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Meta-analysis

Meta Analysis the Effect of Cadmium Exposure on Chronic Renal Filure in Adults

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ABSTRACT

Background: Heavy metals, such as cadmium, are heavy metals that are hazardous to health. Chronic exposure to cadmium is associated with decreased glomerular filtration rate and increased risk of chronic renal failure. This study was conducted to determine how much influence cadmium exposure has on the incidence of chronic kidney failure in adults. The purpose of this study was to analyze the effect of cadmium exposure on the incidence of chronic kidney failure in adults.
Subject and Method: This study is a systematic review and meta-analysis using the PRISMA flowchart with PICO as follows, Population: Adults. Intervention: Exposure to Cadmium. Comparison: No Cadmium Exposure. Outcome: Chronic Renal Failure. Search articles using several databases including PubMed, Google Scholar, and Science Direct with the search keywords "adults" AND "cadmium exposure" AND "chronic kidney failure". The articles submitted ranged from 2013 to 2021. Analysis was performed using RevMan 5.3 as a statistical program.
Results: There are 11 articles, originating from the continents of Asia and Europe. The results of the meta-analysis showed that exposure to cadmium increased the risk of developing chronic renal failure in adults by 2.81 times compared with adults who were not exposed to cadmium and was statistically significant (aOR = 2.81; 95% CI = 1.74 to 4.51; p < 0.001).
Conclusion: Cadmium exposure may increase the risk of chronic kidney failure in adults.
Keywords: cadmium, chronic renal failure, adults

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BACKGROUND

Heavy metals, such as cadmium and lead, are heavy metals that are hazardous to health. The maximum level of Cadmium (Cd) in the body determined by SNI 7387: 2009 is 0.1 mg/kg. Cadmium with low exposure can cause hepatotoxic effects, changes in blood sugar levels, complications of diabetes, chronic kidney disease, and changes in cell structure. On the other hand, high levels of cadmium can cause itai-itai disease. Renal tubular damage begins at urine cadmium concentrations ranging between 0.5 and 2 g urine Cd/g creatinine, and has effects on bone that show an increased risk of osteoporosis even at urinary cadmium below 1 g Cd/g creatinine. Chronic exposure to cadmium is associated with a decrease in the glomerular filtration rate (GFR) and an increased risk of chronic kidney disease (CKD). Cadmium exposure is associated with renal proximal tubular damage as demonstrated by high excretion of low molecular weight protein (Byber et al., 2015) and albuminuria (Grau-Perez et al., 2017) in urine (Zhu et al., 2019). Chronic kidney failure (CKD) is also a critical health problem. (Chen et al., 2021) reported that the prevalence of CKD was 10.8% in China in the 2007-2010 survey. A recent study showed that subjects with CKD (GFR <60 mL/min/ 1.73 m2) had higher blood or urine cadmium (BCd or UCd) than those with GFR >60 mL/ min/1.73 m2 (Jain, 2020).

A cross-sectional study involved 5,551 participants in the United States (US) in 2009-2010 and 3,689 in Korea in 2011-2012 with age 20 years. Blood cadmium (Cd) and lead (Pb) were measured using different methods by country, inductively coupled plasma mass spectrometry (ICP-MS) in the US and atomic furnace graphite absorption spectrometry (GF-AAS) in Korea. Associations between Cd, Pb and CKD were calculated as prevalence ratios (PR) per logarithm of g/L (Cd) or g/dL (Pb), using a modified Poisson regression model. In the United States, Cd was associated with CKD (PR = 1.12) and high ACR (PR = 1.18) while Pb was associated with low eGFR (PR = 1.31), all p<0.02. The results of this association were also similar in Korea (Hung et al. 2015).

Therefore, researchers are interested in examining the effect of cadmium exposure on the incidence of chronic kidney failure, especially in adults. Researchers used a systematic review approach to relevant studies by conducting a meta-analysis to clearly identify the magnitude of the effect of cadmium exposure on the incidence of chronic kidney failure in adults.

