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Review article

# Cadmium exposure and risk of hypertension: A systematic review and dose-response meta-analysis

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ABSTRACT

*Background:* Exposure to environmental toxic metals represents a significant global public health concern. Many studies have reported that cadmium (Cd) exposure increases the risk of hypertension. Since the shape of such relation has not been well characterized, we assessed it by performing a systematic review and dose-response meta-analysis of human studies.

*Methods:* We searched the literature through September 5, 2024 to identify papers related to Cd, hypertension, and blood pressure. Inclusion criteria were: observational design, adult population, assessment of exposure using Cd biomarkers, and availability of exposure category-specific risk estimates for hypertension. We performed a dose-response meta-analysis of the results from included studies.

*Results:* Of the 18 studies published between 2006 and 2024, most had a cross-sectional design. Cd was measured in whole blood and/or urine in almost all studies, whereas only two studies measured Cd in serum. The dose-response meta-analysis indicated an almost linear relation between urinary Cd concentrations and hypertension risk with RR = 1.18, 95% CI 1.02–1.37 at 2.0 μg/g creatinine compared with no exposure. In contrast, the association between blood Cd concentrations and hypertension risk was non-linear: there was a steep monotonic increase in risk for Cd concentrations below 2 μg/L, reaching a RR of 1.48 (95% CI 1.17–1.86) at 2.0 μg/L, after which a plateau seemed reached. We found similar trends when restricting to studies of Asian population, while when considering North American studies, hypertension risk increased above 1.0 μg/g creatinine.

*Conclusions:* In this dose-response meta-analysis, risk of hypertension showed a non-linear positive association with blood Cd concentrations and a linear positive association with urinary Cd concentrations. Inconsistency in the shape of associations could relate to the different timing of exposure assessed by the biomarkers or the alteration Cd excretion at increasing exposure levels. Mitigation of Cd exposure is confirmed as a public health priority for chronic disease prevention.

## 1. Introduction

Hypertension is an important risk factor for mortality and morbidity worldwide, having a direct influence on the development of cardiovascular and kidney disease (WHO, 2023a). The number of individuals living with hypertension has doubled between 1990 and 2019, from 650 million to 1.3 billion (NCD Risk Factor Collaboration, 2021), and such increase does not appear to be due only to ageing. Two-thirds of individuals with hypertension live in low-income and middle-income countries (WHO, 2023b). Globally, the prevalence of hypertension is slightly higher among males (34%) than females (32%). The sex disparity is age-related: the global age-standardized prevalence of hypertension among individuals aged 30–49 years is 19% for females versus 24% for males (Kario et al., 2024; WHO, 2023a). This pattern of lower hypertension prevalence among females aged under 50 years is observed in most countries worldwide (WHO, 2023b; Zhou et al., 2021). Older age and genetics can increase the risk of high blood pressure, but modifiable risk factors such as high-salt diets, sedentary behavior,

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alcohol consumption, tobacco use (Cecchini et al., 2024; Filippini et al., 2022a; WHO, 2023b), and air pollution exposure (Qin et al., 2021; Signorelli et al., 2019; Yang et al., 2023) contribute to the increased risk of hypertension.

Cadmium (Cd) is a known contaminant that occurs naturally, generally at low levels, in the environment. It is released through volcanic activity, weathering, and erosion (WHO, 2019). However, human activity has greatly contributed to increasing Cd levels in the environment, and the contamination has been detected in air, soil, water, and food (Al-Makki et al., 2022; Mititelu et al., 2023; Sciacca and Conti, 2009; Urbano et al., 2023). In fact, this heavy metal is also produced by various anthropogenic processes, including nickel-Cd batteries, alloys, coatings, pigments, solar cells, and stabilizers (Faroon et al., 2012; Ghaderpoori et al., 2020; WHO, 2019). Another relevant source of exposure is smoking tobacco (Filippini et al., 2016). In non-smoking populations, diet is the most important contributor (Urbano et al., 2023). Cd-rich foods include pasta and rice, seafood and fresh vegetables (European Food Safety Authority, 2009; Filippini et al., 2018; Yang et al., 2024) but also offal, mushrooms, and chocolate (Birgisdottir et al., 2013; Madeddu et al., 2011).

Cd has a well-documented impact on human health, being associated with an increased risk of some cancers (Fanfani et al., 2024; Filippini et al., 2019; Filippini et al., 2020a; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012), type 2 diabetes (Filippini et al., 2022b), atherosclerosis and dyslipidemia (Mao et al., 2023; Tinkov et al., 2018; Wang et al., 2024), and cardiovascular disease (Verzelloni et al., 2024). In recent decades, numerous studies have reported a positive association between exposure to Cd and hypertension; however, the results are not yet fully conclusive (Al-Makki et al., 2022; Aramjoo et al., 2022; Caciari et al., 2013) between Cd exposure and risk of hypertension. The present report builds on previous meta-analyses by including studies examining a range of exposure matrices (urine, serum and whole blood) and by evaluating hypertension risk as a study endpoint. Finally, this report assesses the shape of these associations, which has not been previously explored.

## 2. Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines (Page et al., 2021), and it was registered in the PROSPERO database (no. CRD42022360751). PRISMA checklist is reported in Supplementary Appendix A1.

### 2.1. Literature search and study selection

We defined the inclusion criteria according to the Population, Exposure, Comparator, Outcomes, and Study design (PECOS) statement: "What is the shape of the association between exposure to Cd, assessed through any biomarker based on heavy metal concentration, and risk of hypertension in adults, in observational studies?" (Morgan et al., 2018). Then, we performed online literature searches in EMBASE, PubMed, and Web Of Science databases through September 5, 2024, using keywords linked to "cadmium", "blood pressure", and "hypertension." No language restrictions were applied. When necessary, we also contacted the authors of included studies to request additional information for data analysis. Details about the search strategies are reported in Supplementary Table S1.

