Research

Heavy Metal Exposure and Renal Impairment: A Systematic Review of Observational Studies

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Abstract

Background: Environmental exposure to toxins has been strongly in its multi-faceted etiology of chronic kidney disease, a serious public health problem affecting individuals, families, and communities. There is a need to synthesize available studies on the effect of heavy metal exposure on renal function, considering the rising global burden of kidney disease. The objective of this study is to determine the association between exposure to heavy metals and renal disease.

Methods: The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) were used to conduct the review. A comprehensive independent search, title, abstract, and full-text screening of available literature on Google Scholar, PubMed, and OAREScience was done between March 2021 and May 2021. The criteria for study inclusion were full-text articles published in English language in the last 20 years (2001-2020), and observational primary human studies reporting the association between heavy metal exposure and renal disease. The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of the included studies.

Results: A total of 552 studies were identified following the search from the different databases. A total of 13 studies were finally included in the review. Heavy metals implicated in the studies include cadmium, lead, mercury, and arsenic, with ten studies showing environmental exposure as the primary source. Ten (10) studies showed an association between heavy metal exposure and renal impairment ($p<0.05$) while only 3 studies reported no association.

Conclusion: Environmental monitoring is needed to stem the tide of heavy metal exposure in view of the growing burden of chronic kidney disease.

Keywords: heavy metal exposure, kidney disease, renal impairment, observational study

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Introduction

Kidney disease has been labelled as one of the most neglected chronic diseases.[1] The risk of kidney disease cuts across persons of all ages and socio-economic status. Therefore, studies targeted at populations are required in order to correctly estimate the burden of kidney disease globally.[1] Several causes have been linked with the pathogenesis of kidney disease with diabetes and hypertension topping the list.[2]

The Global Burden of Disease (GBD) study published in 2023 stated that Chronic kidney disease (CKD) related deaths increased by 138% in 30 years.[3] In 2022, Chronic kidney disease (CKD), was described as one of the commonest chronic diseases, affecting more than 10% of the world's population.[4] with greater burden in low and middle-income countries.[5,6] Also, the number of patients with end-stage kidney disease who died without dialysis treatment was estimated to be between 2.3–7.1 million globally in 2015.[7] In addition, it is believed that annually on a global scale, acute kidney injury accounts for approximately 1.7 million deaths with a total estimate of 5-10 million deaths occurring yearly.[8]

Mitigation of exposures arising from the environment has been recognized as the link between Sustainable developmental goals (SDG) 3 and improved kidney health.[1] The Global Kidney Health Atlas identified a lack of renal-related epidemiological research as one of the gaps in kidney care.[9] Heavy metal exposure from environmental sources such as drinking water has been implicated in the occurrence of chronic kidney disease in various situations. This, in addition to renal complications arising from infections, is known to result in CKD.[10]

Impaired renal function is a precursor for chronic kidney disease which is a serious public health problem which in recent times, have left many households impoverished with an associated decrease in work productivity among those living with the disease.[11]. Renal disease, though known to have an established link with diabetes and hypertension, also has several causes, of which environmental factors have been strongly implicated in its multi-faceted etiology.[2]. The World Health Organization documented that early identification of risk factors can help to forestall the occurrence or slow the progression of acute or chronic kidney disease.[6]

