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Association between cadmium exposure and risk of chronic kidney disease; a systematic review and meta-analysis

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is the twelfth most common cause of death worldwide. The kidneys are the primary site of cadmium accumulation and the most sensitive organ to cadmium toxicity. Therefore, the current study aimed to investigate the relationship between cadmium exposure and the risk of CKD using a systematic review and meta-analysis method.

Materials and Methods: In this systematic review and meta-analysis, databases including PubMed, Scopus, Web of Science, Cochrane, and Google Scholar were searched without time restrictions until September 9, 2023. Data were analyzed using STATA 14 software, and P <0.05 was considered statistically significant.

Results: The results of combining 18 observational studies with a total of 230,790 participants showed that an increase in blood cadmium levels was associated with an increased risk of CKD (OR: 1.42; 95% CI: 1.18, 1.70). This association was significant in cross-sectional studies (OR: 1.21; 95% CI: 1.04, 1.41), case-control studies (OR: 3.08; 95% CI: 1.47, 6.41), and cohort studies (OR: 1.36; 95% CI: 0.85, 2.17). Generally, the relationship between urinary cadmium levels and CKD was not statistically significant (OR: 1.14; 95% CI: 0.84, 1.54). In cross-sectional studies, high urinary cadmium levels reduced the risk of CKD (OR: 0.77; 95% CI: 0.60, 0.99). However, in case-control studies, the relationship between high urinary cadmium levels and risk of CKD was not statistically significant (OR: 0.20; 95% CI: 0.02, 2.40). Since in cohort studies, high urinary cadmium levels were a risk factor for CKD (OR: 1.40; 95% CI: 1.07, 1.83)]. The relationship between cadmium consumption and the risk of CKD was statistically significant (OR: 1.55; 95% CI: 1.00, 2.42), with significance in case-control studies (OR: 18.16; 95% CI: 1.75, 188.64) but not in cohort studies (OR: 1.45; 95% CI: 0.93, 2.25).

Conclusion: Overall, an increase in blood cadmium levels was associated with a 42% increased risk of CKD. Furthermore, cadmium consumption through the diet increased the risk of CKD by 55%.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42023463145).

Implication for health policy/practice/research/medical education:
Heavy metals, including cadmium, are among the factors associated with toxicity. The kidneys are the primary site of cadmium accumulation and the most sensitive organ to cadmium toxicity. An increase in blood cadmium levels increases the risk of CKD by 42%, and cadmium consumption through the diet increases the risk of CKD by 55%. There is no statistically significant association between urinary cadmium levels and CKD. Further studies are needed to confirm the findings..

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Meta-analysis

Introduction

Chronic kidney disease (CKD) is a global public health burden that affects approximately 11 to 13 percent of adults worldwide (1,2). It ranks as the twelfth leading cause of mortality in the world's population (3). Several risk factors are associated with the exacerbation of CKD, including ethnicity, aging, dietary habits, physical activity, and diseases such as high blood pressure, cardiovascular

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disease, obesity, and diabetes (4). As you may know, CKD is a progressive and irreversible disease, and whether exposure to heavy metals plays a role in its development is a vital concern for public health (5-7).

Heavy metals are known environmental toxins, and some of them are linked to CKD (8). Cadmium, a toxic heavy metal derived from agricultural and industrial sources, has multiple adverse effects on human health, including CKD, bone diseases, cardiovascular diseases, infertility, and malignancies (9,10). Potential environmental sources of cadmium include contaminated water or food, smoking, cosmetic and hygiene products, phosphate fertilizers, fuel combustion, and metal waste disposal, among others (11-13).

The kidneys are the primary site of cadmium accumulation and the most sensitive organ to cadmium toxicity (14,15). Substantial evidence suggests that exposure to cadmium may lead to oxidative stress, inflammation, and lipid peroxidation in the kidneys (16,17). Furthermore, data from national health and nutrition surveys conducted from 1999 to 2006 have shown that higher levels of cadmium (Cd) in urine and blood are associated with an increased risk of CKD and albuminuria (18). The toxic effects of cadmium on proximal tubular cells result in reduced reabsorption of low molecular weight proteins, leading to increased urinary excretion of these proteins, a condition referred to as "tubular proteinuria" (16). Some studies have also indicated that cadmium is associated with a decreased estimated glomerular filtration rate (eGFR) (19-23). Therefore, the aim of the current study was to investigate the relationship between cadmium exposure and the risk of CKD using a systematic review and meta-analysis approach.