We implemented retrieved articles into the Rayyan QCRI online application, and removed duplicates. Two authors (TF and VG) conducted independent reviews of publication titles and abstracts, and evaluated full-text publications for inclusion. In the event of reviewer disagreement, we sought a third author (PV) to facilitate resolution. We considered a study eligible for inclusion if: (1) exposure to Cd was assessed through a biomarker with specified levels of the metal; (2) the outcome of interest was hypertension incidence or prevalence; (3) it was an observational study (cross-sectional, case-control, or cohort study); (4) effect estimates were provided using hazard ratio (HR), rate/risk ratio (RR) or odds ratio (OR), along with the corresponding 95% confidence interval (CI). Furthermore, we conducted a comprehensive review of the reference lists of included studies and other relevant reviews. Finally, we employed backward and forward citation retrieval techniques to identify any additional pertinent papers (EUnetHTA JA3WP6B2-2 Authoring Team, 2019).

### 2.2. Risk of bias assessment

We evaluated the quality of included studies using the Risk of Bias for Non-randomized Studies of Exposures (ROBINS-E) tool (Morgan et al., 2019). We considered seven domains, including: (1) bias due to confounding; (2) bias in selecting participants in the study; (3) bias in exposure classification; (4) bias due to departures from intended exposures; (5) bias due to missing data; (6) bias in outcome measurement; (7) bias in the selection of reported results (Morgan et al., 2019). In Supplementary Table S2, we present criteria for risk of bias evaluation performed by two authors (VG, PV). In the event of a discrepancy, we consulted a third author (TF) to reach a final decision. We classified a study as having a moderate or high risk of bias if it was deemed moderate or high risk, respectively, in $\geq$1 domain. Otherwise, we designated the study as having a low risk of bias.

### 2.3. Statistical analysis

We synthesized the evidence through both qualitative and quantitative approaches. In the qualitative approach, the inclusion criteria were configured through PECOS criteria. In the quantitative synthesis, we compared the prevalence or incidence of hypertension across different levels of Cd exposure. We used a restricted maximum likelihood random-effects model to conduct a dose-response meta-analysis (Orsini, 2021). We used a one-stage approach to analyze hypertension risk according to increasing Cd exposure (Crippa et al., 2019). In particular, we employed the mean or median value of the intermediate quantile whenever available. In the absence of a mean or median value for the highest and lowest exposure categories, we defined a value 20% higher or lower than the closest cut-point (Iamandii et al., 2024; Veneri et al., 2023). We converted serum Cd concentrations to whole blood considering that 90% of Cd is within erythrocytes while the remaining is bound to metallothionein proteins (Filippini et al., 2020b). To assess potential non-linear associations, we employed a restricted cubic spline model with knots at three fixed points (10th, 50th, and 90th percentiles) of Cd exposure (Crippa et al., 2019). The reference for the dose-response meta-analysis was set to 0, with no *a priori* assumptions regarding the shape of the association between Cd exposure and the outcome. We also compared results assuming a linear relation. Whenever possible, we stratified analyses by sex, smoking, geographical area (Asia versus North America), and study design. We also conducted sensitivity analyses excluding studies that did not adjust for smoking or alcohol intake. We assessed heterogeneity of studies using the graphical overlay of study-specific curves showing the influence of variation across studies (Murad et al.; Orsini et al., 2022). Finally, we assessed the presence and influence of publication bias using funnel plots with Egger's test (Egger et al., 1997; Lin et al., 2020) and trim-and-fill analysis (Duval and Tweedie, 2000). We conducted all data analyses using 'meta', 'mkspline', and 'drmeta' routines of Stata software (v18.0, Stata Corp., College Station, TX, 2023).

## 3. Results

### 3.1. Study selection and characteristics of included studies

After removal of duplicates, we retrieved 1431 studies. Of these, we excluded 1342 after title and abstract screening, yielding a final number

of 89 articles for full-text assessment, from which we excluded 71 for the following reasons: insufficient or unsuitable data (n = 34), wrong outcome (n = 25), overlapping population (n = 6), or wrong publication type (n = 6). This resulted in a total of 18 studies eligible for final analysis. The PRISMA flow-chart of the literature search is presented in Fig. 1. Table 1 provides a summary of the characteristics of the 18 included studies (Al-Saleh et al., 2006; Eum et al., 2008; Franceschini et al., 2017; Hu et al., 2024; Jeon et al., 2022; Kaneda et al., 2022; Kwon et al., 2022; Lee et al., 2016; Noor et al., 2018; Oliver-Williams et al., 2018; Qu et al., 2022; Shi et al., 2019; Tang et al., 2022; Tellez-Plaza et al., 2008; Wang et al., 2020; Wu et al., 2019, 2023; Zhong et al., 2021). The articles were published between 2006 and 2024. Most populations were from China (n = 7) (Hu et al., 2024; Qu et al., 2022; Shi et al., 2019; Wang et al., 2020; Wu et al., 2019, 2023; Zhong et al., 2021), USA (n = 5) (Franceschini et al., 2017; Noor et al., 2018; Oliver-Williams et al., 2018; Tang et al., 2022; Tellez-Plaza et al., 2008), and South Korea (n = 4) (Eum et al., 2008; Jeon et al., 2022; Kwon et al., 2022; Lee et al., 2016), with one study each from Japan (Kaneda et al., 2022) and Saudi Arabia (Al-Saleh et al., 2006). We included 14 cross-sectional studies (Eum et al., 2008; Franceschini et al., 2017; Hu et al., 2024; Jeon et al., 2022; Kaneda et al., 2022; Kwon et al., 2022; Lee et al., 2016; Noor et al., 2018; Qu et al., 2022; Shi et al., 2019; Tang et al., 2022; Tellez-Plaza et al., 2008; Wang et al., 2020; Wu et al., 2023), 2 case-control studies (Al-Saleh et al., 2006; Wu et al., 2019), and 2 cohort studies (Oliver-Williams et al., 2018; Zhong et al., 2021). Ages of participants ranged from 18 up to 93 years, with average values from 38.5 to 62.0 years. The definition of hypertension across studies was generally homogeneous, with cutoffs for systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 140/90 mm Hg, although one older study (Al-Saleh et al., 2006) used higher values (SBP/DBP ≥160/96 mm Hg). Two most recent studies used lower cutoffs (SBP/DBP ≥135/85 mm Hg (Noor et al., 2018) and ≥130/80 mmHg (Tang et al., 2022) corresponding to the 2017 US guidelines (Whelton et al., 2018).