Certain heavy metals have been linked with chronic renal impairment following exposure to environmental contamination of water bodies.[12] Rural communities in low and middle-income countries are disproportionately affected by the ecological and health impact of human activities which often are as a result of exploitation of the environment and with poor regulation.[13] Heavy metal pollution not only stem from occupational and environmental sources, but have been found to be associated with crude oil pollution.[14] The exploration and exploitation of crude oil in man's environment especially in the Niger Delta region of Nigeria dates back to the 1950s.[15] Crude oil is the chief source of energy and wealth for many oil-producing countries.[16] Also, a wide range of chemical products are derived from it and economies of many nations and global industrial developments also depend on its sale and exports.[17] Furthermore, despite the vast opportunities for harnessing and converting this natural resource into wealth in the oil-producing communities, particularly in Sub-Saharan Africa (SSA), the inhabitants are often exposed to environmental and health hazards associated with these oil-prospecting or oil-producing activities including heavy metal pollution.[18] With rapid urbanization and increased technological advancement, often associated with scaled up oil-prospecting activities which frequently takes place in rural settings where majority of the residents who live below poverty lines and fraught with limited basic social amenities in the presence of environmental pollution arising from these processes.[13] Also, the prevalence of non-infectious diseases such as diabetes and hypertension are on the increase in these poor communities, combined with exposure to environmental pollutants and toxins heralds an exponential growth in the global occurrence and development of renal disease.[6]

The kidneys are very vital in the sustenance of human life. Chronic Kidney disease is typically described by a gradual and permanent loss of the nephrons which is characterized by a decrease in the glomerular filtration rate (GFR). Heavy metals such as Arsenic (As), Lead (Pb), Mercury (Hg), and Cadmium (Cd) persists in the environment and are known to be nephrotoxins. It is documented that chronic, low dose exposure of heavy metals, particularly the metal mixture i.e. when more than one heavy metals are involved, is common.[19] The adverse effects are synergistic and can have deleterious effects on the kidneys.[20] The resultant effects include an increased in the heavy metal content of the body, changes in the cellular system of the kidneys, enlargement of the kidneys, deoxyribonucleic acid (DNA) and mitochondrial damage, and trigger of the oxidative stress mechanism, reducing the antioxidant capacity of the body.[19]

In recent times, man has frequently been exposed to heavy metals which are toxic in nature, from several environmental sources such as coal combustion, waste incineration and from natural crude and gas.[18,19,20] Mining wastes such as tailings and smelter slag also contain significant amounts of heavy metals which frequently lead to surface and ground water contamination.[21] Heavy metals that are usually part of

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the waste include cadmium, arsenic, lead, chromium, copper, nickel, and zinc. The wastes are normally dispersed over large plots of land and they constitute environmental and human health risks. The soil particles contaminated with heavy metals from these wastes, are usually dispersed by wind and rain currents from the source or area of pollution to non-contaminated surroundings.[22] Upon settling of the particles on the earth surface, the toxic metals may spread into the environment, seep into and may result in soil and water pollution.[23] These metals have been documented to be an important risk factor in certain disease etiology. Normally, essential minerals such as sodium (Na), potassium (K), magnesium (Mg) and calcium (Ca) are required in increased levels for metabolic and physiological functioning of the body. Also, trace minerals (manganese, iron, cobalt, copper and zinc) are needed in low levels as agents of metabolism and enzymatic body reactions and processes. However, heavy metals which are also toxic, even in trace amounts are hazardous to the human body.[24] There are no known function of these toxic heavy metals and their potential adverse effects could be acute or chronic poisoning.[22] Toxic amounts of these metals can lead to several illnesses such as central nervous system dysfunction, decreased energy levels, haematological, pulmonary, renal and hepatic disorders. Chronic exposure to these heavy metals may result in insidious onset of neurological, degenerative diseases such as multiple sclerosis, Parkinson's disease, Alzheimer's disease and muscular dystrophy. Cadmium and lead are capable of causing cancers and are the most toxic of the heavy metals. Potential sources via which humans are exposed to these heavy metals are mainly environmental in nature and they include oil pollution house paint, food and contaminated drinking water sources, mining, industrial and agricultural activities, and smoking.[12,25] Dental amalgam and second-hand smoking are other important sources of cadmium, lead and mercury. [12, 14, 20] This review highlights the gaps in evidence reported on the association between heavy metal exposure and renal impairment. It identifies the different heavy metals that are implicated in the occurrence of renal disease in SSA. It also pools the evidence available on the different forms of renal impairment associated with heavy metal exposure. The objective of this review is to examine the association between heavy metal exposures and renal impairment.

