Science of the Total Environment 906 (2024) 167165

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

# Association of cadmium environmental exposure with chronic kidney disease: A systematic review and meta-analysis

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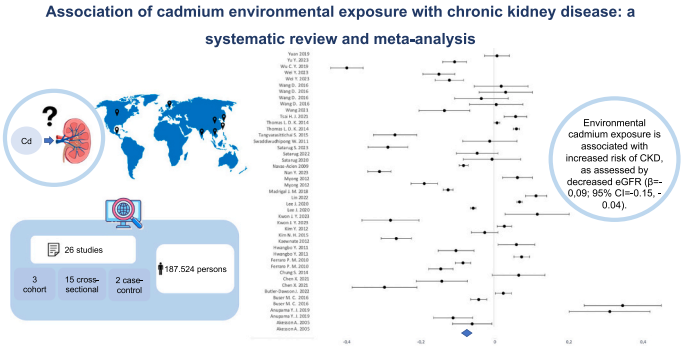
## HIGHLIGHTS

- The understanding of cadmium's impact on kidney disease (CKD) is still limited.
- We reviewed the association between cadmium exposure and CKD via meta-analysis.
- We demonstrated an inverse association between cadmium exposure and eGFR levels.
- Our findings deepen the knowledge on cadmium's effects on kidney.
- We emphasized the need to reduce environmental cadmium pollution.

## GRAPHICAL ABSTRACT




## ARTICLE INFO

Editor: Lidia Minguez Alarcon

*Keywords:*
Cadmium
Meta-analysis
Systematic review
CKD

## ABSTRACT

*Background:* Several observational studies investigated the relationship between environmental cadmium exposure and risk of chronic kidney disease (CKD). However, results from epidemiological studies are conflicting and wide variabilities have been reported.
*Objectives:* We conducted a meta-analysis to evaluate the relationship between environmental cadmium exposure and CKD risk, as assessed by decreased estimated Glomerular Filtration Rate (eGFR) in adults.
*Methods:* PubMed, Embase and the Cochrane library databases were searched for studies published up to July 2023. A random-effects model using the restricted maximum likelihood (REML) method was used to calculate the overall estimate to assess the association between cadmium exposure and eGFR. Subgroup analysis, funnel plot, Egger's test, and the trim-and-fill method were also conducted.
*Results:* Thirty-one articles, 3 cohorts, 2 case-control and 26 cross-sectional studies, across 8 countries, involving 195.015 participants were included. The meta-analysis demonstrated an inverse association between high cadmium exposure and eGFR levels (standardized regression coefficient $\beta = -0.09$; 95 % CI $= -0.15, -0.04$). The subgroup analysis showed that the inverse association was significantly higher for blood cadmium exposure ($\beta = -0.12$; 95 % CI $= -0.18, -0.06$) than for urinary concentrations ($\beta = -0.04$; 95 % CI: $-0.10$, 0.03) or dietary

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https://doi.org/10.1016/j.scitotenv.2023.167165
Received 8 June 2023; Received in revised form 14 September 2023; Accepted 15 September 2023
Available online 25 September 2023

exposure (β = −0.03; 95 % CI = −0.19, 0.14). Stratified analysis by different study design also showed an inverse association between cadmium exposure and eGFR, more evident in the cross-sectional studies (β = −0.11; 95 % CI = −0.18, −0.03) than in the cohort (β = −0.05; 95 % CI = −0.26, 0.17) and in the case-control studies (β = −0.05; 95 % CI = −0.32, 0.21).

*Discussion:* Our meta-analysis indicated that environmental cadmium exposure is associated with increased risk of CKD, as assessed by decreased eGFR, and this association is more evident for blood cadmium concentrations than for urinary concentrations or dietary exposure. Nevertheless, additional high quality prospective studies are needed to confirm the association between cadmium exposure and risk of CKD.

## 1. Introduction

Cadmium is a heavy metal and a widespread environmental pollutant that leads to a number of toxic effects on several body tissues and organs (Cho et al., 2013). Exposure to cadmium primarily occurs through the ingestion of contaminated food and water and, to a significant extent, through inhalation and cigarette smoking (Genchi et al., 2020; Satarug et al., 2010).

Previous studies have determined that environmental cadmium may have a toxic effect particularly on the renal system, with a possible role in causing proximal tubule damage and chronic kidney disease (CKD) (Rafati-Rahimzadeh et al., 2017; Akesson et al., 2005).

CKD is an emerging global public health problem (Levey et al., 2007): it affects approximately 8–16 % of the global population and it is often under-diagnosed (Coresh et al., 2007). According to the KDIGO (Kidney Disease Improving Global Outcomes) guidelines, it is defined, as the presence of kidney damage persistent for >3 months, as assessed by a decline of the glomerular filtration rate (GFR) below 60 mL/min/1.73 $m^2$, presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens, or other morphological or biochemical markers of kidney lesions with or without changes of GFR (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012, 2013).

Previous studies have proposed several mechanisms to explain the link between cadmium exposure and CKD risk. Namely, chronic exposure leads to cadmium accumulation in the epithelial cells of the proximal tubule, resulting in a variety of toxic effects including renal epithelial cells' apoptosis and functional impairment (Prozialek and Edwards, 2012). Chronic exposure to cadmium can cause both renal proximal tubular damage and decline in GFR in experimental animal models (Thijssen et al., 2007).

However, results from epidemiological studies linking cadmium exposure to the risk of CKD are conflicting (Byber et al., 2015) and wide variabilities have been reported in terms of CKD prevalence. The possible association between cadmium and CKD has yet to be clearly elucidated: this lack of strong evidence underscores the need for additional research in this field.

A meta-analysis published by Jalili et al. (Jalili et al., 2021) has recently analyzed the available published information about the association between exposure to heavy metals and the risk of CKD. Their results suggested that exposure to cadmium may increase CKD in adults, focusing exclusively on cadmium levels in urine and blood. However, our meta-analysis extends this investigation by considering the additional dimension of dietary cadmium intake. Furthermore, it is important to note that the studies included in their analysis were heterogeneous, thereby warranting further investigations to comprehensively understand the relationship between cadmium exposure and CKD risk.

Thus, we performed a meta-analysis of the available epidemiological studies in order to re-evaluate and update the evidence regarding the relationship between cadmium exposure and kidney disease endpoints, as assessed by decrease of estimated GFR (eGFR).

## 2. Methods

### 2.1. Literature search

PubMed, Embase and the Cochrane Library databases were examined to identify epidemiological studies assessing the association of cadmium exposure with CKD.

We conducted the literature search using MeSH terms and text words for the following keywords: "cadmium", "environmental exposure", "environmental contaminant", "environmental pollution", "chronic kidney disease", "ckd", "renal/kidney insufficiency" "renal/kidney failure", "proteinuria".

We took advantage of PubMed's automatic term mapping function to enlarge our research and we used Boolean operators such as "AND" and "OR" to combine search terms. We applied the same search strategy to Embase and the Cochrane library, with the necessary adaptations (see Appendix A.1).

All three searches were developed in collaboration with a librarian, through the service of assistance in bibliographic research offered by the University of Florence (https://sba.unifi.it/cmpro-v-p-1872.html).