Cd concentrations were measured in blood (n = 7) (Al-Saleh et al., 2006; Eum et al., 2008; Jeon et al., 2022; Kwon et al., 2022; Lee et al., 2016; Wang et al., 2020; Wu et al., 2023), serum (n = 2) (Hu et al., 2024; Kaneda et al., 2022), and urine (n = 6) (Franceschini et al., 2017; Noor et al., 2018; Oliver-Williams et al., 2018; Shi et al., 2019; Wu et al., 2019; Zhong et al., 2021), with three studies measuring Cd in both blood and urine (Qu et al., 2022; Tang et al., 2022; Tellez-Plaza et al., 2008). In general, studies that assessed Cd exposure through whole blood employed μg/L as the unit of measurement, whereas studies that examined urine generally employed μg/g creatinine. In the latter studies, two employed different units of measurement (μg/L) and included creatinine as a covariate in the multivariable model.

### 3.2. Risk of bias assessment

Results of our study quality assessment by risk of bias are presented in Supplementary Table S3. We identified 8 of the included studies as being at moderate risk of bias (Al-Saleh et al., 2006; Franceschini et al., 2017; Hu et al., 2024; Jeon et al., 2022; Qu et al., 2022; Shi et al., 2019; Wang et al., 2020; Zhong et al., 2021), due to selection of participants in polluted areas with Cd contamination (Jeon et al., 2022; Shi et al., 2019; Wang et al., 2020), not adjusting for smoking (Al-Saleh et al., 2006; Hu