Method

Eligibility Criteria: The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) was used as an inclusion guideline for the review.[26] Studies included in this review were human studies involving people of all ages that reported association between heavy metal exposure and renal disease. Study designs were descriptive and analytical studies involving human populations. Outcomes reported included different forms of renal dysfunction. Full-text articles published in English language in the last 20 years (2001-2020), and observational primary studies reporting the association between heavy metal exposure and renal disease were included in the review. Case reports, reviews, unpublished manuscripts and conference abstracts were excluded. Studies whose outcomes of interest were not measured or reported were also excluded.

Search Strategy: A comprehensive search on available literature on several databases such as Google Scholar, Pubmed, and OAREScience was done between March 2021 and May 2021. Researchfor life was the interface through which the OAREScience was searched. The search for each database and relevant literature were identified and exported into a reference manager. Electronic search strategy for the different databases using MeSH terms were used. The search strategy for PubMed was "(""heavy metal""[Title/Abstract] OR ""heavy metal poisoning""[MeSH Terms] OR ""mercury""[MeSH Terms] OR ""lead""[MeSH Terms] OR ""cadmium""[MeSH Terms] OR ""arsenic""[MeSH Terms]) AND (""pollution""[Title/Abstract] OR ""poisoning""[MeSH Terms] OR ""petroleum pollution""[MeSH Terms] OR ""air pollution""[MeSH Terms] OR ""water pollution""[MeSH Terms]) AND (""renal impairment""[Title/Abstract] OR ""renal insufficiency""[MeSH Terms] OR ""acute kidney injury""[MeSH Terms] OR ""renal insufficiency, chronic""[MeSH Terms] OR ""renal insufficiency, chronic""[MeSH Terms] OR ""acute kidney injury""[MeSH Terms] OR ""kidney failure, chronic""[MeSH Terms] OR ""renal insufficiency""[MeSH Terms] OR ""renal insufficiency""[MeSH Terms] OR ""acute kidney injury""[MeSH Terms])" The date of coverage for this search was from 2001 to 2020. The search strategy used for Google Scholar was ("heavy metal pollution" OR "cadmium" OR "lead" OR "mercury" OR "arsenic") AND ("renal impairment" OR "renal insufficiency" OR "kidney disease") The search strategy used to search on the OAREScience database was “heavy metal pollution OR cadmium OR lead OR mercury OR arsenic AND renal impairment OR renal insufficiency OR kidney disease” The search for OAREScience was limited to the field of medicine, public health and environmental sciences. The limits applied to all the search strategy were date and language restrictions based on the stated eligibility criteria. No restriction was applied to the location of the studies. Only original research articles published in English whose full texts were accessible were included.

Selection of Articles: The process of study selection also included screening of titles, abstracts and full texts. The titles, abstracts and full texts of available searched studies from the databases were screened based on the

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eligibility criteria. The selected full texts articles that met the eligibility criteria were saved in a folder and duplicate entries were manually removed. Studies that did not meet the screening or eligibility criteria were excluded from the review. The screening process was done independently by two authors (EI, KC). Conflicting opinions on the eligibility status of any of the selected articles was resolved by critical assessment of the article and reached consensus by the authors.

Data extraction and Synthesis: The relevant information from the included articles was extracted independently and subsequently reviewed by the authors. (EI, KC). Data extraction was done using a predesigned table which captured information on the first author's name, publication year, region and country where study was done, study population, methodological aspects of the study (study setting, design, sample size, technique, summary measures), heavy metal isolated, concentrations reported, source and method of assessment or analysis, reported outcome measures and methods of assessment etc. The outcome of interest of review of the included studies included all forms of renal impairment which included both acute and chronic kidney diseases. Early renal dysfunction was indicated by presence of renal biomarkers measured in urine. The summary tables of findings of included studies are shown in Table 1.

The results of included studies were pooled by narrative synthesis. Meta-analysis could not be used to summarize the review findings because of the inherent heterogeneity observed from the retrieved studies.