Materials and Methods

Study design

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (24), and the protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42023463145.

Search strategy

To access relevant sources, databases including PubMed, Scopus, Web of Science, Cochrane, and the Google Scholar search engine were searched without time restrictions until September 9, 2023. Standard keywords and Medical Subject Headings (Mesh) were utilized to perform a comprehensive search, including Chronic Kidney Disease, Chronic Kidney Insufficiency, Chronic Renal Disease, Chronic Renal Insufficiency, and Cadmium. These keywords were combined using Boolean operators (AND, OR) for advanced searching. Additionally, a manual search of the reference lists of primary studies that underwent the systematic review process was conducted. The search strategy for PubMed is outlined below: (Cadmium [Title/Abstract]) AND (Chronic Kidney Disease [Title/Abstract] OR Chronic Kidney Insufficiency [Title/Abstract] OR Chronic Renal Disease [Title/Abstract] OR Chronic Renal Insufficiency [Title/Abstract])

PICO components

- Population: cohort, case-control, and cross-sectional studies investigating the association between cadmium and CKD.
- Intervention: cadmium exposure.
- Comparison: general population.
- Outcomes: The primary outcome was the association between cadmium exposure and the risk of CKD. The secondary outcome involved assessing this association within subgroups such as study type and age of participants.

Inclusion criteria

Observational studies evaluating the relationship between cadmium exposure and CKD.

Exclusion criteria

Systematic reviews, narrative reviews, studies with incomplete full-text availability, low-quality studies, qualitative studies, studies lacking necessary data for analysis, studies examining the combined effects of cadmium and another factor on CKD, studies investigating the relationship between factors other than cadmium exposure and CKD, and duplicate studies were excluded.

Quality assessment

After identifying eligible studies, two independent authors assessed the quality of observational studies using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) quality assessment checklist (25). This checklist consists of 22 questions, with a final score ranging from 0 to 44. The cutoff point for inclusion in this study was a score of 14 or higher. Any discrepancies in the assessment of the checklist questions were resolved through discussion and consensus between the two authors.

Data extraction

Two authors performed data extraction from the studies separately. The authors entered the extracted data into a checklist, including: researcher name, country, study type, participants' age, publication year, sample size, individuals in the comparison group, blood and urine cadmium levels, odds ratio (OR) for the association between cadmium exposure and the risk of CKD, along with a 95% confidence interval (CI). A third researcher reviewed the data extracted by the two previous researchers to address any discrepancies.

Statistical analysis

The odds ratio index was conducted to assess the association between cadmium and CKD. The logarithm of the OR in each study was calculated and used for result aggregation. To assess heterogeneity, the Cochrane Q test and I^2 statistic were used. In this study, a random-effects model was employed. Data analysis was conducted using STATA 14 software, and statistical significance was set at $P < 0.05$.

Results

Study selection

Initially, 322 articles were found. After reviewing their titles, 125 duplicate studies were removed. The abstracts of 197 articles were reviewed, and 26 articles were excluded due to the unavailability of full text. Of remaining 171 articles, 38 were excluded due to incomplete required information, and 115 were excluded based on other exclusion criteria. Finally, 18 articles were included in the systematic review and meta-analysis (Figure 1).

In this study, 18 observational studies (7 cross-sectional studies, 7 cohort studies, and 4 case-control studies) with a total of 230 790 participants were examined. The information from the reviewed articles is presented in Table 1.

Figure 2 shows that the association between blood cadmium levels and CKD is statistically significant (OR: 1.42; 95% CI: 1.18, 1.70), with a 42% increase in the risk of CKD with an increase in blood cadmium levels.

In Figure 3, the association between blood cadmium levels and CKD was examined based on the study type. The association between blood cadmium levels and CKD was estimated in cross-sectional studies (OR: 1.21; 95% CI: 1.04, 1.41), case-control studies (OR: 3.08; 95% CI: 1.47, 6.41), and cohort studies (OR: 1.36; 95% CI: 0.85, 2.17). The association between blood cadmium levels and CKD was not statistically significant in cohort studies. However, cross-sectional and case-control studies showed a positive and significant association between blood cadmium levels and CKD.

In Figure 4, we assessed the association between blood cadmium levels and CKD based on participants' age groups. We found that this relationship was present in the age groups of 40 to 49 years (OR: 0.74; 95% CI: 0.07, 7.95), 50 to 59 years (OR: 1.04; 95% CI: 0.79, 1.37), 60 to 69 years (OR: 1.69; 95% CI: 1.14, 2.51), and 70 years and older (OR: 1.59; 95% CI: 1.28, 1.97).