SUBJECT AND METHOD

1. Study Design

This research was conducted using a meta-analysis research design with PRISMA flow chart guidelines. Article searches were performed using the following databases: PubMed, Google Scholar and Science Direct. Some of the keywords used are “cadmium exposure” AND “chronic kidney disease” AND “adult” AND “adjusted odd ratio”.

2. Inclusion Criteria

The inclusion criteria for this research article were articles 2013-2021 using English, cohort study design, case control, and cross-sectional, adjusted Odds Ratio (aOR) relationship size, the subject of pregnant women taking folic acid with birth defects.

3. Exclusion Criteria

The exclusion criteria for this research article were the statistical results of bivariate analysis, and multivariate adjusted hazard ratio (aHR) and adjusted Relative Risk (aRR) as well as full paper articles before 2013.

4. Variable Operation Definition

The articles included in this study were PICO-adjusted. The search for articles was carried out taking into account the eligibility criteria determined using the following PICO model: Population= adults, Intervention= exposed to cadmium, Comparison= not exposed to cadmium, Outcome= chronic renal failure.

Cadmium is Cadmium (Cd) is a silver-white metal, soft, shiny, insoluble in bases, easy to react, and produces Cadmium Oxide when heated. Cd has atomic number 48, atomic weight 112.411, melting point 321^{o}C, boiling point 767^{o}C and has a density of 8.65 g/cm3.

Chronic kidney failure is a clinical symptom secondary to irreversible and chronic changes in kidney function or structure. The highest complications can cause death, especially in cardiovascular history. The diagnosis of chronic renal failure is based on chronic decline in kidney function and structural damage to the kidney. The best available indicator of overall kidney function is the glomerular filtration rate (GFR) which is equal to the total amount of fluid filtered through all functioning nephrons per unit of time.

5. Study Instrument

The results of the search for articles obtainned from the database have been identified, then each study was assessed based on the eligibility criteria. The quality and design of the research analyzed in the meta-analysis is very important because it affects the results. Assessment of study quality using the Critical Appraisal Checklist for Cross-Sectional Study, Critical Appraisal Skills Program for Cohort Study, and Critical Appraisal Checklist for Case-Control Study.

The 12 questions used in the checklist for the cross-sectional study are as follows:

1. Does this objective clearly address the research focus/problem?
2. Is the research method (research design) suitable to answer the research question?
3. Is the research subject selection method clearly written?
4. Does the sampling method give rise to bias (selection)?
5. Does the research sample taken represent the designated population?
6. Was the sample size based on pre-study considerations?
7. Was a satisfactory response achieved?
8. Are the research instruments valid and reliable?
9. Was statistical significance assessed?
10. Was a confidence interval given for the main outcome?
11. Are there any confounding factors that have not been taken into account?
12. Are the results applicable to your research?

The 11 questions used in the checklist for the Cohort study are as follows:

1. Does this research have a clear research focus?
2. Did the writer use an appropriate method to answer the question?
3. Is the cohort method applicable?
4. Is exposure accurately measured to minimize bias?
5. Were research results measured accurately to minimize bias?
6. Did the author identify all confounding factors? Have the authors taken into account confounding factors in the design and/or analysis?
7. Was the follow-up of the subjects of this study complete?
8. What are the results of this study?
9. Are the research results reliable?
10. Can the results of the study be applied to the local population?
11. Are the results of this study consistent with other studies?

The 11 questions used in the checklist for the case-control study are as follows:

1. Does the case control study clearly address the clinical problem?
2. Did the researcher use the correct method to answer the research question?
3. Was the case selected in the right way?
4. Were the controls selected the right way?
5. Is exposure accurately measured to minimize bias?
6. Did the researcher take into account the influence of all potential confounding factors in the study? Has the researcher controlled for the influence of all potential confounding factors in the design or analysis of the data?
7. How big is the effect of exposure?
8. How precise is the estimation of the exposure effect?
9. Are the results reliable?
10. Are the results applicable to the local (local) population?
11. Are the results of this study compatible with other available evidence?