Risk of Bias Assessment/Grade of Evidence: The assessment of quality of the included studies was done using the Newcastle-Ottawa Quality Assessment Scale (adapted for cross sectional studies).[27] It is a star-scored scale containing 7 items within 3 main domains and has maximum score of 10. A study is considered "very good" quality or very low risk of bias if it has a score between 9-10, "good" quality/low risk of bias if it has a score between 7-8, "satisfactory" quality of 5-6 and unsatisfactory/high risk of bias if score is 0-4. The assessment for risk of bias was independently done by 2 authors and conflicting opinions were resolved by agreed consensus upon introduction of a third experienced expert. The domains were selection (with a maximum of 5 stars), comparability (maximum of 2 stars) and outcome (maximum of 3 stars). The items within the selection domain are representativeness of the sample, sample size, non-respondents, assessment of exposure (risk factor). Comparability among the outcome groups was within the comparability domain while assessment of outcome, and statistical test were within the outcome domain. The studies choose samples that are truly or somewhat representative of the average in the target population or not. Sample size selected by the study was justified and satisfactory or not. If the comparability between respondents and non-respondents' characteristics was established, and the response rate was satisfactory, 1 star was assigned. If the response rate is unsatisfactory, or no description of the response rate, none was assigned.

If the study applied validated measurement tool to ascertain the risk factors, two stars were assigned. Additionally, one star was assigned if the study applied a non-validated measurement tool which are available or described. The subjects in different outcome groups are comparable: the study controlled for the confounding factors or not. The study applied independent blind assessment, record linkage, self-report or no description. If it used independent blind assessment or record linkage, 2 stars were assigned. If it used self-report, one star was assigned.

If the statistical test used to analyze the data was clearly described and appropriate, and the measurement of the association was presented, including confidence intervals and probability level (i.e., p-value), one star was assigned.

Results

A total of 552 studies were identified following the search from the different databases. Ninety-nine (99) studies were produced from PubMed, 36 from Google Scholar and 417 from OAREScience. A total of 548 studies were subjected to title and abstract screening after removal of 4 duplicate studies. Five hundred and eight (508) studies were excluded after screening titles and abstracts. Forty (40) articles were retrieved and assessed for relevance and further evaluation. Sixteen (16) articles whose full texts were not available were excluded. A total of 24 full text articles were assessed for eligibility. Eleven (11) studies did not meet the eligibility criteria and so were excluded. Reasons for exclusion include 4 studies did not assess association between heavy metal and renal impairment, 4 did not measure the review's outcome of interest, 3 studies were either case reports or reviews. A total of 13 studies were finally included and used for the systematic review. This is shown in Figure 1[26]

Study Findings: All selected studies measured association between heavy metal exposure and various forms of renal impairment. The risk of bias assessment for all studies was low and the quality of the studies using the NOS assessment scale were mainly very good (10 studies) and good (3 studies). See table 3

Characteristics of Included Studies: All studies (13) involving 13,763 participants (Table 1) determine heavy metal exposure and renal impairment. Most of the studies (11) were done in adult population, 1 carried out in all ages, the other in adolescents and adults. The

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studies were done between 2002 and 2015 and cut across diverse continents such as Asia (8), Europe (3), America (1), and Africa (1). Most of the studies were community based (10) while 3 was occupationally related setting. Majority of the included studies (11) were cross-sectional studies, (1) cohort study and (1) case control study. Sources of heavy metal exposure were environmental (10 studies), while 3 were occupational exposure.

Four heavy metals (Cd, Pb, Hg, Ars) were analysed in the thirteen included studies (table 2). Five (5) studies measured only cadmium exposure and renal impairment, six studies assessed Cd/Pb co-exposure and renal impairment, three studies measured Cd/Pb/Ars co-exposure and renal impairment, one study examined Cd/Pb/Hg co-exposure and renal impairment. Also, one study assessed Hg and renal impairment as well as arsenic exposure and renal impairment. Samples used for heavy metal measurement in the included studies include only urine (6 studies), only blood (1 study), blood, urine, hair/nail (1 study), blood/urine (5 studies), environmental sample (drinking water)/urine (1 study).