Figure 5 shows that the association between urinary cadmium levels and CKD is not statistically significant (OR: 1.14; 95% CI: 0.84, 1.54).

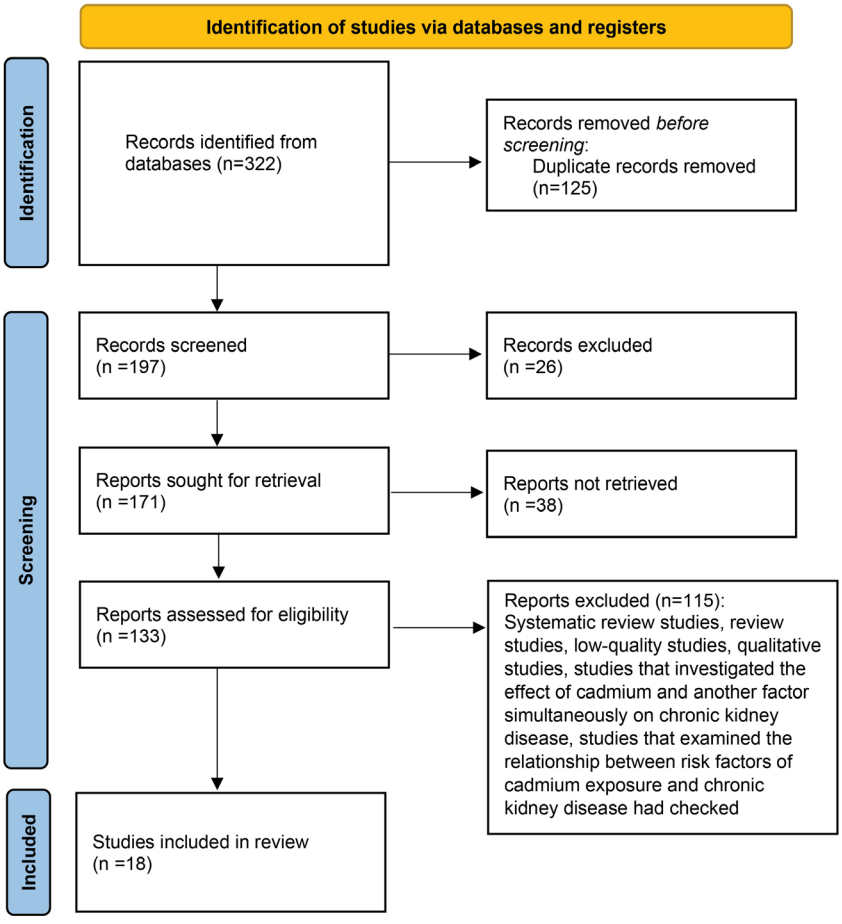

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Summary of the information available in the reviewed articles