6. Data Analysis

Research data were analyzed using the RevMan 5.3 application, to calculate the effect size and heterogeneity of the study. The results of data processing are presented in the form of forest plots and funnel plots.

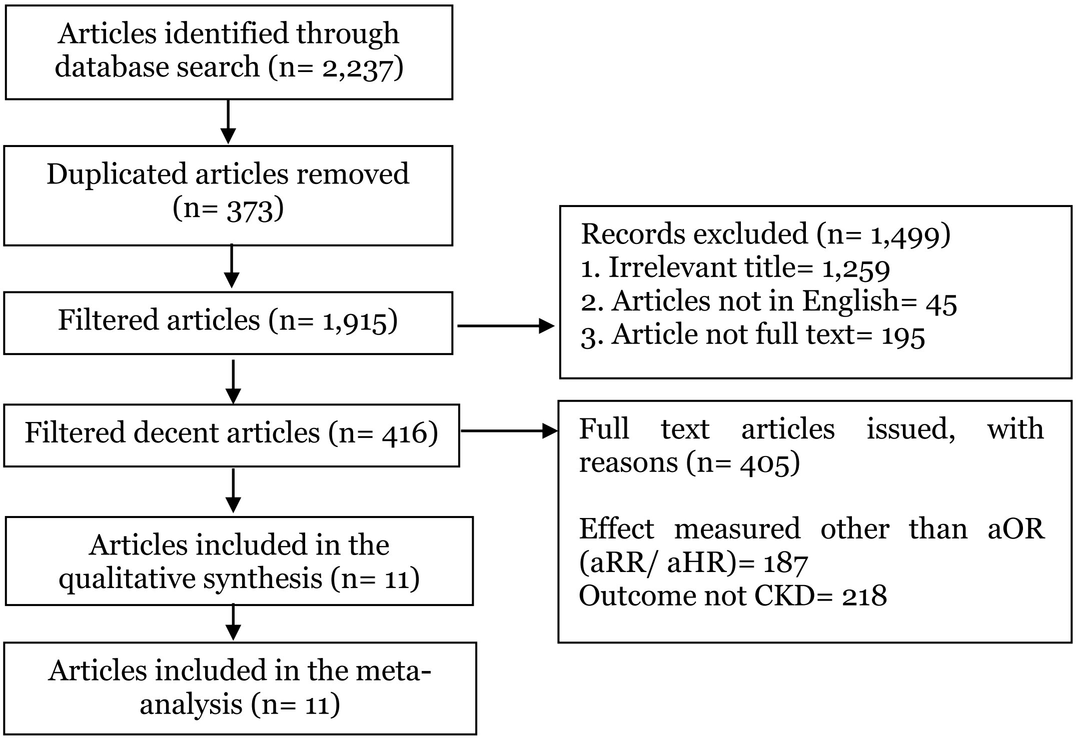

Figure 1. PRISMA Flowchart

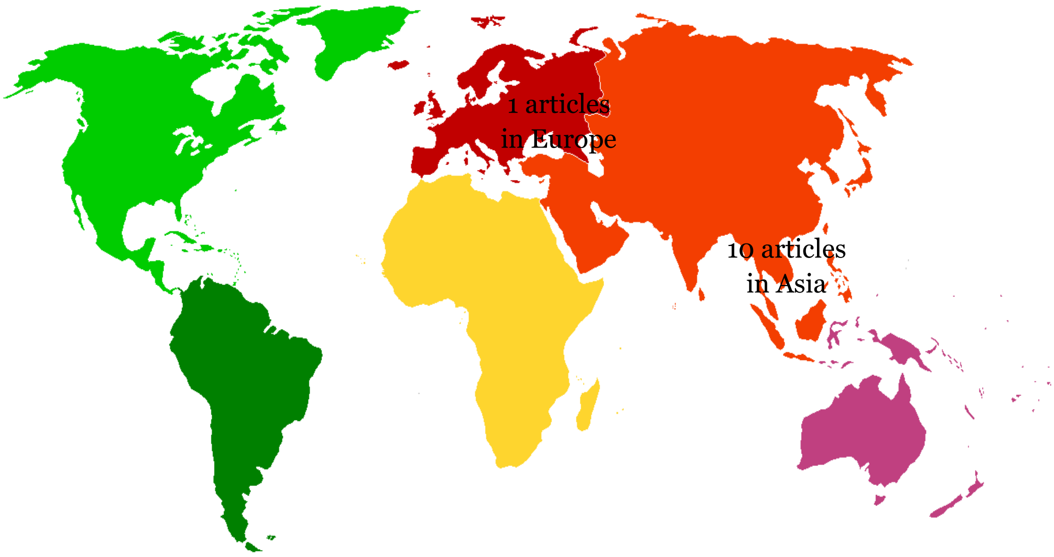

Figure 2. Map of Research Area

Table 1. Results of Quality Assessment of the Cohort Study of the Effect of Cadmium Exposure on Chronic Kidney Failure in Adults.

Primary Study	Criteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Wang et al. (2021)	1	1	1	1	1	1	1	1	1	1	1	1	12
Shi et al. (2018)	1	1	1	1	1	1	1	1	1	1	1	1	12
Satarug et al. (2018)	1	1	1	1	1	1	1	1	1	1	1	1	12
Sommar et al. (2013)	1	1	1	1	1	1	1	1	1	1	1	1	12

Note: Answer 1= Yes; Answer 0= No

Table 2. Results of Quality Assessment of Cross-Sectional Studies The Effect of Cadmium Exposure on Chronic Kidney Failure in Adults.

Studi Primer	Kriteria												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Tsai et al. (2021)	1	1	1	1	1	1	1	1	1	1	1	1	12
Madrim et al. (2021)	1	1	1	1	1	1	1	1	1	1	1	1	12
Kim et al. (2015)	1	1	1	1	1	1	1	1	1	1	1	1	12
Chung et al. (2013)	1	1	1	1	1	1	1	1	1	1	1	1	12

Note: Answer 1= Yes; Answer 0= No

Table 3. Results of Quality Assessment Case Control Studies The Effect of Cadmium Exposure on Chronic Kidney Failure in Adults.

Primary Study	Criteria											Total
	1	2	3	4	5	6	7	8	9	10	11	
Wu et al. (2019)	1	1	1	1	1	1	1	1	1	1	1	11
Anupama et al. (2019)	1	0	1	1	1	1	1	1	1	1	1	10
Hsueh et al. (2021)	1	1	1	1	1	1	1	1	1	1	1	11

Note: Answer 1= Yes; Answer 0= No

Table 4. Description of Primary Studies included in Meta-analysis

Author (Year)	Study Period	Country	Study Design	Sample Size	P Population	I Intervention	C Comparison	O Outcome	aOR (CI 95%)