We used Endnote reference manager software to collect and organize search outcomes and remove duplicate articles.

### 2.2. Inclusion and exclusion criteria

Inclusion criteria encompassed human observational studies, including cross-sectional, cohort and case-control studies that reported measurements of cadmium exposure at the individual (biological monitoring; personal sampling; measurements in food or drinking water) and area level.

The study eligibility criteria also included studies written in the English language, published up to July 2023 that investigated the relationship between cadmium exposure and CKD, whereas reviews, letters to the editor, abstracts, controlled trials, case reports, interventional studies, and in vitro or animal studies were not included. The search strategy was designed to align with the PECO framework:

- Population (P): We sought studies involving a population of individuals exposed to cadmium through contaminated environments or other exposure routes.
- Exposure (E): Our focus was on studies that reported measurements of cadmium exposure, which could be either continuous values or exposure categories in quartiles.
- Comparison (C): We aimed to identify studies that compared individuals with different levels of cadmium exposure or compared exposed individuals with unexposed or low-exposed individuals.
- Outcome (O): The primary outcome of interest was the presence or risk of chronic kidney disease (CKD), which we defined as an eGFR <60 mL per minute per 1.73 $m^2$. Only the studies that considered eGFR as outcome entered the analysis.

### 2.3. Outcome of interest

The renal outcome determining eligibility for inclusion was CKD, defined by creatinine clearance <60 mL per min by the Cockroft-Gault

formula (Cockcroft and Gault, 1976), or by a decreased eGFR (<60 mL per min per 1.73 $m^2$) by the Modification of Diet in renal Disease (MDRD) equation (Levey et al., 1999) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) prediction equation (Levey et al., 2009). Studies based exclusively on markers of tubular function such as tubular phosphate reabsorption, serum chloride, urinary β2MG or kidney injury molecule-1 (KIM1) were not eligible.

### 2.4. Study selection

Two investigators independently reviewed titles and abstracts to determine the relevancy of the documents on the basis of the study selection criteria; then the full texts of the selected articles were assessed in detail against the eligibility criteria. In addition, the systematic search was completed by the manual search to identify additional primary studies. Any disagreement that arose between the reviewers at each stage of the study selection process were discussed.

### 2.5. Data extraction

After identifying articles for inclusion, we extracted the overall features of individual studies, as reported in Table 1. For each included study, all relevant data were extracted, including first author, publication date, title, location of study, study design, age group(s) of participants, sex distribution of participants, sample size, exposure assessment methods, definition of kidney disease outcome, statistical analysis approaches, point estimate and confidence intervals of crude and adjusted effect size(s), and level of adjustment.

### 2.6. Quality assessment

We used the Risk of Bias (ROB) Rating Tool developed by the Office of Health and Translation (OHAT) (NTP (National Toxicology Program), 2019) to evaluate the internal quality of each included study. The OHAT tool is consistent with the other existing ROB tools (e.g. Navigation Guide), with substantial overlapping of ROB domains and/or questions. The OHAT tool consists of an overall set of questions catered to each experimental stream of evidence, addressing main bias domains as follows:

1. Selection bias: did selection of study participants result in appropriate comparison groups?
2. Confounding bias: did the study design or analysis account for important confounding and modifying variables?
3. Attrition/exclusion bias: were outcome data complete without attrition or exclusion from analysis?
4. Detection bias exposure characterization: can we be confident in the exposure characterization?
5. Detection bias outcome characterization: can we be confident in the outcome assessment?
6. Selective reporting bias: were all measured outcomes reported?
7. Other bias: were there no other potential threats to internal validity?

Each question within the tool can receive one of five possible responses: “Definitely Low Risk of Bias”, “Probably Low Risk of Bias”, “Probably High Risk of Bias”, or “Definitely High Risk of Bias”, with a statement of justification based on the study text. The OHAT tool does not apply an overall rating for each study. Additionally, OHAT instructs that studies should not be removed from consideration of the overall body of evidence as a result of “probably high” or “definitely high” ratings.

### 2.7. Statistical analysis

The articles we included in the meta-analysis reported different association and different exposure measurement scales, which meant that some pre-processing was needed to homogenize the magnitude of effect observed in each study. If sex-specific estimates or different exposure measures were available, then they were regarded as 2 different studies.

Given the different association measures, before conducting the meta-analysis, all the association measures were harmonized by converting the various association measures into standardized regression coefficients (see Appendix A.2) (Nieminem et al., 2013).

Through the homogenization procedure, 45 estimates of the standardized regression coefficient were defined. To calculate the overall estimate to assess the association between cadmium exposure and eGFR and to consider the possible non-independence of the observations, since some of the individual studies included in the meta-analysis reported two effect estimates, we performed a multilevel meta-analytical model under a common mixed-effects framework with a mixmeta R package (Sera et al., 2019). For each included study we considered the adjusted estimate for the greatest number of confounders, except for heavy metals.

Forest plots were visually inspected to assess heterogeneity. Moreover, we used meta-regression models to evaluate systematic differences by method of cadmium exposure assessment (blood cadmium, urinary cadmium and dietary cadmium), study location (outside or inside United States), smoke adjustment and by study design and eGFR metric (as continuous or dichotomous variable).

Sensitivity analysis was performed to evaluate robustness and stability by considering the adjusted estimate for heavy metals, when available, and by sequentially excluding one study at a time (see Appendix A.3).

We evaluated the potential publication bias using a funnel plot and Egger tests, with $P < 0.1$ indicating significant publication bias. We also evaluated the publication bias using the nonparametric “trim-and-fill” method (see Appendix A.4).

All statistical analyses were carried out using Stata version 17.1 (Stata Corp., College Station, TX) and RStudio software (version 2022.02.3).

## 3. Results

### 3.1. Search results and study characteristics

The article selection process for the inclusion of the studies in the present review is illustrated in the PRISMA flow diagram in Fig. 1. The initial searches in the three databases identified 1466 articles. From these records, 1037 remained after removing the duplicates. We reduced the number of included studies to 54 after screening the titles and abstracts together with a second reviewer. We then performed a full-text evaluation, which brought the total number down to 26 published articles that met our inclusion criteria. Moreover, 5 studies were added after manual search. The general characteristics of the 31 selected studies are reported in Table 1. Among the 31 studies, 26 articles had a cross-sectional design (Akesson et al., 2005; Buser et al., 2016; Butler-Dawson et al., 2021; Chen et al., 2021; Chung et al., 2014; Ferraro et al., 2010; Hwangbo et al., 2011; Kim et al., 2015; Lee et al., 2020; Madrigal et al., 2019; Myong et al., 2012; Navas-Acien et al., 2009; Tangvarasittichai et al., 2005; Tsai et al., 2021; Yuan et al., 2020; Satarug et al., 2020; Lin et al., 2022; Satarug et al., 2022; Kaewnate et al., 2012; Kim and Lee, 2012; Wang et al., 2016; Kwon et al., 2023; Nan et al., 2023; Satarug et al., 2023; Wei et al., 2022; Yu et al., 2023), whereas 3 had a prospective cohort design (Swaddiwudhipong et al., 2012; Thomas et al., 2014; Wang et al., 2021) and 2 had a case-control design (Anupama et al., 2019; Wu et al., 2019).