Author, year of publication, sex of participants	Country	Type of Study	Sample size in CKD patients	Mean age in CKD patients	Sample size in compare group	Mean age in compare group	Cadmium exposure assessment (blood, urinary and dietary)	Blood Cd	Urinary Cd	Cadmium intake
Hwangbo Y, 2011, Men (21)	Korea	Cross-sectional	87	51	248	40.01	Blood Cd	1.29–1.88 µg/L	NR	NR
Hwangbo Y, 2011, Men (21)	Korea	Cross-sectional	87	51	240	40.01	Blood Cd	> 1.88 µg/L	NR	NR
Hwangbo Y, 2011, Women (21)	Korea	Cross-sectional	86	55.1	222	40.3	Blood Cd	1.29–1.88 µg/L	NR	NR
Hwangbo Y, 2011, Women (21)	Korea	Cross-sectional	98	55.1	207	40.3	Blood Cd	> 1.88 µg/L	NR	NR
Wu CY, 2019 (26)	Taiwan	Case-Control	47	65.14	147	64.21	Blood Cd	0.80–1.30 µg/L	NR	NR
Wu CY, 2019 (26)	Taiwan	Case-Control	153	65.14	142	64.21	Blood Cd	> 1.30 µg/L	NR	NR
Shi Y, 2023 (27)	USA	Cross-sectional	NR	NR	NR	NR	Blood Cd	> 0.300 µg/L	NR	NR
Kim NH, 2015 (28)	Korea	Cross-sectional	128	57	1669	45	Blood Cd	1.17 µg/L	NR	NR
Navas-Acien A, 2009 (29)	USA	Cross-sectional	502	67.6	3237	44.7	Blood Cd	>0.6 µg/L	NR	NR
Navas-Acien A, 2009 (29)	USA	Cross-sectional	475	67.6	2442	44.7	Blood Cd	>0.4–0.6 µg/L	NR	NR
Navas-Acien A, 2009 (29)	USA	Cross-sectional	503	67.6	4271	44.7	Blood Cd	>0.2–0.4 µg/L	NR	NR
Wang R, 2022 (30)	China	Cohort	457	66.19	2614	63.56	Blood Cd	NR	NR	NR
Hsueh YM, 2021 (31)	Taiwan	Case-Control	47	65.1	147	64.2	Blood Cd	>0.80–1.30 µg/L	NR	NR
Hsueh YM, 2021 (31)	Taiwan	Case-Control	153	65.1	142	64.2	Blood Cd	>1.30 µg/L	NR	NR
Chung S, 2014 (32)	Korea	Cross-sectional	83	46	1922	46	Blood Cd	2.08 µg/L	NR	NR
Anupama YJ, 2019 (1)	India	Case-Control	69	49.2	69	48.9	Blood and urinary Cd	>6 µg/L	54.5 µg/L	NR
Chen X, 2021 (33)	China	Cross-sectional	NR	NR	NR	NR	Blood and urinary Cd	2.20 µg/L	4.88 µg/g cr	NR
Wei Y, 2022 (34)	China	Cohort	1578	93.3	1133	89.24	Blood and urinary Cd	>2.85 µg/L	>2.27 µg/g cr	NR
Wei Y, 2022 (34)	China	Cohort	1578	93.3	1133	89.24	Blood and urinary Cd	1.34–2.85 µg/L	1.13–2.27 µg/g cr	NR
Wei Y, 2022 (34)	China	Cohort	1578	93.3	1133	89.24	Blood and urinary Cd	0.72–1.34 µg/L	0.62–1.13 µg/g cr	NR
Lyu YB, 2021 (35)	China	Cohort	NR	NR	NR	NR	Blood and urinary Cd	0.96 µg/L	0.61 µg/L	NR
Ferraro PM, 2010 (18)	USA	Cross-sectional	NR	NR	NR	NR	Blood and urinary Cd	> 1 mcg/L	> 1 mcg/g	NR
Zhou TT, 2021 (36)	China	Cohort	592	>60	NR	NR	Urinary Cd	NR	NR	NR
Tsai HJ, 2021 (37)	Taiwan	Cohort	155	55.1	2292	55.1	Urinary Cd	NR	log per 1 µg/L	NR
Shi Z, 2018 (27)	China	Cohort	2107	51	NR	NR	Dietary Cd	NR	NR	36.9 µg/d
Shi Z, 2018 (27)	China	Cohort	2107	51	NR	NR	Dietary Cd	NR	NR	29.6 µg/d
Shi Z, 2018 (27)	China	Cohort	2107	51	NR	NR	Dietary Cd	NR	NR	23.2 µg/d
Thomas LD, 2014, Men (38)	Sweden	Cohort	200	60	NR	NR	Dietary Cd	NR	NR	≥20 µg/d
Thomas LD, 2014, Men (38)	Sweden	Cohort	193	59	NR	NR	Dietary Cd	NR	NR	17–20 µg/d
Thomas LD, 2014, Women (38)	Sweden	Cohort	85	63	NR	NR	Dietary Cd	NR	NR	>14 µg/d
Thomas LD, 2014, Women (38)	Sweden	Cohort	84	61	NR	NR	Dietary Cd	NR	NR	12–14 µg/d
Wang X, 2021 (39)	China	Case-Control	347	>35	120	>35	Dietary Cd	NR	NR	>2.2 g

NR, Not reported; CKD, Chronic kidney diseas; Cd, cadmium.