Wang et al. (2021)	1998-2006	China	Cohort	467	Men and women over 25 years who consume rice irrigated by water from rivers in polluted areas	Exposure to cadmium metal in polluted areas	Exposure to cadmium metal in polluted areas	Chronic Kidney Failure	18.16 (1.75-188.85)
Shi et al. (2018)	1989-2011	China	Cohort	8429	Household members with dietary intake at the age of 45-54 years	Diet pattern and intake of cadmium	Not exposed to cadmium intake	Chronic Kidney Failure	4.05 (2.91-5.63)
Satarug et al. (2018)	2003-2006	Bangkok, Thailand	Cohort	395	Men and women aged 16-87 years living in cadmium polluted areas in Thailand	Exposure to cadmium metal in polluted areas	Exposure to cadmium metal in polluted areas	Chronic Kidney Failure	2.978 (1.066-8.317)
Sommar et al. (2013)	December 2006	Swedia	Cohort	465	Patients on the Swedish Renal Registry (SRR) with Chronic Renal Failure	The content of cadmium in the blood of living patients with a diagnosis of chronic kidney failure	Does not contain cadmium levels in the blood of patients with a diagnosis of chronic kidney failure	Chronic Kidney Failure	1.17 (0.99-1.38)
Tsai et al. (2021)	December 2020 – March 2021	Taipei, Taiwan	Cross-sectional	200	Adult patients with chronic renal failure stage 3a-5D and follow-up patients in the nephrology and hemo-dialysis department	Patients with a history of exposure to heavy metals, especially cadmium	The patient was not exposed to the heavy metal cadmium	Chronic Kidney Failure	30.3 (2.25-408.5)
Madrim et al. (2021)	April 2019 – December 2019	Kuala lumpur, Malaysia	Cross-sectional	240	Kepong resident 18 years old	Exposure to cadmium in the presence of cadmium-creatinine levels in the urine	Not exposed to cadmium in the absence of cadmium-creatinine in the urine	Chronic Kidney Failure	4.72 (2.33-9.59)