Besides other characteristics, the studies differ for the definition of the exposure: blood cadmium (μg/L), urinary cadmium (μg/g cr or μg/L) and dietary cadmium exposure (μg/d). Among the 31 articles, 8 of them reported estimates for both urinary and blood cadmium, while 3 studies reported estimates stratified by gender, 1 study reported estimates for both urinary and blood cadmium and by gender, and the remaining 19

**Table 1**
Description of epidemiological studies on cadmium exposure and CKD, in alphabetical order.

| First author | Year | Study design | Sampling frame | Sex | Age | Location | Sample size | Exposure measure | Outcome measure | Covariates | Results |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Akesson A. | 2005 | Cross-sectional | All women 50–59 years in the community of Lund, southern Sweden (n = 10,766) | F | 50–59 | Sweden | 816 | Blood cadmium (μg/L) Median (5–95 % percentiles) 0.38 (0.16–1.8); Urinary cadmium (μg/L) Median (5–95 % percentiles) 0.52 (0.24–1.3) | GFR (mL/min/1.73 $m^2$) | Age, BMI, smoking, blood lead, diabetes, hypertension, NSAIDs | Cadmium in both blood and urine was associated with eGFR reduction |
| Anupama Y.J. | 2019 | Case-control | Rural population in Shivamogga district in South India | All | ≥18 years | South India | 138 | Blood cadmium (μg/L) and Urinary cadmium (μg/L) | GFR < 60 mL/min/1.73 $m^2$ | None | There was no association between urinary cadmium and CKD |
| Buser M. C. | 2016 | Cross-sectional | Non-institutionalized civilian population of the United States in 2007–2008, 2009–2010, 2011–2012 | All | ≥20 years | United States | 4875 | Blood cadmium (μg/L) Mean (lower 95 %, upper 95 %) 0.51 (0.49, 0.52); Urinary cadmium (μg/L) Mean (lower 95 %, upper 95 %) 0.35 (0.34, 0.37) | GFR (mL/min/1.73 $m^2$) | Age, sex, race/ethnicity, education, alcohol consumption, smoking status, BMI, diabetes, hypertension, weak/failing kidney, serum cotinine, ln urinary creatinine | Blood cadmium showed statistically significant inverse association with eGFR levels. While with increased eGFR, there was increased U-Cd. |
| Butler-Dawson J. | 2021 | Cross-sectional | Sugarcane cutters from a sugarcane plantation in Guatemala employed at the sugarcane agribusiness during 2017–2018 | M | ≥18 years | Guatemala | 222 | Urinary cadmium (μg/L) Median (interquartile range) 0.14 (0.02, 0.26) | GFR (mL/min/1.73 $m^2$) | Baseline age, HbA1c, systolic blood pressure, BMI, time of collection, time point, urine creatinine | Urine cadmium was significantly associated with lower eGFR. |
| Chen X. | 2021 | Cross-sectional | Inhabits living in three villages (two cadmium-contaminated areas and one control area) located in Southeastern China | All | ≥35 years | Southeastern China | 456 | Blood cadmium (μg/L) Median (interquartile range) 4.69 (2.00–9.26); Urinary cadmium (μg/g cr) Median (interquartile range) 4.69 (2.76–11.24) | GFR (mL/min/1.73 $m^2$) | Baseline age, UCd, UNAG, UALB, BCd, sex, smoking, drinking, BMI, hypertension | Blood cadmium was positively associated with the incidence of CKD. |
| Chung S. | 2014 | Cross-sectional | Korea adults in 2008 (n = 36,872,028) | All | ≥20 years | Korea | 2005 | Blood cadmium (μg/L) Quartiles (Q) Q1 0.44 (μg/L) Q2 0.80 (μg/L) Q3 1.17 (μg/L) Q4 2.08 (μg/L) | GFR < 60 mL/min/1.73 $m^2$ | Age, sex, smoking, drinking, education status, occupation, hypertension, diabetes, carbohydrate intake | Increased blood cadmium levels were associated with reduced eGFR. |
| Ferraro P. M. | 2010 | Cross-sectional | Non-institutionalized civilian population of the United States in 1999–2006 | All | ≥20 years | United States | 5426 | Blood cadmium (μg/L) Mean ± standard deviation | GFR < 60 mL/min/1.73 $m^2$ | Age, gender, race/ethnicity, BMI | Moderately high levels of urinary and blood cadmium were |

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**Table 1** (*continued*)

| First author | Year | Study design | Sampling frame | Sex | Age | Location | Sample size | Exposure measure | Outcome measure | Covariates | Results |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 0.40 ± 0.38; Urinary cadmium (μg/g cr) Mean ± standard deviation 0.29 ± 0.35 | | | associated with a higher proportion of CKD |
| Hwangbo Y. | 2011 | Cross-sectional | South Korean population | All | ≥20 years | South Korea | 1909 | Blood cadmium (μg/L) GM 1.57 men GM 1.49 women | GFR < 74.7 mL/min/1.73 $m^2$ for men and <65.4 mL/min/1.73 $m^2$ for women | Age, sex, education, menopause status, smoking, urbanization, BMI, hypertension, diabetes | elevated blood cadmium levels were associated with lower eGFR in women |
| Kaewnate Y. | 2012 | Cross-sectional | Residents of 13 cadmium-contaminated villages (during January 2009–January 2010) and residents of non-cadmium-polluted village located in the same province were selected as the control area | All | ≥30 years | Thailand | 1085 | Urinary cadmium (μg/g cr) Mean ± standard deviation 9.75 ± 4.99 in cd-exposed; 1.34 ± 1.42 in non-exposed | GFR < 60 mL/min/1.73 $m^2$ | Age, sex, smoking, and alcohol intake status | Increased urinary levels of Cd was associated with an increased risk of renal dysfunction |
| Kim N. H. | 2015 | Cross-sectional | Korea adults in 2011 | All | ≥20 years | Korea | 1797 | Blood cadmium (μg/L) Mean ± standard deviation 1.17 ± 0.68 | GFR < 60 mL/min/1.73 $m^2$ | Age, sex, BMI, smoking, hyperlipidemia, hypertension, diabetes and other metals | Cd exposure was associated with CKD particularly in adults with hypertension or diabetes |
| Kim Y. | 2012 | Cross-sectional | 20 households in South Korea | All | ≥20 years | South Korea | 5984 | Blood cadmium (μg/L) GM (95%CI) 0.967 (0.946–0.988) all; 0.780 (0.755–0.806) in men; 1.194 (1.159–1.231) in women | GFR < 60 mL/min/1.73 $m^2$ | Age, sex, residence area, education 9/10 level, smoking, alcohol intake, hypertension, diabetes, and hemoglobin status, and exposure to other metals (Cd, Pb, or Hg) | Blood cadmium levels did not show a significant inverse association with eGFR |
| Kwon J. | 2023 | Cross-sectional | Three environmentally vulnerable areas: a low-exposure abandoned metal mine area (LEAMM), high-exposure abandoned metal mine area (HEAMM), refinery area, and control area unaffected by contamination | All | ≥18 years | South Korea | 298 | Blood cadmium (μg/L) GM 1.89 (1.75; 2.04) in the heavy metal exposure area 0.89 (0.78, 1.02) in the control area; Urinary cadmium (μg/L) GM 2.11 (1.90, 2.35) in the heavy metal exposure area; 1.11 (0.85, 1.44) in the control area | GFR < 60 mL/min/1.73 $m^2$ | Sex, age, and smoking history, period of residence, alcohol consumption history, and intake of locally grown rice | Increased blood cadmium was associated with reduced eGFR. |