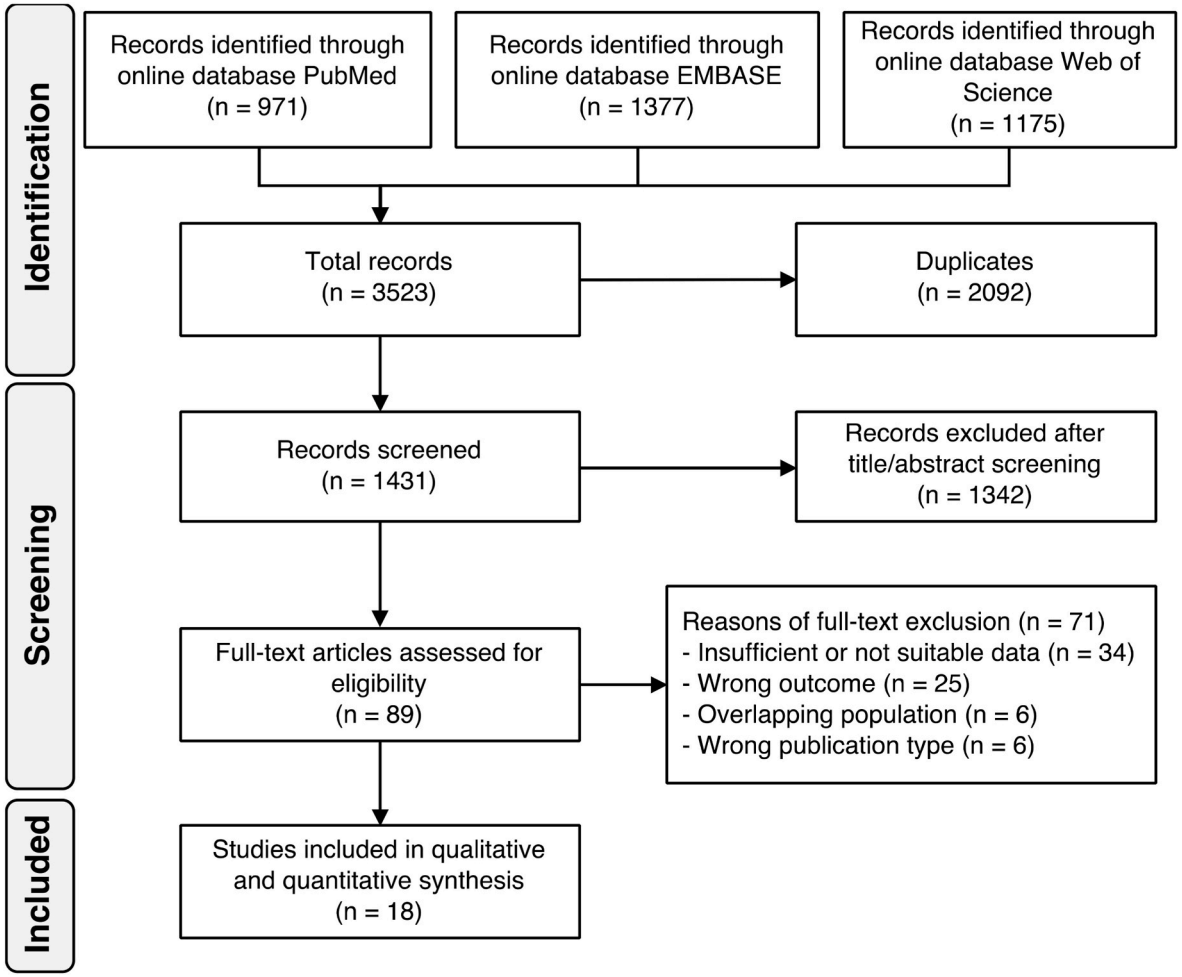


**Fig. 1.** PRISMA flow-chart of the literature search.

**Table 1**
Characteristics of included studies in systematic review and meta-analysis of cadmium and risk of hypertension.

| Reference | Region | Study population n = total (M/F) | Study design | Age (years) mean (SD) range | Specimen | Cd levels Mean (SD) range | Hypertension criteria | Adjustment factors |
|---|---|---|---|---|---|---|---|---|
| Al-Saleh et al. (2006) | Saudi Arabia | Saudi women n = 183 (0/183) | case-control | 59.7 (10.0) 45–93 | Whole blood (μg/L) | 0.833 (0.860) 0.142–6.925 | SBP>160 mmHg DBP>96 mmHg Anti-HTN drug use High BP at the examination | Age, body mass index, creatinine, hemoglobin, parity, number of pregnancies, marital status, menopausal status, duration of menopause, physical activity, history of oral contraceptives, smoking status, family history of hypertension, intake of calcium supplements, intake of vitamin D supplements, intake of other vitamins and/or minerals, family income, attended school, use of contraceptive, history of breast-feeding, average duration of breast-feeding and the average number of breast-feedings |
| Eum et al. (2008) | South Korea | KNHANES 2005, n = 1902 (958/944) | cross-sectional | 45.5 | Whole blood (μg/L) | 1.67 0.18–5.52 | SBP≥140 mmHg DBP≥90 mmHg Self-report HTN | Age, sex, education, smoking status, alcohol intake, body mass index, family hypertension history, and blood lead level |
| Franceschini et al. (2017) | US | Strong Heart Study (1989–1991), n = 3714 (40.6% M) | cross-sectional | 56.2 (8.0) | Urine (μg/g creatinine) | 0.94 (0.92–0.96)[a] 0.01–78.48 | SBP≥140 mmHg DBP≥90 mmHg Anti-HTN drug use | Age, sex, geographic area, body mass index, smoking and estimated glomerular filtration rate |
| Hu et al. (2024) | China | Elderly population from Tongling city (2019) n = 2372 (1113/1259) | cross-sectional | 72.0 | Serum (μg/L) | Non-HTN 1.10 (0.33–1.72)[b] NHTN 1.34 (0.62–1.885)[b] | SBP≥140 mmHg DBP≥90 mmHg Self-report anti-HTN drug use Self-report HTN | Age, sex, physical activity, body mass index, diabetes, serum creatinine, total cholesterol, and high-density lipoprotein cholesterol |
| Jeon et al. (2022) | South Korea | Male firefighters from Deagu (2015–2017) n = 215 (215/0) | cross-sectional | 42.0 (8.5) 24–58 | Whole blood (μg/dL) | 5.14 (0.22–24.06)[b] | SBP>140 mmHg DBP>90 mmHg Anti-HTN drug use | Age, body mass index, smoking status, alcohol intake, exercise level, education level, work schedule, work department, and diabetes mellitus |
| Kaneda et al. (2022) | Japan | Iwaki Health Promotion Project (2014) n = 1144 (433/711) | cross-sectional | >19 57 (41–66)[b] | Serum (ng/mL) | 0.06 (0.05–0.08)[b] | SBP≥140 mmHg DBP≥90 mmHg | Age, sex, body mass index, smoking status, alcohol drinking, total cholesterol, triglycerides, high-density cholesterol, low-density cholesterol, and blood sugar |
| Kwon et al. (2022) | South Korea | KNHANES 2008–2012, n = 5752 (2919/2833) | cross-sectional | 42.43 (18.2) | Whole blood (μg/L) | 0.94 (0.93–1.36)[b] 0.02–6.42 | SBP≥140 mmHg DBP≥90 mmHg Self-report anti-HTN drug use Self-report HTN | Age, sex, educational level, monthly family income, smoking, alcohol consumption, natural log-transformed lead, body mass index, regular exercise, presence of diabetes, menopausal status (women only), and survey year |
| Lee et al. (2016) | South Korea | KNHANES 2008–2013 n = 11979 (5920/6059) | cross-sectional | ≥19 | Whole blood (μg/L) | Males 0.788 (0.771–805)[a] Females 1.133 (1.110–1.157)[a] | SBP≥140 mmHg DBP≥90 mmHg Self-report anti-HTN drug use | Sex, age, residence area, education level, smoking and drinking status, body mass index, physical activities, serum creatinine, and hemoglobin |
| Noor et al. (2018) | US | NHANES 2001–2014 n = 3982 (1996/1985) | cross-sectional | Males 43.2 Females 46.3 | Urine (μg/L) | Males 0.23[a] Females 0.27[a] | SBP≥135 mmHg DBP≥85 mmHg HTN treatment | Creatinine, age, sex, race/ethnicity, body mass index, estimated glomerular filtration rate, alcohol, education, smoking, physical activity, poverty, and total caloric intake |