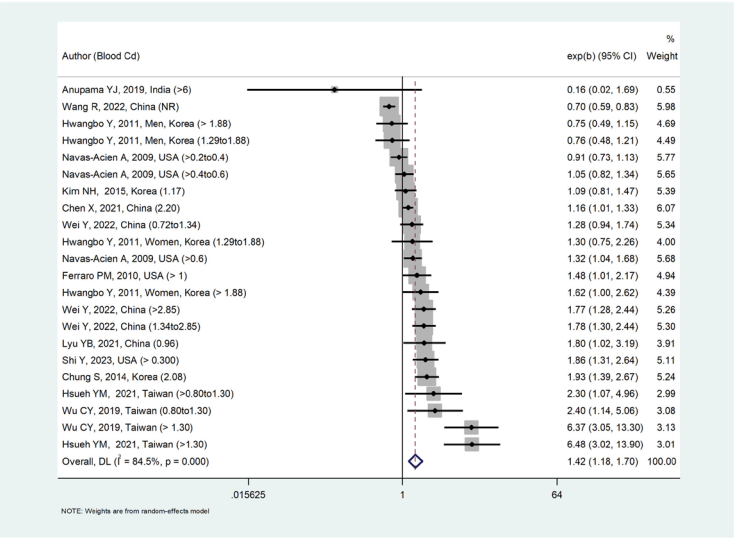

Figure 2. Forest plot of the association between blood cadmium level and chronic kidney disease, with its 95% confidence interval (The number in parentheses indicates the blood cadmium level in units of micrograms per liter).

In Figure 6, the association between urinary cadmium levels and CKD in cross-sectional studies was statistically significant, indicating that high urinary cadmium levels prevent the development of CKD (OR: 0.77; 95% CI: 0.60, 0.99). However, the association between urinary cadmium levels and CKD was not statistically significant in case-control studies (OR: 0.20; 95% CI: 0.02, 2.40). It should be noted that the number of studies examined in these subgroups was less than three, which is a significant factor in the final result. On the other hand, the association between urinary cadmium levels and CKD was statistically significant in cohort studies. It identified cadmium as a risk factor for developing CKD (OR: 1.40; 95% CI: 1.07, 1.83).

In Figure 7, we assessed the association between urinary cadmium levels and CKD based on participants' age groups. We found that this relationship was present in the age groups of 40 to 49 years (OR: 0.20; 95% CI: 0.02, 2.40), 50 to 59 years (OR: 0.76; 95% CI: 0.40, 1.42), and 70 years and older (OR: 1.63; 95% CI: 1.28, 2.08).

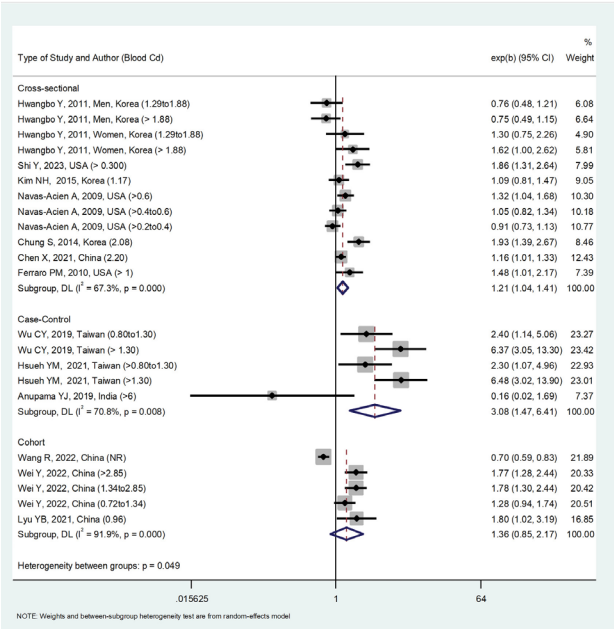

Figure 3. Forest plot of the association between blood cadmium level and chronic kidney disease by type of studies, with its 95% confidence interval (The number in parentheses indicates the blood cadmium level in units of micrograms per liter).

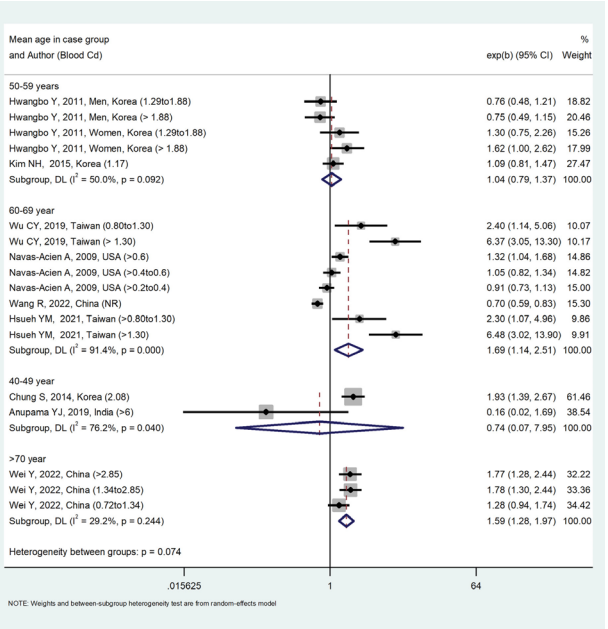

Figure 4. Forest plot of the association between blood cadmium level and chronic kidney disease by age group, with its 95% confidence interval (The number in parentheses indicates the blood cadmium level in units of micrograms per liter).