Author (Year)	Study Period	Country	Study Design	Sample Size	P Population	I Intervention	C Comparison	O Outcome	aOR (CI 95%)
Kim et al. (2015)	January 2011 – December 2011	Korea	Cross-sectional	1,797	Participants aged 20 years except pregnant women	Exposure to the heavy metal cadmium in the blood	Not exposed to heavy metal cadmium	Chronic Kidney Failure	1.09 (0.81-1.47)
Chung et al. (2013)	2007-2009	Korea	Cross-sectional	2,005	Participants aged 20 years and having blood cadmium and lead checked	Exposure to the heavy metal cad-mium in the blood	Not exposed to heavy metal cadmium	Chronic Kidney Failure	1.93 (1.39-2.67)
Wu et al. (2019)	2019	Taipei, Taiwan	Case-control	438	Men and women with a diagnosis of CKD Stage 3-5 in the last 3 months	Exposure to the heavy metal cadmium in the blood	Not exposed to heavy metal cadmium	Chronic Kidney Failure	4.31 (2.04-9.13)
Anupama et. al. (2019)	August 2015 – May 2016	Karnataka, South India	Case-control	69	Men and women aged 18 years, except pregnant women and aged > 75 years	Exposure to the heavy metal cadmium in the blood	Not exposed to heavy metal cadmium	Chronic Kidney Failure	0.16 (0.01-1.12)
Hsueh et al. (2021)	May 2018 – May 2019	Taipei, Taiwan	Case-control	220	Adult patient with nephrological complaints	Exposure to the heavy metal cadmium in the blood	Not exposed to heavy metal cadmium	Chronic Kidney Failure	6.48 (3.02-13.9)

RESULTS

The article review process using the PRISMA flowchart can be seen in Figure 1. The total articles obtained were 11 articles spread across 2 continents, namely Asia and Europe.

Tables 1, 2 and 3 show the assessment of the research quality of 11 articles using critical appraisal questions according to the study design.

Table 4 shows 11 articles on the effect of Cadmium Exposure on Chronic Kidney Failure in Adults that meet the qualitative and quantitative requirements.

a. Forest plot

The forest plot in Figure 3 shows that cadmium exposure in adults increased the risk of chronic renal failure by 2.81 times compared to those not exposed to cadmium and was statistically significant (aOR= 2.81; 95% CI= 1.74 to 4.51; p<0.0001) and the results were statistically significant. Significant. The heterogeneity of the research data showed I^2= 89% so that the distribution of the data was declared heterogeneous (random effect model).

With subgroup analysis, the cohort study design obtained statistical results (aOR= 2.96; 95% CI= 1.13 to 7.76; p= 0.03). These results were statistically significant, then for the case control study design the results were obtained (aOR = 3.41; 95% CI = 1.11 to 10.42; p = 0.03). the results were statistically significant. Cross-sectional study design obtained statistical results (aOR = 2.39; 95% CI = 1.17 to 4.88; p = 0.02).

b. Funnel plot

The funnel plot in Figure 4 shows a publication bias which is indicated by the asymmetry of the right and left plots where 7 plots are on the right and 4 plots are on the left. The plots on the right and on the left of the graph appear to have a standard error (SE) between 0 and 1.5. Bias also occurs from the imbalance in the distance between studies on both the right and left sides of the funnel plot.