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**Table 1** (*continued*)

| First author | Year | Study design | Sampling frame | Sex | Age | Location | Sample size | Exposure measure | Outcome measure | Covariates | Results |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lee J. | 2020 | Cross-sectional | General United States population from 1999 to 2016 | All | ≥18 years | United States | 46,748 | Blood cadmium (μg/L); Urinary cadmium (μg/g cr) | GFR < 60 mL/min/1.73 $m^2$ | Age, age-squared, sex, diabetes, hypertension, BMI, race/ethnicity, smoking, socioeconomic status | Increased exposure to cadmium showed significant association with increased prevalence of CKD. |
| Lin Y. | 2022 | Cross-sectional | General population in the rural areas of Gongcheng Yao Autonomous County | All | ≥30 years | Southwest region of China | 2775 | Urinary cadmium (μg/g cr) | GFR (mL/min/1.73 $m^2$) | Age, gender, BMI, education level, smoking status, ethnicity and other metals | No association was found between Cd and eGFR |
| Madrigal J. M. | 2018 | Cross-sectional | U.S. population | All | ≥20 years | United States | 12,577 | Blood cadmium (μg/L) GM (95 % CI) Q1 0.15 (0.14–0.15) Q2 0.27 (0.27–0.27) Q3 0.45 (0.44–0.45) Q4 1.14 (1.11–1.17) | GFR < 60 mL/min/1.73 $m^2$ | Age, race,/ethnicity, education level, alcohol consumption, cigarette smoking, BMI, self reported weak kidneys, hypertension, diabetes | Increased cadmium concentration was associated with decreased eGFR, especially among females. |
| Myong J. P. | 2012 | Cross-sectional | Korean population | All | 20–65 years | Korea | 2992 | Blood cadmium (μg/L) GM (95 % CI) in men: Q1 0.49 (0.21–0.78) Q2 1.00 (0.82–1.19) Q3 1.45 (1.25–1.70) Q4 2.28 (1.77–3.24) GM (95 % CI) in women: Q1 0.52 (0.23–0.78) Q2 1.01 (0.83–1.19) Q3 1.45 (1.23–1.69) Q4 2.33 (1.76–3.74) | GFR < 60 mL/min/1.73 $m^2$ | Age, gender, education, total household income per month, occupation, smoking, alcohol consumption | Blood cadmium was associated with lower eGFR levels particularly in women |
| Nan Y. | 2023 | Cross-sectional | Non-institutionalized US population | All | ≥40 years | United States | 1669 | Blood cadmium (μg/L) Median (25–75 % percentiles): 0.31 (0.18; 0.56) | GFR < 60 mL/min/1.73 $m^2$ | Age, sex, race/ethnicity, educational attainment, PIR, smoking status, alcohol consumption, BMI, physical activity, diabetes, hypertension, multimetal lipids and other blood metals | The authors found a positive association between exposure to the blood Cd and decreased kidney function |
| Navas-Acien A. | 2009 | Cross-sectional | Civilian non-institutionalized US population | All | ≥20 years | United States | 14,778 | Blood cadmium (μg/L) GM (95 % CI) 0.48 (0.46–0.50) | GFR < 60 mL/min/1.73 $m^2$ | Age, sex, race/ethnicity, education, menopausal status, smoking, alcohol consumption, BMI, serum cotinine, hypertension, diabetes | Increased blood cadmium was strongly associated with reduced eGFR. |

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**Table 1** (*continued*)

| First author | Year | Study design | Sampling frame | Sex | Age | Location | Sample size | Exposure measure | Outcome measure | Covariates | Results |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Satarug S. | 2020 | Cross-sectional | Residential areas in Bangkapi, suburb of Bangkok, between 2001 and 2003 | All | 16–60 | Thailand | 392 | Urinary cadmium (μg/L) Mean ± standard deviation 0.25 ± 0.68 | GFR (mL/min/1.73 $m^2$) | Age, smoking, diabetes, hypertension, use of medications, educational level, occupation, family health history | Increased urinary cadmium was associated with a decline in kidney function and women were more susceptible than men |
| Satarug S. | 2022 | Cross-sectional | Adults from residential areas in Bangkok, between 2001 and 2003 and from subsistence farming areas of Mae Sot District between 2004 and 2005 | All | | Thailand | 734 | Urinary cadmium GM ± standard deviation 2.34 ± 8.98 (μg/L) | GFR (mL/min/1.73 $m^2$) | Age, gender, BMI, diabetes, smoking, hypertension | The authors found a Cd-dose-related eGFR reduction |
| Satarug S. | 2023 | Cross-sectional | Participants from a high exposure area of the Mae Sot District and a low exposure location in Nakhon-Si-Thammarat | All | | Thailand | 603 | Urinary cadmium (μg/L) Mean ± SD: 7.94 ± 10.65 in Males with eGFR > 60; 16.42 ± 16.22 in males with eGFR < 60; 9.11 ± 11.9 in women with eGFR > 60; 10.49 ± 12.46 in females with eGFR < 60 | GFR < 60 mL/min/1.73 $m^2$ | Age, BMI, diabetes, sex, Cd/Cr ratio, sex, hypertension, smoking | Increased urinary cadmium was associated with reduced eGFR |
| Swaddiwudhipong W. | 2011 | Prospective cohort | Residents of 12 rural villages in Mae Sot District, northwestern Thailand | All | ≥15 years | Thailand | 436 | Urinary cadmium (μg/g cr) Mean ± standard deviation 9.5 ± 1.6 | GFR (mL/min/1.73 $m^2$) | Age, gender, BMI, diabetes, hypertension, urinary stone | Increased urinary cadmium was associated with reduced eGFR |
| Tangvarasittichai S. | 2015 | Cross-sectional | Residents of Cd contaminated villages in rural northern Thailand | All | ≥30 years | Northern Thailand | 535 | Urinary cadmium (μg/g cr) Median (interquartile range) 8.3 (6.4–10.7) | GFR < 60 mL/min/1.73 $m^2$ | Age, gender, smoking, alcohol drinking, BMI, diabetes, Cla/g CT, U-Protein/g CT | Increased urinary cadmium excretion showed an association with increased prevalence of CKD. |
| Thomas L. D. K. | 2014 | Prospective cohort | All men born between 1918 and 1952 and living in Orebro and Vastmanland counties + all women born between 1914 and 1949 living in Uppsala and Vastmanland counties | All | ≥45 years | Sweden | 74,307 | Dietary cadmium exposure (μg/d) Mean ± standard deviation 19 μg/day ±3.7 in men; 13 μg/day ±3.1 in women | GFR < 60 mL/min/1.73 $m^2$ | Age, height, weight, alcohol consumption, mean energy intake, smoking, aspirin use, hypertension, level of education | Dietary cadmium exposure was not associated with CKD risk |
| Tsai H. J. | 2021 | Cross-sectional | General population living in Southern Taiwan from June 2016 to September 2018 | All | ≥18 years | Southern Taiwan | 2447 | Urinary cadmium (μg/L) Median (interquartile range) 0.8 (0.5–1.4) | GFR < 60 mL/min/1.73 $m^2$ | Age, sex, diabetes, hypertension, BMI, SBP, DBP, occupation, house decoration in the past six months, burning incense, fasting glucose, log triglyceride, hemoglobin, uric acid | Increased urinary cadmium excretion was not significantly associated with CKD risk |
| Wang D. | 2016 | Cross-sectional | General population of Jiang-shan City, Zhejiang Province of China | All | ≥18 years | China | 896 | Blood cadmium (μg/L) Median (25–75 % | GFR (mL/min/1.73 $m^2$) | Age, education, smoking status, blood 9/10 Pb, urinary | No association was found between Urinary Cd and eGFR |