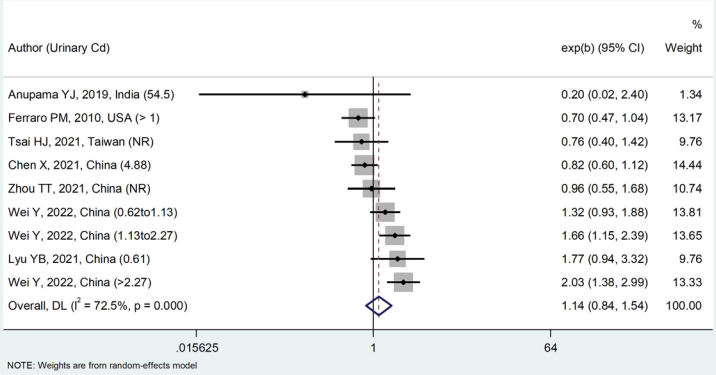

Figure 5. Forest plot of the association between urine cadmium level and chronic kidney disease, with its 95% confidence interval (The number in parentheses indicates the urine cadmium level in units of µg/g cr and µg/L).

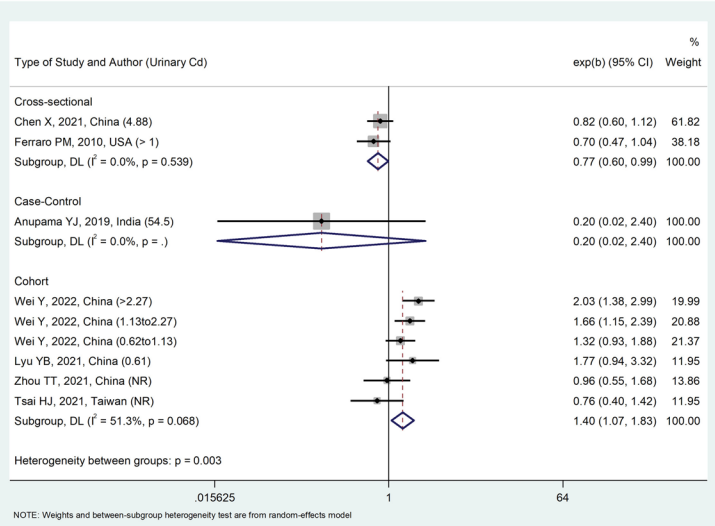

Figure 6. Forest plot of the association between urine cadmium level and chronic kidney disease by type of studies, with its 95% confidence interval (The number in parentheses indicates the urine cadmium level in units of µg/g cr and µg/L).

In Figure 8, the association between cadmium consumption through the diet and CKD was statistically significant (OR: 1.55; 95% CI: 1.00, 2.42).

The association between cadmium consumption and CKD was significant in case-control studies (OR: 18.16; 95% CI: 1.75, 188.64) but not significant in cohort studies (OR: 1.45; 95% CI: 0.93, 2.25) (Figure 9).

The association between cadmium consumption and CKD was significant in individuals aged 50 to 59 years (OR: 2.11; 95% CI: 1.10, 4.08) but not significant in the age group of 60 to 69 years (OR: 0.90; 95% CI: 0.77, 1.06) (Figure 10).

Discussion

The results obtained from the combination of 18 studies under investigation showed that as blood cadmium levels increase, the risk of developing CKD also increases. Furthermore, cadmium consumption leads to an increased risk of CKD. The association between blood cadmium levels and CKD was not statistically significant in the 40–59 age group. Still, it was statistically positive and significant in the 60-year-old and older age groups. The association between urinary cadmium levels and CKD was not statistically significant in the 40–59 age group. Additionally, it was statistically positive and significant in the 70-year-old and older age groups. This indicates that in individuals with increased blood or urinary cadmium levels, the risk of CKD increases with age. Conversely, the association between cadmium consumption through the diet and CKD was positive and significant in individuals aged 50 to 59 years but not significant in the 60 to 69-year-old age group. This suggests that cadmium consumption is considered a risk factor for CKD in individuals under the age of 60 years.