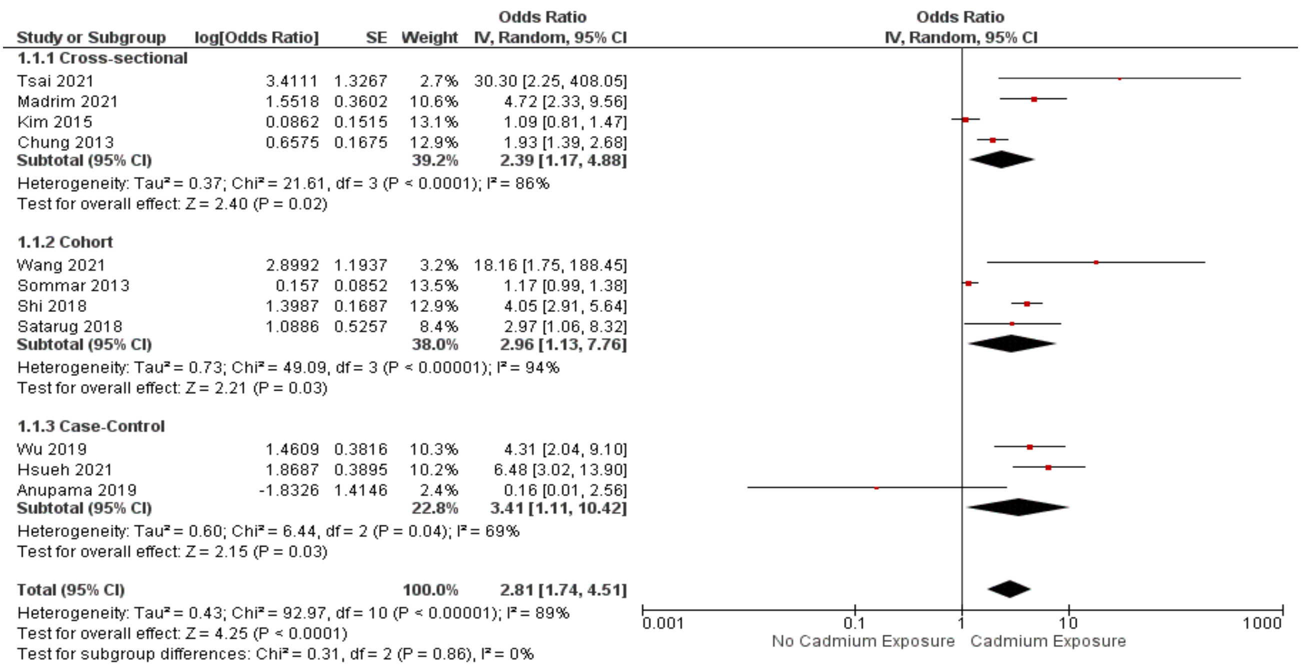

Figure 3. Forest plot of the effect of cadmium exposure on chronic renal failure in adults

