefficient and 95 % confidence interval) (DL: The DerSimonian and Laird random effects analysis; CI: confidence interval).

paired DNA synthesis, and disrupted cellular signaling, all of which can hinder normal growth processes (57). Cadmium can disrupt calcium homeostasis in the body. It can accumulate in bones, replacing calcium and impairing their structural integrity (49). These effects on bone health can contribute to a decrease in height in children. Cadmium exposure can also suppress immune function, making children more susceptible to infections and illnesses (50). Frequent infections can negatively impact growth and contribute to growth failure (58). The extent and severity of the effects may depend on other factors such as the level and duration of exposure, genetic susceptibility, and overall nutritional status.

This meta-analysis has some strengths. This study presents the first systematic review and meta-analysis examining the association between cadmium exposure and growth failure in children. The study included a relatively high sample size and no publication bias was detected for the associations. Furthermore, various subgroup analyses were performed, which revealed the potential sources of heterogeneity across the results of the previous studies. Several limitations should be acknowledged in this meta-analysis. First, there was significant heterogeneity for analyses. Stratified analysis revealed that differences in cadmium assessment methods, type of sample, study design, and level of adjustment for confounders contributed to this heterogeneity. Second, a proportion of the included studies were cross-sectional, which are more prone to selection and recall biases compared with cohort studies. Third, a low number of studies were included in subgroup analyses; thus, the findings obtained from the subgroups should be interpreted with caution. Finally, while most studies adjusted the results for potential confounders, some presented unadjusted effect sizes which may be at risk of bias.

In conclusion, this meta-analysis revealed a negative association between cadmium exposure and growth indicators in infants/children. Further research with larger and more diverse study populations, along with better adjustment for potential confounders, especially with prospective cohort design, is warranted to obtain more robust conclusions.

Table II. Subgroup analysis for the association between cadmium and growth indicators of children

			Test of association		Test of heterogeneity		
Continuous outcome	**Subgroup**	**Studies (effect sizes)**	**β**	**95 % CI**	**I^2 (%)**	***p***	**Publication bias**
Height	Overall	4 (4)	-0.06	-0.12 to -0.01	27.6	0.24	0.65
	Prospective cohort	1 (1)	-0.11	-0.17 to -0.05	–	–	
	Cross-sectional	3 (3)	-0.02	-0.08 to 0.04	0.0	0.98	
	ICP-MS	1 (1)	-0.11	-0.17 to -0.05	–	–	
Weight	GFAAS	3 (3)	-0.02	-0.08 to 0.04	0.0	0.98	0.88
	Adjusted	3 (3)	-0.07	-0.14 to 0.01	46.2	0.15	
	Not-adjusted	1 (1)	-0.03	-0.14 to 0.08	–	–	
	Urine	1 (1)	-0.11	-0.17 to -0.05	–	–	
	Blood	3 (3)	-0.02	-0.08 to 0.04	0.0	0.98	
	Overall	6 (6)	-0.07	-0.16 to 0.03	76.5	0.001	
	Prospective cohort	1 (1)	-0.14	-0.20 to -0.08	–	–	
	Cross-sectional	5 (5)	-0.05	-0.17 to 0.08	72.4	0.006	
	ICP-MS	2 (2)	-0.14	-0.20 to -0.08	0.0	0.92	
	GFAAS	3 (3)	0.03	-0.09 to 0.15	68.7	0.04	
	FAAS	1 (1)	-0.42	-0.71 to - 0.13	–	–	
	Adjusted	2 (2)	-0.09	-0.18 to 0.01	78.7	0.03	
	Not-adjusted	4 (4)	-0.06	-0.27 to 0.15	78.5	0.003	
	Urine	2 (2)	-0.14	-0.20 to -0.08	0.0	0.92	
	Blood	4 (4)	-0.03	-0.18 to 0.12	78.0	0.003	
BMI	Overall	3 (3)	0.03	-0.03 to 0.10	0.0	0.71	0.34
	ICP-MS	1 (1)	-0.01	-0.13 to 0.11	–	–	
	GFAAS	2 (2)	0.05	-0.03 to 0.13	0.0	1.00	
	Adjusted	2 (2)	0.02	-0.06 to 0.10	0.0	0.47	
	Not-adjusted	1 (1)	0.05	-0.06 to 0.16	–	–	
	Urine	1 (1)	-0.01	-0.13 to 0.11	–	–	
	Blood	2 (2)	0.05	-0.03 to 0.13	0.0	1.00	
BMI Z-score	Overall	3 (5)	0.02	-0.20 to 0.24	66.5	0.01	0.39
	Prospective cohort	2 (4)	0.04	-0.30 to 0.21	62.0	0.04	
	Cross-sectional	1 (1)	0.21	0.02 to 0.40	–	–	
	Boy	2 (2)	-0.18	-0.67 to 0.31	80.8	0.02	
	Girl	2 (2)	0.08	-0.15 to 0.31	0.0	0.40	