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**Table 1** (*continued*)

| First author | Year | Study design | Sampling frame | Sex | Age | Location | Sample size | Exposure measure | Outcome measure | Covariates | Results |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | percentiles)<br>1.34 (0.38–2.88) in men;<br>0.49 (0.31–0.92) in women<br>Urinary cadmium (μg/L)<br>Median (25–75 %)<br>0.41 (0.23–0.67) in men;<br>0.33 (0.18–0.60) in women | | Cd, and urinary creatinine status | |
| Wang X. | 2021 | Prospective cohort | Inhabits living in three villages (two cadmium-contaminated areas and one control area) located in Southeastern China | All | ≥35 years | Southeastern China | 467 | Life-time dietary cadmium intake<br>Median (interquartile range)<br>2.26 (0.73–9.34) | GFR (mL/min/1.73 $m^2$) | Age, sex, smoking, drinking, BMI, hypertension, UNAG, UALB | High dietary cadmium exposure was not associated with CKD risk |
| Wei Y. | 2023 | Cross-sectional | Participants were recruited for the Healthy Aging and Biomarkers Cohort Study in 2017, an ongoing perspective survey conducted in longevity areas in China | All | ≥80 years | China | 1535 for blood cadmium and 1176 for urinary cadmium | Blood cadmium (μg/L) and Urinary cadmium (μg/L) | GFR < 60 mL/min/1.73 $m^2$ | Sex, age, education level, marital status, residence, health insurance, smoking status, alcohol intake status, TG, HDLC, and BMI, hypertension, diabetes, cardiovascular disease, and heart disease | Cd exposure was associated with increased risk of CKD |
| Wu C. Y. | 2019 | Case-control | Clinically confirmed CKD patients and age-gender matched healthy controls | All | ≥18 years | Taiwan | 658 | Red blood cell cadmium (μg/L)<br>Mean ± standard error<br>2.43 ± 0.23 in cases;<br>1.22 ± 0.04 in controls | GFR < 60 mL/min/1.73 $m^2$ | Age, sex, educational level, alcohol, coffee, and tea intake, analgesic use, diabetes, hypertension, and urinary creatinine, total urinary arsenic, and other metals | Red blood cell cadmium was associated with increased incidence of CKD |
| Yu Y. | 2023 | Cross-sectional | Adults aged 18 to 75 years who lived in rural areas for at least 5 years | All | ≥18 years | China | 2210 | Urinary cadmium (μg/g cr)<br>Median (25–75 % percentiles);<br>2.68 (1.30, 5.92) | GFR < 60 mL/min/1.73 $m^2$ | Sex, age, ethnicity, smoking, drinking, BMI, hypertension, cardiovascular diseases, area and self-reported kidney diseases. | The authors found an association between exposure to Cd and CKD risk. |
| Yuan T. H. | 2019 | Cross-sectional | Adult residents living in 10 townships in the vicinity of a petrochemical industry between 2009 and 2012 | All | 35 years | Taiwan | 2069 | Urinary cadmium (μg/g cr)<br>Mean ± standard deviation<br>0.88 ± 0.72 | GFR < 60 mL/min/1.73 $m^2$ | Age, gender, BMI, education level, smoking status, cholesterol, hypertension, diabetes mellitus, living near a major road | eGFR was inversely associated with urinary concentrations of cadmium. |

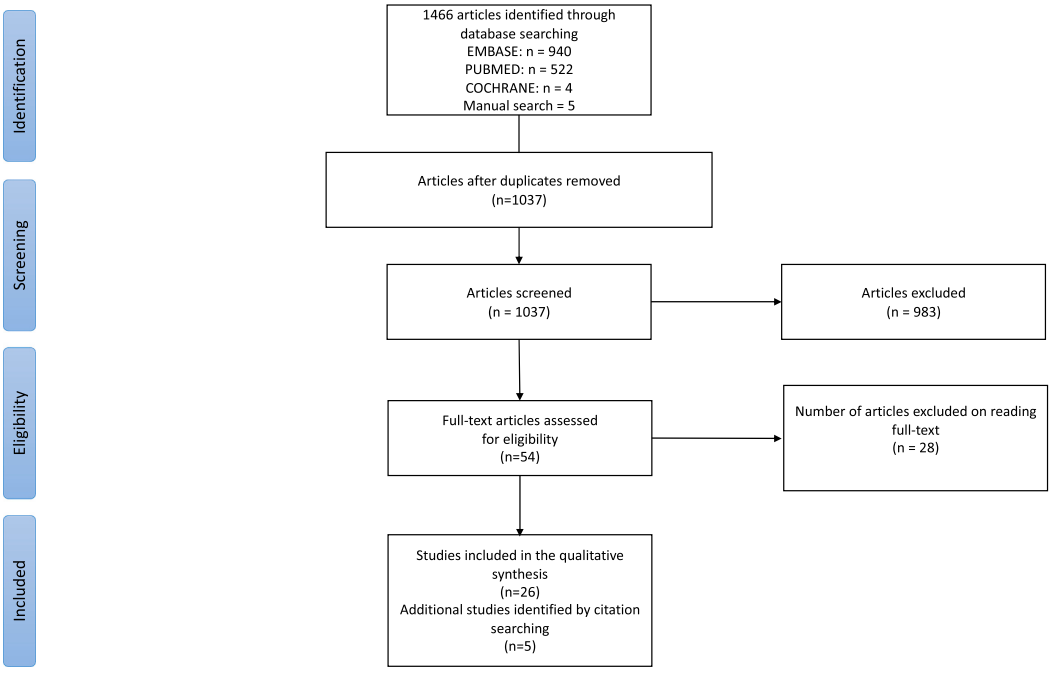


**Fig. 1.** PRISMA flow-diagram for selection of the included studies.

studies exclusively presented estimates for either urinary, blood or dietary cadmium exposure.