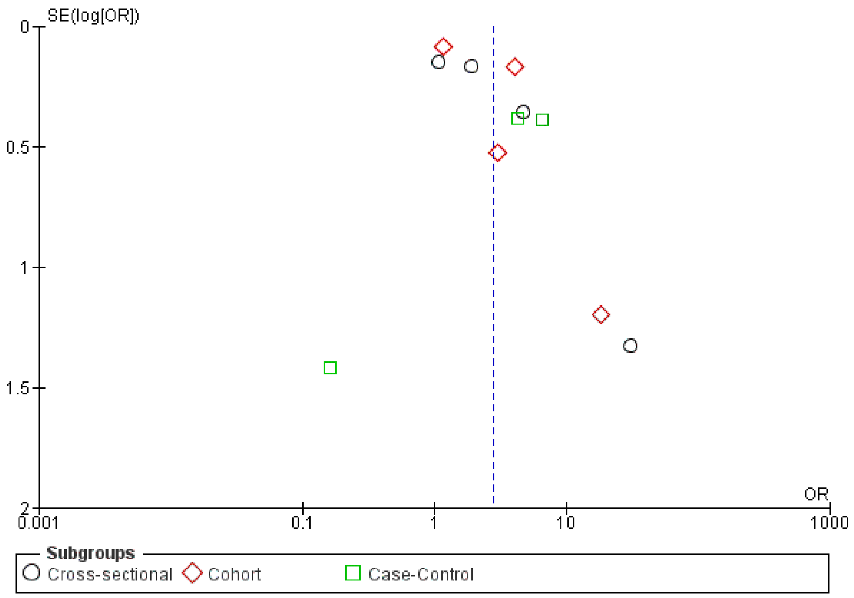

Figure 4. Funnel plot of the effect of cadmium exposure on chronic renal failure in adults

DISCUSSION

Research in Sweden suggests that half of the total cadmium content in the kidneys (10 g/g renal cortex) is obtained from consumption of contaminated food and half comes from cigarette smoke (Byber et al. 2015). According to Akerstrom et al. (2013), the content of cadmium in urine has a correlation with the content of cadmium in the blood. Increased content of cadmium in urine can be an indicator of the body as a cause of albuminuria or chronic kidney failure. The presence of cadmium in the body triggers a decrease in the glomerular filtration rate. In line with the research of Hellstrom et al. (2001), adjusting for age and sex gave an increase of 1.8 (RR = 1.8; 95% CI = 1.3 to 2.3) in the cadmium-exposed population compared to the group not exposed to the incidence of chronic renal failure.

In the study of Satarug et al. (2018) levels of cadmium in urine showed a correlation with a 2.98-fold greater chance of CKD prevalence (p=0.037). The research of Lyu et al. (2021), among the adult population in China aged 18 years and over, cadmium exposure was positively associated with the risk of chronic kidney disease. After adjusting for confounding factors, the results of the logistic regression showed that the lowest quartile (Q1) was compared with the odds ratio (OR) of the highest quartile (Q5) of blood cadmium (aOR = 1.80; 95% CI = 1.02 to 3.20), urinary cadmium (aOR) = 1.77; 95% CI = 0.94 to 3.31) and creatinine-adjusted urinary cadmium (aOR = 1.94; 95% CI = 1.11 to 3.37).

Several studies in Korea suggest that increased levels of cadmium in the blood are associated with a decrease in the glomerular filtration rate in women (Hwangbo, et al. 2011). In line with several similar studies in populations in the United States (Ferraro et al. 2010).

According to Dewi's research (2020), heavy metal particles of cadmium (Cd) can stick to the hands and then enter the body through the digestive tract. This research was conducted on people who still drink Musi River water every day. The interaction between a person's body or skin and Musi

River water allows respondents to be exposed to the heavy metal cadmium. The potential for cadmium to enter the bloodstream through the direct interaction of contaminated Musi river water. The concentration of cadmium in Musi River water was 0.003 mg/L in March 2018, 0.004 mg/L in September and 0.003 mg/L in November with a limit of 0.1 mg/L. According to Permenkes (2017), the maximum cadmium for sanitation hygiene is 0.005 mg/L. Low levels of cadmium in river water can also affect health if used for daily activities continuously.

Human cadmium exposure can be measured using biomarkers found in urine and blood. Cadmium in blood can indicate acute exposure, whereas cadmium in urine indicates total metal load. Acute exposure to cadmium through the respiratory tract 4-10 hours after exposure can cause symptoms such as dyspnea, cough, chest tightness, pulmonary edema, and so on. Meanwhile, chronic exposure can cause kidney problems, cardiovascular disorders and cancer (Mariadi et al., 2021).

AUTHOR CONTRIBUTION

Fathia Mutiara Zahra is the main researcher who chooses the topic, searches for and collects research data. Setyo Sri Raharjo and Bhisma Murti analyzed the data and examined research documents.

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This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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