(*continued on next page*)

**Table 1** (*continued*)

| Reference | Region | Study population n = total (M/F) | Study design | Age (years) mean (SD) range | Specimen | Cd levels Mean (SD) range | Hypertension criteria | Adjustment factors |
|---|---|---|---|---|---|---|---|---|
| Oliver-Williams et al. (2018) | US | Strong Heart Study (1989–1991), n = 3047 (1278/1769) | cohort follow-up up to 2006 | 55.3 (49.4–62.6)[b] | Urine (μg/g creatinine) | 1.1 (0.6–1.8)[b] | SBP≥140 mmHg DBP≥90 mmHg Anti-HTN drug use | Sex, age, center, estimated glomerular filtration rate, body mass index, education level, alcohol consumption, diabetes status, triglycerides, total cholesterol, high-density lipoprotein cholesterol, physical activity, and smoking |
| Qu et al. (2022) | China | China National Human Biomonitoring 2017–2018 n = 11037 (5533/5504) | cross-sectional | 18–79 | Whole blood (μg/L) and Urine (μg/g creatinine) | Blood 0.82 (0.37–2.53) Urine 0.64 (0.31–1.30) | SBP≥140 mmHg DBP≥90 mmHg Self-report anti-HTN drug use Self-report HTN | Sex, age, body mass index, regions, education, smoking status, alcohol consumption, family history of hypertension, residence area, rice consumption, red meat consumptions, vegetable consumptions, fasting blood glucose, total cholesterol, high-density cholesterol |
| Shi et al. (2019) | China | Occupationally exposed workers n = 395 (395/0) | cross-sectional | Non-HTN 38.5 (10.2) HTN 44.6 (8.4) | Urine (μg/L) | Non-HTN 1.79 (1.02–2.38)[b] HTN 1.65 (0.99–2.55)[b] | SBP≥140 mmHg DBP≥90 mmHg | Age, employee duration, body mass index, occupation, factories, smoking status, drinking water source, and urinary creatinine concentration |
| Tang et al. (2022) | US | NHANES 2011–2018 n = 5175 (2588/2587) | cross-sectional | ≥20 | Whole blood (μg/L) | non-NHA 0.33 (0.32–0.33)[a] NHA 0.42 (0.41–0.44)[a] | SBP≥130 mmHg DBP≥80 mmHg Self-report anti-HTN drug use | Age, sex, education, annual household income, cotinine level, alcohol use, body mass index |
| Tang et al. (2022) | US | NHANES 2011–2018 n = 11599 (5717/5882) | cross-sectional | ≥20 | Urine (μg/g creatinine) | non-NHA 0.206 (0.201–0.211)[a] NHA 0.322 (0.300–0.345)[a] | SBP≥130 mmHg DBP≥80 mmHg Self-report anti-HTN drug use | Age, sex, education, annual household income, cotinine level, alcohol use, body mass index |
| Tellez-Plaza et al. (2008) | US | NHANES 1999–2004 n = 14487 (50.0% M) | cross-sectional | 46.5 (28.3) | Whole blood (nmol/L) and Urine (nmol/mmol creatinine) | 3.77 (3.63–3.92)[a] 0.27 (0.26–0.28)[a] | SBP≥140 mmHg DBP≥90 mmHg Self-report anti-HTN drug use Self-report HTN diagnosis | Age, sex, race/ethnicity, education, smoking status, cotinine, alcohol intake, body mass index, menopause status, antihypertensive medication, blood lead (and urine creatinine levels for urine cadmium) |
| Wang et al. (2020) | China | Southwestern China population Polluted n = 602 (267/335) Unpolluted n = 214 (93/121) | cross-sectional | 40–75 | Whole blood (μg/L) | Polluted 3.91 (2.62–6.39)[b] Unpolluted 2.01 (1.08–4.92)[b] | SBP≥140 mmHg DBP≥90 mmHg Self-report anti-HTN drug use Self-report HTN diagnosis | Age, sex, body mass index, smoking status and education levels |
| Wu et al. (2019) | China | Population from Union hospital, Wuhan (2015–2017) n = 994 (558/436) | case-control | HTN 57.06 (8.42) Non-HTN 56.33 (7.62) | Urine (μg/L) | HTN 0.93 (0.51–1.64) Non-HTN 0.80 (0.44–1.35)) | SBP≥140 mmHg DBP≥90 mmHg Self-report anti-HTN drug use Self-report HTN diagnosis | Urinary creatinine, age, sex, body mass index, smoking and drinking status, pack-year smoking, income and education levels |
| Wu et al. (2023) | China | Guangdong Provincial Residents' Chronic Disease and Nutrition Surveillance Survey (2015–2016) n = 3029 (1372/1657) | cross-sectional | HTN 62.0 (53.2–69.3)[b] Non-HTN 48.6 (36.3–58.7)[b] | Whole blood (μg/L) | HTN 2.54 (1.44–4.58)[b] Non-HTN 2.12 (1.25–4.21)[b] | SBP≥130 mmHg DBP≥80 mmHg Anti-HTN drug use | Age, sex, region, education level, drinking status, smoking status, family history of hypertension and anti-hypertensive use, body mass index, total cholesterol, triglycerides, and fasting blood glucose |
| Zhong et al. (2021) | China | Wanjiang cohort 2014–2015 n = 1303 (577/726) | cohort follow-up 2014–2019 | 46.0 (15.3) | Urine (μg/g creatinine) | 2.35 (1.15–5.22)[b] | SBP≥130 mmHg DBP≥80 mmHg Self-report anti-HTN drug use HTN diagnosis | Age, sex, smoking, drinking, body mass index and blood pressure at baseline, five metals |