Byber and colleagues conducted a study involving 34 groups and over 3000 participants to investigate the

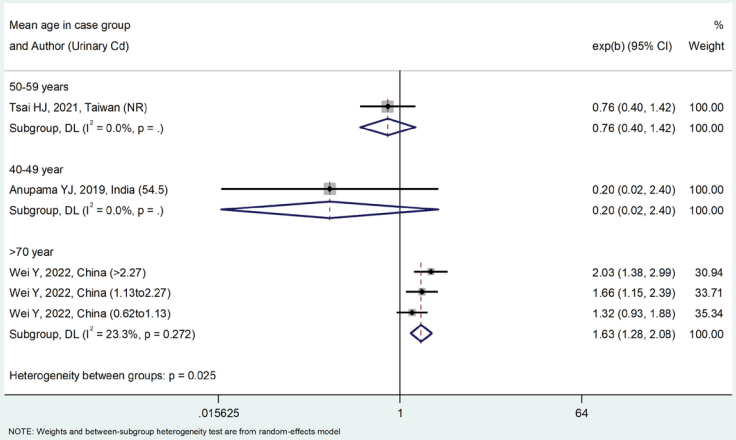

Figure 7. Forest plot of the association between urine cadmium level and chronic kidney disease by age group, with its 95% confidence interval (The number in parentheses indicates the urine cadmium level in units of μg/g cr and μg/L).

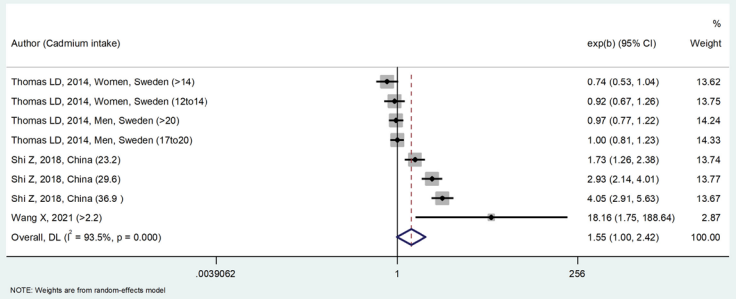

Figure 8. Forest plot of the association between cadmium intake and chronic kidney disease, with its 95% confidence interval (The number in parentheses indicates the amount of cadmium used).

association between cadmium exposure and CKD. They demonstrated that overall, there was no convincing evidence of an increased risk of CKD progression in populations exposed to cadmium (7). The results of this study do not align with the findings of the current research. In the current meta-analysis, we concluded that exposure to cadmium increases the risk of CKD.

A case-control study by Li and colleagues in China, involving 940 participants and aimed at examining the relationship between plasma cadmium levels and the prevalence of kidney lithiasis, showed that the kidney lithiasis ratio was highest in the highest quartile of plasma cadmium compared to the lowest quartile (OR: 1.16; 95% CI, 1.12 to 2.32) (40). In a prospective cohort study conducted by Sotomayor and colleagues, which included 672 kidney transplant recipients, plasma cadmium concentration was associated with an increased risk of graft failure (HR: 1.96, 95% CI: 1.56–2.47). Furthermore, the results indicated that plasma cadmium was independently associated with an increased risk of long-term graft failure and related kidney function decline (41). The results of these two studies are consistent with our research findings, as in all these studies, there was a direct relationship between blood cadmium levels and the incidence of kidney disease. Elevated blood cadmium levels were considered a risk factor for kidney disease. The kidneys are organs that are more exposed to cadmium toxicity, and this may explain the similarity in the results of these studies.

In a previous study conducted in Sweden by Hellström et al to investigate the relationship between cadmium exposure and end-stage renal disease in individuals undergoing renal replacement therapy, the results showed that the risk of end-stage renal disease in the cadmium-exposed population was higher compared to the non-exposed group (MH-RR (Mantel-Haenszel rate ratio), 1.8; 95% CI, 1.3 to 2.3) (42). In a prospective study by Oosterwijk et al involving 226 diabetic patients, both cadmium exposure (HR: 1.37, 95% CI: 1.06–1.78) and smoking (HR: 3.77, 95% CI: 1.72–8.29) were associated with an increased risk of renal function decline (43). A systematic review by Moody et al aimed at examining the