Studies also differ for the definition of the renal outcome: eGFR was used as a continuous variable in 10 articles, and as a dichotomous variable in 21, namely eGFR < 60 mL/min/1.73 $m^2$, or eGFR < 74.7 mL/min/1.73 $m^2$ for men and <65.4 mL/min/1.73 $m^2$ for women.

The studies reported estimates adjusted for various confounding factors. In particular, some studies present estimates adjusted with and without other heavy metals (e.g. lead). Some studies also present stratified estimates (e.g. in non-smokers or in men and women).

The publication dates of these studies were between 2005 and 2023, and they were carried out in the US, China, Sweden, Taiwan, Thailand, South Korea, South India and Guatemala.

These studies comprised a total sample size of 195.015 subjects and the number of participants across these studies varied from 222 up to 74.307 subjects.

Twenty-one studies were designed to calculate OR, 1 to calculate HR, and 9 to calculate regression coefficients.

### 3.2. Overall meta-analysis

The overall meta-analysis results, considering the possible non-independence of the observations with the multilevel meta-analysis, demonstrated an inverse association between cadmium exposure and eGFR levels (β = −0.09; 95 % CI = −0.15, −0.04; standardized regression coefficient), with high heterogeneity ($I^2$ = 88.8 %).

### 3.3. Subgroup analysis

In the meta-regression model investigating the role of different exposure types (Fig. 2), we found an inverse association between blood cadmium exposure and eGFR (β = −0.12; 95 % CI = −0.18, −0.05), whereas the results of urinary and dietary cadmium exposures showed a weaker association with eGFR (respectively, β = −0.04; 95 % CI: −0.10; 0.03 and β = −0.03; 95 % CI: −0.19, 0.14), with high heterogeneity ($I^2$ = 87.5 %).

We also performed meta-regression models investigating the role of study design (Table 2) and we found a more evident inverse association between cadmium exposure and eGFR particularly for cross-sectional studies (β = −0.11; 95 % CI = −0.18, −0.03), and a less evident association for the cohort (β = −0.05; 95 % CI = −0.26, 0.17) and the case-control studies (β = −0.05; 95 % CI = −0.32, 0.21) with high heterogeneity ($I^2$ = 98.4 %).

Meta-regression models with study location showed that exposure to cadmium was related to a higer risk of reduced eGFR among the studies performed in the United States (β = −0.11; 95 % CI = −0.26, 0.04), compared to the studies performed in other countries (β = −0.09; 95 % CI = −0.17, −0.02).

Meta-regression models considering smoking adjustment showed a more evident inverse association between cadmium exposure and eGFR among the studies that adjusted for smoking (β = −0.11; 95 % CI = −0.18, −0.03), compared to the studies that did not (β = −0.07; 95 % CI = −0.22, 0.08).

We also considered meta-regression models comparing studies using eGFR as continuous variable and as dichotomous variable. An inverse association persisted between cadmium exposure and eGFR levels in both subgroups (respectively, β = −0.07; 95 % CI: −0.19, 0.05 and β = −0.11; 95 % CI: −0.19, −0.03), with high heterogeneity ($I^2$ = 98.6 %).

### 3.4. Sensitivity analysis

As a sensitivity analysis we evaluated the effect on the summary results of considering the adjusted estimate for the greatest number of confounders and for heavy metals, when it was available.

The overall results demonstrated an inverse association between cadmium exposure and eGFR levels (β = −0.09; 95 % CI = −0.14, −0.04; standardized regression coefficient), with high heterogeneity ($I^2$ = 87.1 %).

To evaluate the robustness and stability of the relation, we performed sensitivity analyses by sequentially excluding one study at a time. The results showed that the effect estimates were stable and ranged from −0.06 (95 % CI = −0.12, −0.01) to −0.08 (95 % CI = −0.13, −0.03) (see Appendix A.3).

### 3.5. Publication bias

The funnel plot for Fig. 3 shows some asymmetry. However, Begg and Mazumdar's test for rank correlation gave a p-value of 0.69,

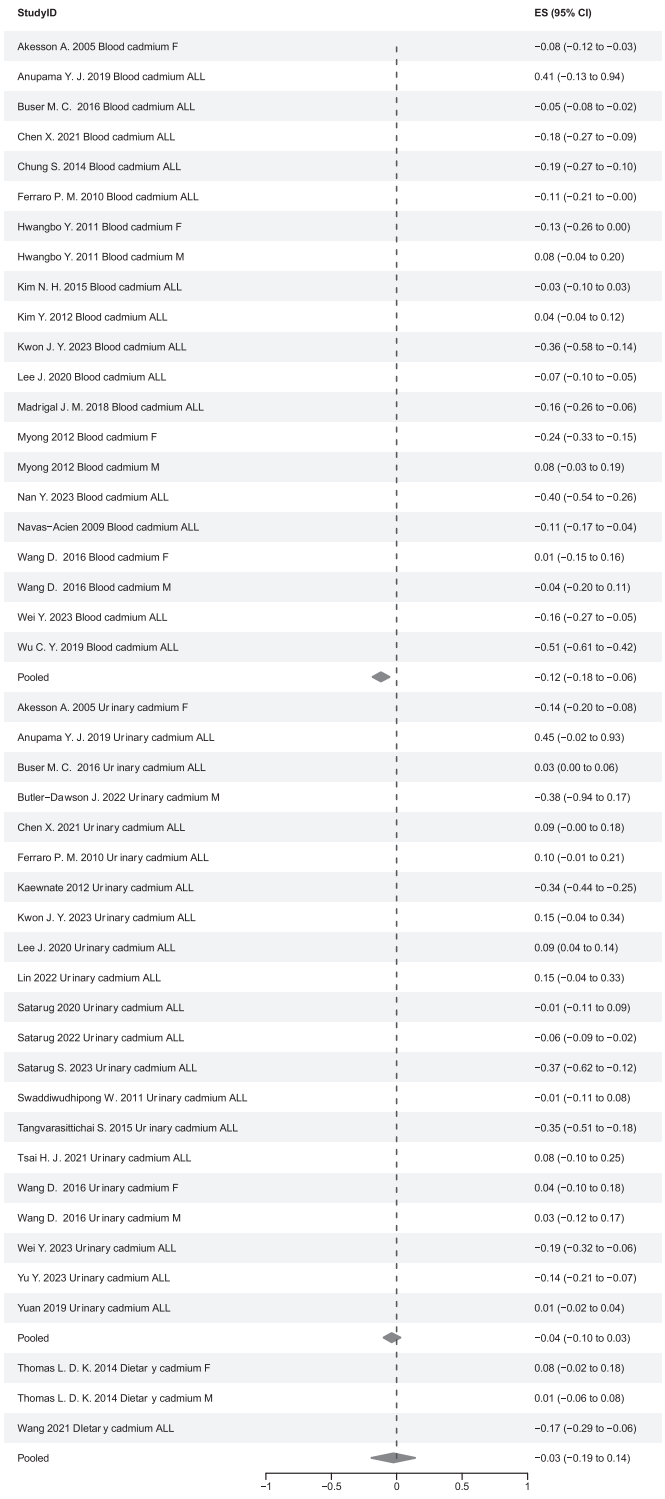


**Fig. 2.** Forest plot for the association between cadmium exposure and eGFR levels stratified by exposure type.

suggesting no evidence of publication bias. Egger's test for a regression intercept gave a p-value of 0.03, revealing potential evidence of publication bias, but the slope coefficient (slope = 0.02; p = 0.32) did not achieve statistical significance.