Note: [a]geometric mean and 95% confidence interval; [b]Median (range interquartile). BP: blood pressure; DBP: systolic blood pressure; F: females; HTN: hypertension; M: males; SBP: systolic blood pressure.

et al., 2024), or missing data for more than 10% of participants (Franceschini et al., 2017; Qu et al., 2022; Zhong et al., 2021). We judged the remaining studies as being at low risk of bias (Eum et al., 2008; Kaneda et al., 2022; Kwon et al., 2022; Lee et al., 2016; Noor et al., 2018; Oliver-Williams et al., 2018; Tang et al., 2022; Tellez-Plaza et al., 2008; Wu et al., 2019, 2023).

### 3.3. Dose-response meta-analysis

The curves assessing the shape of the association between Cd exposure and risk of hypertension (Fig. 2) showed an almost linear relation for urine concentrations, with summary RRs of 1.18 (95% CI 1.02–1.37) at 2.0 μg/g creatinine and 1.33 (95% CI 1.10–1.61) at 4.0 μg/g creatinine, compared with 0 μg/g creatinine. Conversely, when evaluating blood Cd, there was a non-linear association with a steep increase in risk up to 2 μg/L/Cd after which a plateau seemed reached, with RRs compared to no exposure of 1.48 (95% CI 1.17–1.86), 1.53 (95% CI 1.23–2.07), and 1.65 (95% CI 1.18–2.31) at 2.0, 4.0 and 6.0 μg/L, respectively. Due to limited data stratified by sex and smoking status, we could not perform dose-response analyses in such subgroups.

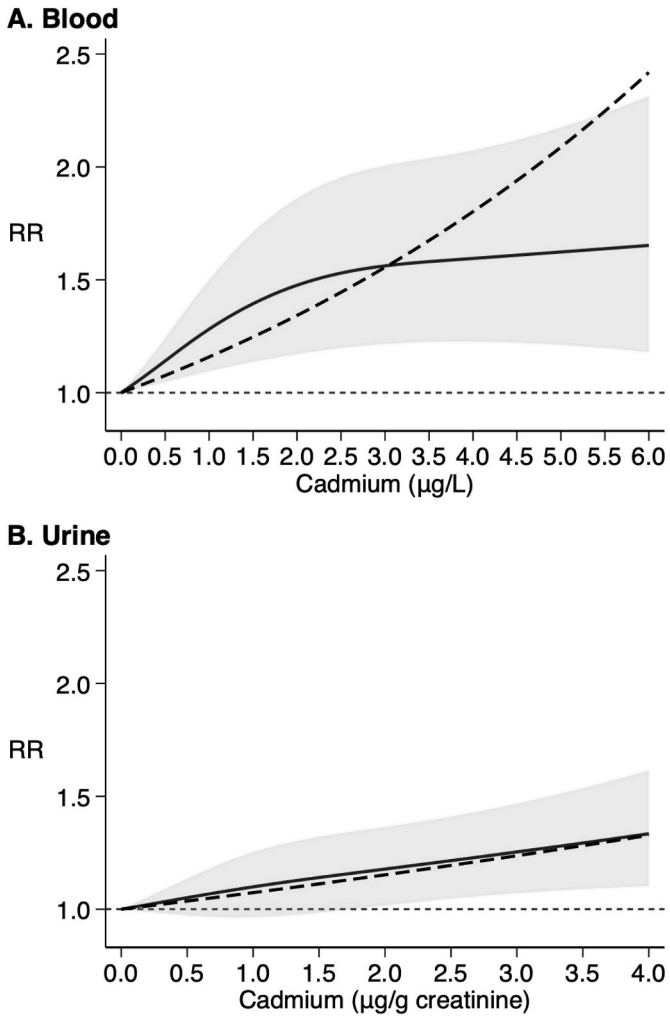


**Fig. 2.** Dose-response meta-analysis according to increasing cadmium exposure assessed through blood (A) and urine (B) concentrations and risk of hypertension. Spline curve (solid black line) with 95% confidence limits (gray area). Long dash black line indicates linear assumption of the relation between cadmium and risk of hypertension. RR: risk ratio.

Nonetheless, sensitivity analyses excluding studies (Al-Saleh et al., 2006; Hu et al., 2024) not adjusting for smoking yielded almost identical results (Supplementary Fig. S1), not unexpectedly considering the limited number of smokers (n = 9, 0.05%) in one study (Al-Saleh et al., 2006). Similarly, exclusion of studies not adjusting for alcohol intake (Al-Saleh et al., 2006; Franceschini et al., 2017; Hu et al., 2024; Wang et al., 2020) did not appreciably affect the dose-response relation between urinary Cd concentrations and hypertension risk (Supplementary Fig. S2), while the shape of the curve demonstrated a linear relation for blood Cd. Finally, exclusion of the two studies using different cutoffs for hypertension definition yielded similar results to the overall analysis (Supplementary Fig. S3).

Analyses stratified by geographical area were not feasible for blood Cd in the North American population, but those restricted to Asian population showed comparable results (Fig. 3). Similarly, when using urinary Cd, we found an almost linear relation in Asian population, while in North American population, hypertension risk increased above 1.0 μg/g creatinine, although the analysis was limited by small numbers of studies and a narrower range of Cd exposure. Due to the majority of the studies with cross-sectional design, we were unable to conduct analyses restricted to the two prospective cohort studies, though both investigations measured urinary Cd concentrations and reported almost linear risk increase of hypertension (Oliver-Williams et al., 2018; Zhong et al., 2021).