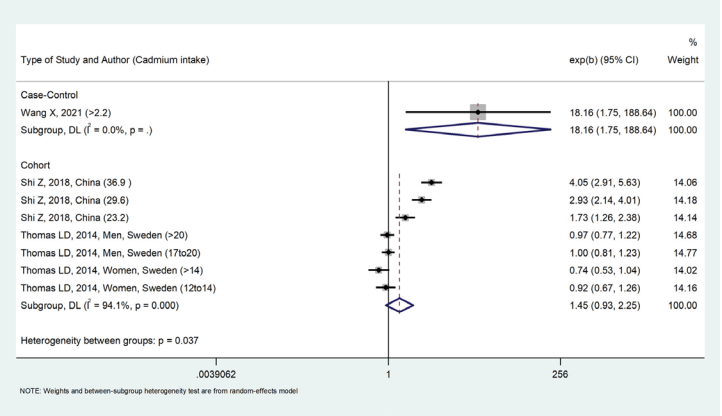

Figure 9. Forest plot of the association between cadmium intake and chronic kidney disease by type of studies, with its 95% confidence interval (The number in parentheses indicates the amount of cadmium used).

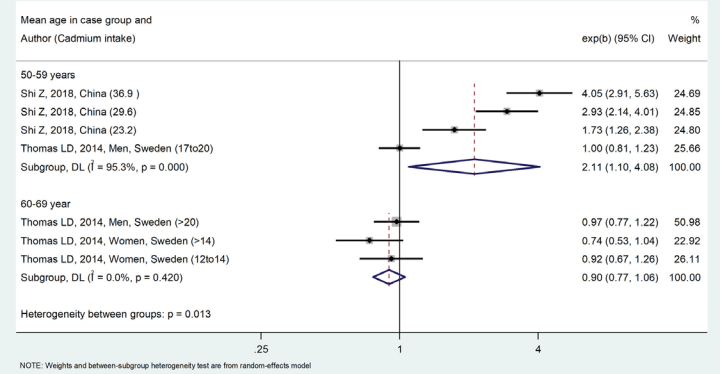

Figure 10. Forest plot of the association between cadmium intake and chronic kidney disease by age group, with its 95% confidence interval (The number in parentheses indicates the amount of cadmium used).

relationship between toxic metals and CKD reported the negative effects of continuous exposure to heavy metals on the development of CKD (44). The results of the recent study by Little et al showed that exposure to cadmium increases the risk of CKD ≥ stage 3 by almost 20% (OR: 1.20; 95% CI: 1.15–1.26, *P* <0.0001) (45). These studies are consistent with the findings of our current research, as they all demonstrate that cadmium exposure increases the risk of end-stage renal disease, CKD, and renal function decline.

Conclusion

Based on the results of this study, overall, an increase in blood cadmium levels increases the risk of CKD by 42%. Additionally, cadmium consumption through the diet increases the risk of CKD by 55%. However, there was no statistically significant association between urinary cadmium levels and CKD. Further studies are needed to confirm our research findings.

Limitations of the study

Due to the data available from the reviewed studies, it was impossible to analyze based on the amount of cadmium and the duration of cadmium exposure. Different units of measurement for cadmium were used, and information on the duration of cadmium exposure was incomplete in the basic articles. Therefore, we could not compare the effect of low levels of cadmium exposure with high levels on the risk of CKD. In the studies examined, the relationship between cadmium exposure and the risk of kidney disease was not reported by gender, and we could not conduct an analysis based on the gender of the patients. Access to the full text of some studies was not possible. The number of studies was limited, and this small number was divided into three categories (studies assessing blood cadmium levels, studies assessing urinary cadmium levels, and studies assessing the effect of dietary cadmium intake). This difference in study types may have contributed to differences in the findings, and we were unable to combine all articles in one chart.

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Authors' contribution

Conceptualization: Mehrdad Abbaszadeh, Somayeh Barakeh and Hassan Pakdel.
Data curation: Ahmad Pakdel, and Hassan Pakdel.
Formal analysis: Hassan Pakdel.
Funding Acquisition: Mehrdad Abbaszadeh, Somayeh Barakeh and Hassan Pakdel.
Investigation: Somayeh Barakeh.
Methodology: Mehrdad Abbaszadeh, Ahmad Pakdel, and Hassan Pakdel.
Project administration: Mehrdad Abbaszadeh
Resources: Mehrdad Abbaszadeh, Somayeh Barakeh and Hassan Pakdel.
Supervision: Mehrdad Abbaszadeh.
Validation: Mehrdad Abbaszadeh and Somayeh Barakeh.
Visualization: Somayeh Barakeh, Ahmad Pakdel and Hassan Pakdel.
Writing–original draft: Mehrdad Abbaszadeh
Writing–review and editing: Somayeh Barakeh, Ahmad Pakdel and Hassan Pakdel.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website with (ID: CRD42023463145). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support

None.

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