Since the funnel plot seems to suggest the presence of publication bias, we also used the nonparametric "trim-and-fill" method (Duval and Tweedie, 2000) to account for publication bias: it indicated no evidence of potentially missing studies from our meta-analysis and estimated the mean effect size based on the observed studies to be the same of the estimate with the imputed studies (see Appendix A.4).

**Table 2**
Results of subgroup analysis.

| Characteristic | β (95 % CI) | $I^2$ |
|---|---|---|
| All studies | −0.09 (−0.15; −0.04) | 88.8 % |
| Study design | | |
| Cross-sectional | −0.11 (−0.18; −0.03) | 98.4 % |
| Cohort | −0.05 (−0.26; 0.17) | |
| Case-control | −0.05 (−0.32; 0.21) | |
| Location | | |
| USA | −0.11 (−0.26; 0.04) | 98.5 % |
| Other countries | −0.09 (−0.17; −0.02) | |
| Smoking adjustment | | |
| Smoke-adjusted | −0.11 (−0.18; −0.03) | 98.6 % |
| Not adjusted | −0.07 (−0.22; 0.08) | |
| eGFR | | |
| Continuous | −0.07 (−0.19, 0.05) | 98.6 % |
| Dichotomous | −0.11 (−0.19; −0.03) | |

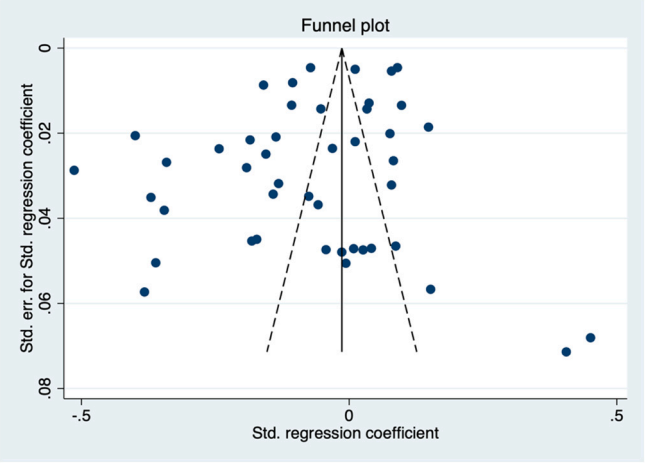


**Fig. 3.** Funnel plot of cadmium exposure and eGFR modification.

### 3.6. *Quality assessment of individual studies*

Fig. 4 summarizes the ROB assessment for each included study, using the OHAT tool. The OHAT framework appraises every study by three key domains of bias including detection bias, selection bias and confounding bias.

Detection bias for exposure assessment was classified as "low" for twenty-four of the included studies, given these studies employed objectively measured cadmium using blood and urinary samples; detection bias for exposure assessment was classified as "probably high" for two of the included studies, given these studies employed food-frequency questionnaires to obtain an estimate of the life-time dietary cadmium intake. Detection bias for outcome assessment was classified as "low" or "probably low" for twenty of the included studies because outcome was assessed using validated methods. Confounding bias was appraised as "high" in six studies, for which the authors did not control some key confounding variables like hypertension and diabetes in their analysis. Confounding bias was appraised as "probably high" for four of the included studies, given the authors didn't control for smoking, a potentially strong confounder. Selection bias was classified as "probably low" for almost all the included studies as the same exclusion and inclusion criteria were used both for exposed and unexposed groups. None of the 31 articles were excluded for being assessed at a high risk of bias in one domain, and the majority of them were rated with "low risk" and "low probability risk" in most domains.

| | Selection Bias | Confounding Bias | Attrition/ Exclusion Bias | Detection bias: Exposure Characterization | Detection Bias: Outcome Characterization | Selective Reporting Bias | Other Sources of Bias |
|---|---|---|---|---|---|---|---|
| Akesson A. 2005 | + | + | + | ++ | + | ++ | + |
| Anupama Y. 2019 | + | -- | + | ++ | + | - | + |
| Buser M. C. 2016 | + | + | + | ++ | + | ++ | ++ |
| Butler-Dawson J. 2021 | + | - | + | ++ | ++ | ++ | + |
| Chen X. 2021 | + | + | + | ++ | + | + | + |
| Chung S. 2014 | + | + | + | ++ | + | ++ | + |
| Ferraro P. M. 2010 | + | -- | + | ++ | + | ++ | ++ |
| Hwangbo Y. 2011 | + | + | + | ++ | ++ | ++ | + |
| Kaewnate Y. 2012 | + | -- | - | ++ | + | + | + |
| Kim Y. 2012 | + | + | + | ++ | + | + | + |
| Kim N. H. 2015 | + | + | + | ++ | ++ | ++ | + |
| Kwon J. Y. 2023 | + | -- | + | ++ | ++ | + | + |
| Lee J. 2020 | + | + | - | ++ | ++ | + | + |
| Lin Y. 2022 | + | -- | + | ++ | + | - | + |
| Madrigal J. M. 2018 | + | + | + | ++ | ++ | ++ | + |
| Myong 2012 | + | -- | - | ++ | + | ++ | + |
| Nan Y. 2023 | + | + | + | ++ | ++ | + | + |
| Navas-Acien 2009 | + | + | + | ++ | + | + | + |
| Satarug S. 2020 | + | + | + | ++ | ++ | + | + |
| Satarug S. 2022 | + | + | - | ++ | + | + | + |
| Satarug S. 2023 | + | + | + | ++ | + | ++ | + |
| Swaddiwudhipong W. 2011 | + | - | + | ++ | + | ++ | + |
| Tangvarasittichai S. 2015 | - | + | - | ++ | + | + | + |
| Thomas L. D. K. 2014 | + | + | + | - | - | ++ | + |
| Tsai H. J. 2021 | + | - | + | ++ | + | ++ | + |
| Wang D. 2016 | + | -- | + | ++ | + | + | + |
| Wang 2021 | + | + | - | - | ++ | ++ | + |
| Wei Y. 2023 | + | + | + | ++ | + | + | + |
| Wu C. Y. 2019 | ++ | - | + | ++ | ++ | - | + |
| Yu Y. 2023 | + | -- | + | ++ | + | - | + |
| Yuan 2019 | + | + | - | ++ | ++ | - | + |

**Fig. 4.** Summary of risk of bias judgements (++ low, + probably low, − probably high, −− high) using the OHAT framework.

## 4. Discussion

To the best of our knowledge, this is the most comprehensive meta-analysis to explore the association between cadmium exposure and CKD risk, as assessed by decreased eGFR. Our main results indicate that cadmium exposure is significantly associated with CKD risk. The overall results of the present meta-analysis using a random-effects model strongly suggest that cadmium exposure is a significant risk factor for CKD. Notably, meta-regression models and sensitivity analyses validated the reliability of our meta-analysis. Our findings could have important implications for protecting the populations of cadmium-contaminated areas.