Funnel plots for publication bias showed substantial symmetry of distribution with a low risk of small-study effects for both blood and urine Cd concentrations (Supplementary Fig. S4), thus no studies were added when we performed trim-and-fill analysis. Analysis of study-specific trends (Supplementary Fig. S5) showed moderate heterogeneity for studies using whole blood concentrations for Cd exposure assessment with almost all curves with the 95% CIs. Conversely, when using urinary Cd concentrations, heterogeneity was negligible, with all studies converging to the overall summary RR.

## 4. Discussion

We found epidemiological evidence that Cd exposure is associated with an increased risk of hypertension, with a generally linear relation based on urine concentrations and a non-linear relation based on blood concentrations. Our findings agree with previous literature suggesting higher risk of hypertension among humans with higher exposure to Cd, though statistical analysis assuming a linear relation was generally used in previous systematic reviews and meta-analyses, thus precluding characterization of the shape of the association (Aramjoo et al., 2022; Gallagher and Meliker, 2010). In addition, our results are consistent with recent studies indicating a detrimental effect of Cd exposure on CVD, especially stroke and coronary heart disease (Verzelloni et al., 2024). Also, recent studies reported positive associations between heavy metal exposure, including Cd, and resistant hypertension (Chen et al., 2023; Corbaton Anchuelo et al., 2024), further supporting detrimental effects of Cd on risk of CVD and hypertension.

The positive association between Cd exposure and hypertension risk was similar when assessing Cd exposure through blood and urine, two biomarkers generally linked to recent and long-term exposure to this heavy metal (Vacchi-Suzzi et al., 2016). This difference in exposure timing, i.e. months for blood and years for urine, might explain the non-linear shape emerging in analyses based on blood levels. Previous studies indicate that urinary Cd concentrations are a valid biomarker for long-term exposure, especially at low levels and among non-occupationally-exposed individuals (Vacchi-Suzzi et al., 2016). Conversely, at higher levels, e.g. above 2 μg/g creatinine, some factors may alter protein excretion and consequently urinary Cd concentrations (Chaumont et al., 2012), especially smoking and comorbidities affecting

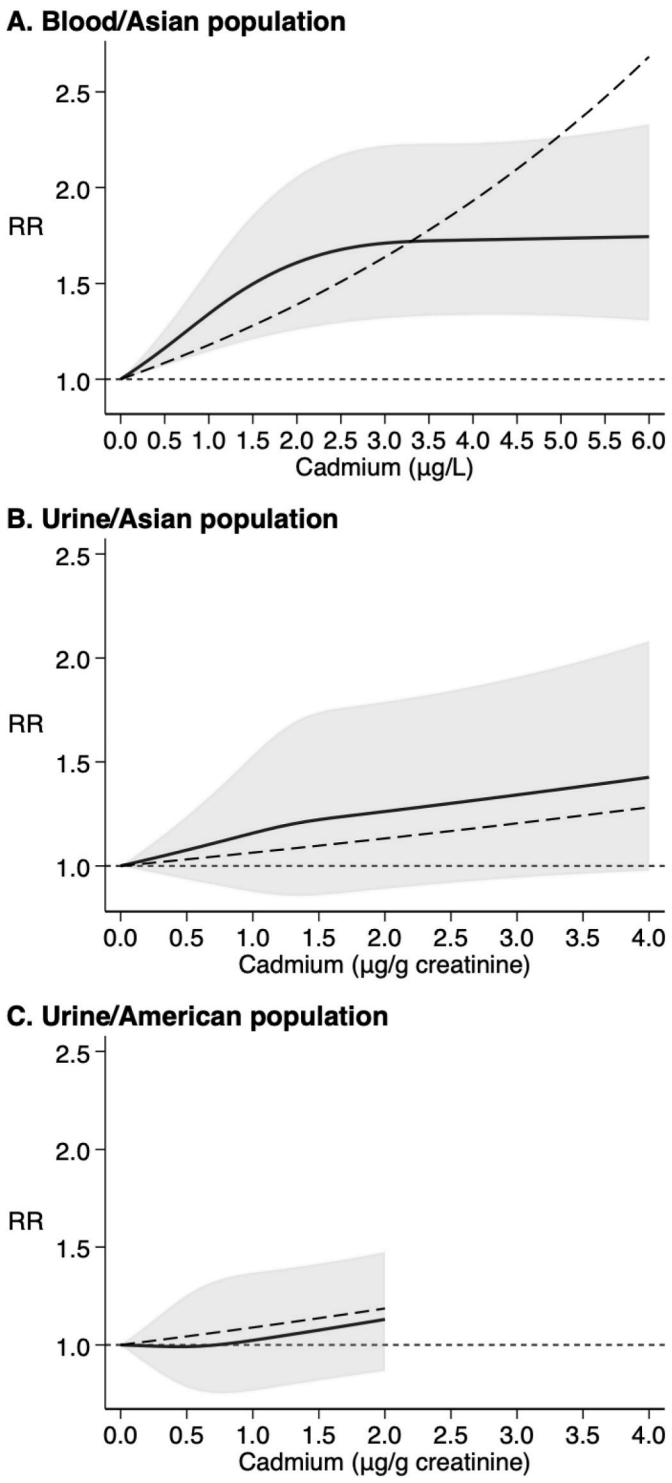


**Fig. 3.** Dose-response meta-analysis according to increasing cadmium exposure assessed through blood and urine concentrations and risk of hypertension in Asian (A: blood; B: urine) and North American populations (C: urine). Spline curve (solid black line) with 95% confidence limits (gray area). Long dash black line indicate linear assumption of the relation between cadmium and risk of hypertension. RR: risk ratio.