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Table II (cont.). Subgroup analysis for the association between cadmium and growth indicators of children

			Test of association		Test of heterogeneity		
Continuous outcome	**Subgroup**	**Studies (effect sizes)**	**β**	**95 % CI**	**I^2 (%)**	***p***	**Publication bias**
BMI Z-score	Both	1 (1)	0.21	0.02 to 0.40	–	–	0.39
	Adjusted	2 (3)	0.13	-0.01 to 0.26	0.0	0.44	
	Not-adjusted	1 (2)	-0.12	-0.77 to 0.53	83.9	0.01	
	Hair	2 (3)	0.00	-0.42 to 0.42	83.0	0.003	
	Blood	1 (2)	0.04	-0.16 to 0.23	0.0	0.80	
WAZ	Overall	8 (12)	-0.01	-0.02 to -0.003	48.9	0.02	0.48
	Prospective cohort	5 (9)	-0.01	-0.02 to -0.002	56..2	0.01	
	Cross-sectional	3 (3)	-0.01	-0.11 to 0.09	35.6	0.21	
	Boy	4 (4)	-0.01	-0.01 to -0.001	0.0	0.92	
	Girl	4 (4)	-0.01	-0.01 to -0.001	0.0	0.93	
	Both	4 (4)	-0.05	-0.15 to 0.05	74.9	0.008	
	Adjusted	5 (8)	-0.01	-0.02 to -0.004	62.1	0.01	
	Not-adjusted	3 (4)	0.00	-0.07 to 0.07	0.4	0.39	
	Hair	2 (3)	0.05	-0.10 to 0.21	0.0	0.88	
	Urine	4 (6)	-0.01	-0.02 to -0.004	74.6	0.001	
	Blood	2 (3)	0.02	-0.05 to 0.08	0.0	0.79	
WHZ	Overall	2 (3)	-0.08	-0.37 to 0.21	69.9	0.03	0.83
	Prospective cohort	1 (2)	-0.11	-0.73 to 0.50	82.1	0.01	
	Cross-sectional	1 (1)	-0.01	-0.13 to 0.10	–	–	
	Hair	1 (2)	-0.11	-0.73 to 0.50	82.1	0.01	
	Blood	1 (1)	-0.01	-0.13 to 0.10	–	–	
HAZ	Overall	8 (12)	-0.01	-0.02 to 0.01	62.3	0.002	0.55
	Prospective cohort	5 (9)	0.02	-0.04 to 0.01	68.8	0.001	
	Cross-sectional	3 (3)	0.01	-0.01 to 0.02	0.0	0.48	
	Boy	4 (4)	0.00	-0.02 to 0.02	5.5	0.36	
	Girl	4 (4)	-0.001	-0.01 to 0.002	0.0	0.68	
	Both	4 (4)	-0.04	-0.11 to 0.03	87.7	0.001	
	Adjusted	6 (9)	-0.01	-0.03 to 0.01	67.4	0.002	
	Not-adjusted	2 (3)	0.03	-0.20 to 0.26	54.4	0.11	
	Hair	2 (3)	-0.02	-0.32 to 0.28	62.6	0.06	
	Urine	3 (5)	-0.02	-0.4 to 0.01	80.9	0.001	
	Blood	3 (4)	0.01	-0.01 to 0.02	0.0	0.98	

ICP-MS: inductively coupled plasma mass spectrometry; GFAAS: Graphite furnace atomic absorption spectrometry; FAAS: Flame atomic absorption spectrometry; WHZ: weight-for-height z score; WAZ: weight-for-age z-score; HAZ: height-for-age z-scores.

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