Cadmium is widely distributed in the environment through industrial and agricultural activities. Humans are exposed to heavy metals through contaminated air, water or food. This is particularly concerning since cadmium has a very long biological half-life (approximately 20–30 years) with a low excretion rate (Branca et al., 2018).

Cadmium accumulates in the renal cortex and induces both tubular damage (Barbier et al., 2005) and decline in GFR: the evidence accumulated from human epidemiological and animal studies seems to confirm that environmental cadmium exposure may be associated with eGFR reduction, so leading to CKD.

Another meta-analysis was recently published by Jalili C. et al. about the association between exposure to heavy metals and the risk of CKD: differently from our analysis, they only considered articles that reported ORs as effect measure (Jalili et al., 2021).

They found an association between exposure to cadmium and a decrease of eGFR (OR = 1.09; 95 % CI: 0.98–1.20). Moreover, subgroup analyses in their work revealed a more pronounced influence of cadmium exposure on eGFR in adults over 65 years old (OR = 1.27; 95 % CI: 1.11–1.46) and where cadmium exposure was measured in blood serum in contrast to urine (OR = 1.10; 95 % CI: 1.00–1.21).

In the present meta-analysis, we found an inverse association between cadmium exposure and eGFR levels, especially when blood cadmium is concerned. Several studies have shown that cadmium levels in blood are more reliable as indicators of long-term cadmium exposure and body burden in respect to urinary cadmium (Wallin et al., 2015). The inverse association between eGFR and blood cadmium and the less evident association between eGFR and urinary cadmium may also be consistent with the hypothesis of reverse causality proposed by Chaumont et al. and Akerstrom et al. (Akerstrom et al., 2013; Chaumont et al., 2012), that claims that the reduced eGFR can decrease the total cadmium excretion by the kidney, so increasing cadmium blood levels in the long term. Nevertheless, the risk of reverse causality also depends on the study design and may mean that blood cadmium is a better and more stable biomarker of cadmium exposure than urinary or dietary cadmium.

With respect to the assessment of exposure levels, we observed variability across the individual studies in their methods to evaluate exposure to cadmium, including the assessment of cadmium at blood and urine level. Regarding differences in exposure levels, we noticed that blood and urine cadmium levels in the included studies are generally low (Kowal et al., 1979) (see Table 1) showing a cadmium-related effect even at low levels of environmental exposure.

Meta-analyses of observational studies are prone to the same biases as the studies they pool evidence across. Therefore, all the selected studies are susceptible to uncontrolled confounding. One particular issue in our systematic review is that only a few of the included studies had an objective measure of exposure to tobacco smoke. Smoking is a potentially very strong confounder, it is therefore important to measure smoking objectively, using a biomarker (such as cotinine) to avoid measurement error bias. The majority of the included studies employed an adjustment approach for smoking status by categorizing participants as "never smokers," "former smokers," or "current smokers." This widely adopted method is a standard practice in epidemiological research to account for potential confounding effects of smoking on the studied outcome. Nonetheless, it is important to recognize that utilizing this categorical adjustment approach may still leave room for residual confounding, which necessitates careful consideration when interpreting the study results. However, the meta-regression model considering smoking adjustment didn't show major differences in the association between the studies that adjusted for smoking and those that did not. In addition, the observational studies that consider dietary cadmium exposure are liable to bias from measurement error in using self-report measures to estimate the dietary intake of cadmium.

We investigated other potential sources of heterogeneity through meta-regression models. We used this to explore whether different study characteristics were associated with the observed differences in the results. These included study design, location, exposure assessment and adjustment for pre-specified potential confounders such as smoking.

We found a more evident inverse association between cadmium exposure and eGFR levels in cross-sectional studies than in cohort studies. Since cross-sectional studies lack the information about temporality, they can be weak in determining a causal association and the results should therefore be interpreted with caution. Moreover, a slight decrease in eGFR (particularly at an effect size of 0.5–1 mL/min) may not necessarily lead to CKD. Although, this is still relevant at a population level and indeed indicates that particular environmental insults, such as cadmium, may affect the kidney function.

Our study exhibited several strengths. First, the large number of total cases provided high statistical power for quantitative assessment of the association between cadmium exposure and CKD risk. Second, confounding factors that might influence cadmium exposure levels were minimized because multivariable-adjusted risk estimates were applied. Third, the association of cadmium exposure with risk of eGFR decrease remains statistically significant according to sensitivity and subgroup analyses, which indicated that the main findings are robust.

However, some limitations exist. Given that the included studies used different methods to assess and categorize cadmium exposure, our findings are likely influenced by the great variability, albeit we subgrouped studies to account for any possible effect of variability in the exposure method.

However, the observed variable degree of heterogeneity among included studies was maintained even after subgroup and sensitivity analyses. We were also unable to assess the dose-response relationship between cadmium exposure levels and eGFR values: the dose-response relationship between cadmium exposure and eGFR levels was limited because of insufficient data from the included studies. Therefore, well-designed studies conducted among additional regions on other continents with different doses of cadmium exposure are necessary.

Moreover, an important problem in our meta-analyses was the difficulty of including all the studies, combining the different association measures. If we did not include all the relevant studies, the meta-analysis would lose external validity. To overcome the obstacle of the different measures used for the exposure variable, we recalculated each effect expressed as a regression coefficient; thus, they could be validly combined in our meta-analysis. The statistical method we used optimized our meta-analysis because it allowed to include a high number of studies.

Moreover, the estimation of the subgroup results was calculated under the assumption that observations were independent, while independence is questionable. Some of the individual studies included in the meta-analysis were considered twice, since they reported several effect estimates: different measures from the same study were considered to generate several different effect size estimates. However, for the estimation of the overall results we considered a model that considered the possible non-independence of the observations, and the results were similar.

Overall, the existing evidence suggests an association between cadmium exposure and increased risk of CKD, as assessed by decreased eGFR in adults. These findings extend our understanding of the adverse effects of cadmium and emphasize that it is crucial to reduce the

environmental cadmium pollution to improve the global health. However, these results should be interpreted cautiously because of the heterogeneity among studies and the different association measures.

## CRediT authorship contribution statement

C.D., F.S. and A.B. conceptualized and designed the study. C.D. and A.F. conducted the literature search and screened the studies for eligibility. C.D. extracted the data, verified the study selection and data extraction. C.D. and F.S. performed the statistical analysis and meta-analysis. F.S. and A.B. provided guidance and oversight for the statistical analysis. C.D. wrote the first draft of the manuscript. F.S., A.C. and A.B. critically reviewed and edited the manuscript for intellectual content. All authors approved the final version of the manuscript for publication.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

## Acknowledgments

This work was supported by the CitieS-Health project (Citizen Science for Urban Environment and Health, Grant agreement ID: 824484). The content of this publication reflects only the authors' view and the Commission is not responsible for any use that may be made of the information it contains. We also thank the faculty of the Master in Epidemiology, University of Turin, Italy, for feedback and comments on this work.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.167165.

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