kidney function (Vacchi-Suzzi et al., 2016). In the case of decreased kidney function, the ability of the body to reabsorb proteins, including Cd-metallothionein, is also decreased, with corresponding increases in Cd excretion (Nordberg et al., 2009). Conversely, blood Cd concentrations may better reflect actual exposure levels. Interestingly, the finding of non-linear relation between Cd blood concentrations and hypertension is consistent with a previous study investigating the relation with blood pressure indicating an increase of both SBP AND DBP at Cd blood concentrations below 2 µg/L and between 2 and 5 µg/L, while no further increase was observed above 5 µg/L among males (Chen et al., 2015).

Although our review included a greater number of studies than previous meta-analysis (Gallagher and Meliker, 2010), we still had insufficient data to evaluate dose-response within some strata of sex and smoking status. A previous investigation (Gallagher and Meliker, 2010) indicated a higher susceptibility to the adverse effects of Cd among women, in many cases also characterized by higher Cd exposure due to increased gastrointestinal absorption of the heavy metal given their low iron status (Amzal et al., 2009; Berglund et al., 1994). Similarly, smoking is known to be an important source of Cd (Filippini et al., 2020b), thus increasing exposure levels among smokers. Current literature shows that blood Cd concentrations among non-smoking individuals reaches 0.09–1.88 µg/L, while among smokers it ranges from 0.22 to 3.75 µg/L, up to 7 µg/L in heavy smokers (Smereczanski and Brzoska, 2023). Despite the lack of sufficient data for stratified analyses, almost all studies controlled for smoking. In addition, our sensitivity analysis that excluded studies not adjusting for smoking produced similar results. Further roles of confounding factors due to dietary sources of Cd exposure in non-smoking populations cannot be excluded. Cereals and vegetables are the main contributors (European Food Safety Authority, 2009) and are generally the main components of several dietary patterns differently associated with Cd exposure (Urbano et al., 2023). However, none of the included studies adjusted for 'healthy' dietary patterns associated with lower hypertension risk such as DASH or Mediterranean diets (Appel et al., 1997; Georgoulis et al., 2024). Furthermore, one study only adjusted for consumption of rice, meat and vegetables (Qu et al., 2022), hampering the implementation of sensitivity analyses taking into account dietary habits.

We performed stratified analyses by geographic region. Despite limited numbers of studies using blood Cd concentrations, the results showed a positive association, especially in Asian studies. The possible non-linear association in North American population based on urinary Cd concentrations is not entirely unexpected, being consistent with what has been observed for risks of CVD and diabetes in association with this biomarker (Filippini et al., 2022b; Verzelloni et al., 2024). In addition, Cd exposure in North American population tended to be lower than in the Asian population, hampering the comparison of the shape of the association at higher levels.

The adverse effects of Cd on the cardiovascular system have been already investigated extensively, with most evidence indicating that Cd exposure affects the vascular system through mechanisms inducing endothelial damage, oxidative stress, and increased inflammation (Almenara et al., 2020; da Cunha Martins et al., 2018; Lin et al., 2021; Rombel-Bryzek et al., 2024; Urbano et al., 2022; Wu et al., 2016). The adverse effects on endothelial function may be mediated by alteration of bioavailability of nitric oxide and increased vasoconstriction (Martins et al., 2021). Alteration of the renin-angiotensin system and calcium homeostasis have been also reported (Angeli et al., 2013; Biagioli et al., 2008). Specific atherogenic mechanisms include enhancement of lipid peroxidation, alteration of lipid and glycosaminoglycan synthesis, prostanoid dysbalance, and upregulation of adhesion molecules (Tinkov et al., 2018). Cd is also known to alter the expression of genes and decrease enzyme activities involved in antioxidant defense systems (Khan et al., 2022).

With respect to strengths and limitations of our review, we included a larger number of studies than previous investigations (Aramjoo et al., 2022; Gallagher and Meliker, 2010), and we implemented for the first time a dose-response meta-analysis, encompassing the entire range of exposure. However, lack of systematic reporting of data stratified by sex and smoking precluded a more refined characterization of the association between Cd and hypertension. Nonetheless, the low risk of publication bias and low-to-moderate heterogeneity of results confirm the

observed positive association in the overall population, especially using urinary Cd as a biomarker of exposure.

The indication of a detrimental association between Cd exposure and hypertension risk is particularly relevant from a public health perspective, considering that hypertension is the primary risk factor for death globally (Oparil et al., 2018) and Cd still persists as an environmental contaminant in several industrialized and developing countries. Though additional investigations are needed, especially prospective studies assessing also the moderating role of sex and smoking, our results contribute evidence that Cd can adversely affect cardiovascular health.

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## CRediT authorship contribution statement

**Pietro Verzelloni:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Vincenzo Giuliano:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Lauren A. Wise:** Writing – review & editing, Writing – original draft, Supervision. **Teresa Urbano:** Writing – review & editing, Software, Data curation. **Claudia Baraldi:** Writing – review & editing, Data curation. **Marco Vinceti:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Tommaso Filippini:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Lauren Wise receives in-kind donations from Kindara.com (fertility apps) and Swiss Precision Diagnostics (home pregnancy tests). She also serves as consultant for Gates Foundation and AbbVie, Inc. All of these relationships are for work unrelated to this manuscript. All other authors have nothing to disclosure.

## Data availability

Data will be made available on request.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.120014.

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