Different terms used to describe renal impairment in the included studies were abnormal renal markers (2 studies), chronic kidney disease (5), early kidney damage (3), albuminuria/myoglobinuria (1 study), and renal impairment (2) Ten (10) studies showed a positive association between heavy metal exposure and renal impairment while only 3 studies reported a negative association.

Discussion

The findings from this review showed that cadmium, lead, mercury, and arsenic were the most implicated heavy metals linking with renal impairment. Also, majority of the studies showed that environmental exposure was the primary sources, and most studies reported a positive association between heavy metal exposure and renal impairment ($p<0.05$)

It is documented that kidney disease is a silent chronic illness with increasing prevalence globally.[140] Renal function can be categorized into normal, when the estimated glomerular filtration rate (eGFR) was ≥ 90 ml/min/1.73 m^2, mild: when GFR 60–89.9 ml/min/1.73 m2, moderate: 30–59.9ml/min/1.73 m^2. Moderate renal insufficiency is further categorized into G3a (eGFR 45–59.9 ml/min/1.73 m^2) and G3b (eGFR 30–44.9 ml/min/1.73 m^2)[41] and severe renal insufficiency: 15–29.9 ml/min/1.73 m^2, respectively [41,42] The case definition for Chronic Kidney Disease of unknown aetiology (CKDu) has been stated as persistent albumin in urine, i.e. albumin–creatinine ratio (ACR) ≥30 mg/g in an initial and repeat urine sample at the next visit, in patients who with no past history of glomerulonephritis, pyelonephritis, renal calculi or snake bite.[30]

The common nephrotoxic metals observed from this review include cadmium, lead, mercury and arsenic. Environmental heavy metals such as cadmium at elevated levels of exposures, have a toxic effect on the kidneys.[43] Nephrotoxicity and renal disease can be determined by evaluation of different biomarkers of renal function such as elevated albumin and protein in urine.[44,41] For instance, increased albuminuria, without a concomitant increase in renal proteins such as the low-molecular weight proteins in urine is indicative of early glomerular injury.[45] However, increase in low-molecular-weight proteins in urine such as beta 2-microglobulin, alpha 1-microglobulin, or retinol-binding protein, and renal tubular enzymes like N-acetyl- beta-D glucosaminidase (NAG) and alanine aminopeptidase (AAP) have been used as biomarkers of renal tubular damage following dysfunction to the absorptive capacity of the proteins by the renal tubules. The glomerular and tubular damage have been observed to occur when urinary cadmium concentrations is within the range 3.6 to 4.2 µg urinary cadmium/g creatinine and 3.7–6.3 µg urinary cadmium/g creatinine respectively.[45] The latter following cadmium exposure from occupational origin.[46,47]

Different authors have investigated renal disorders and kidney biomarkers following exposures of occupational and environmental origin.[30,37,20] Hambach and other Belgian researchers in a cross-sectional study measured the effect of co-exposure of lead on metallurgic refinery workers who had low blood levels of Cadmium.[28] They observed that lead potentiates the strength of association between Cadmium and renal biomarkers. This finding implies that multiple exposure to heavy metals can have synergistic adverse effects on renal function. However, the total population from where the sample was taken was not stated and so it is difficult to say if the sample size used in this study was adequate for the estimation of the study effect and therefore may have biased the study findings. This underlies the importance of policy formulation on workplace exposure to heavy metals and the need for routine and regular health screening. Similarly, another study in Japan on the association between urinary cadmium excretion and renal dysfunction found that urinary cadmium (U-Cd) excretion was significantly associated with renal impairment.[31] This implies that urinary Cd excretion which is a reflection of the Cd load in the body and a proxy measure of environmental Cd exposure correlates with increased prevalence of renal impairment.

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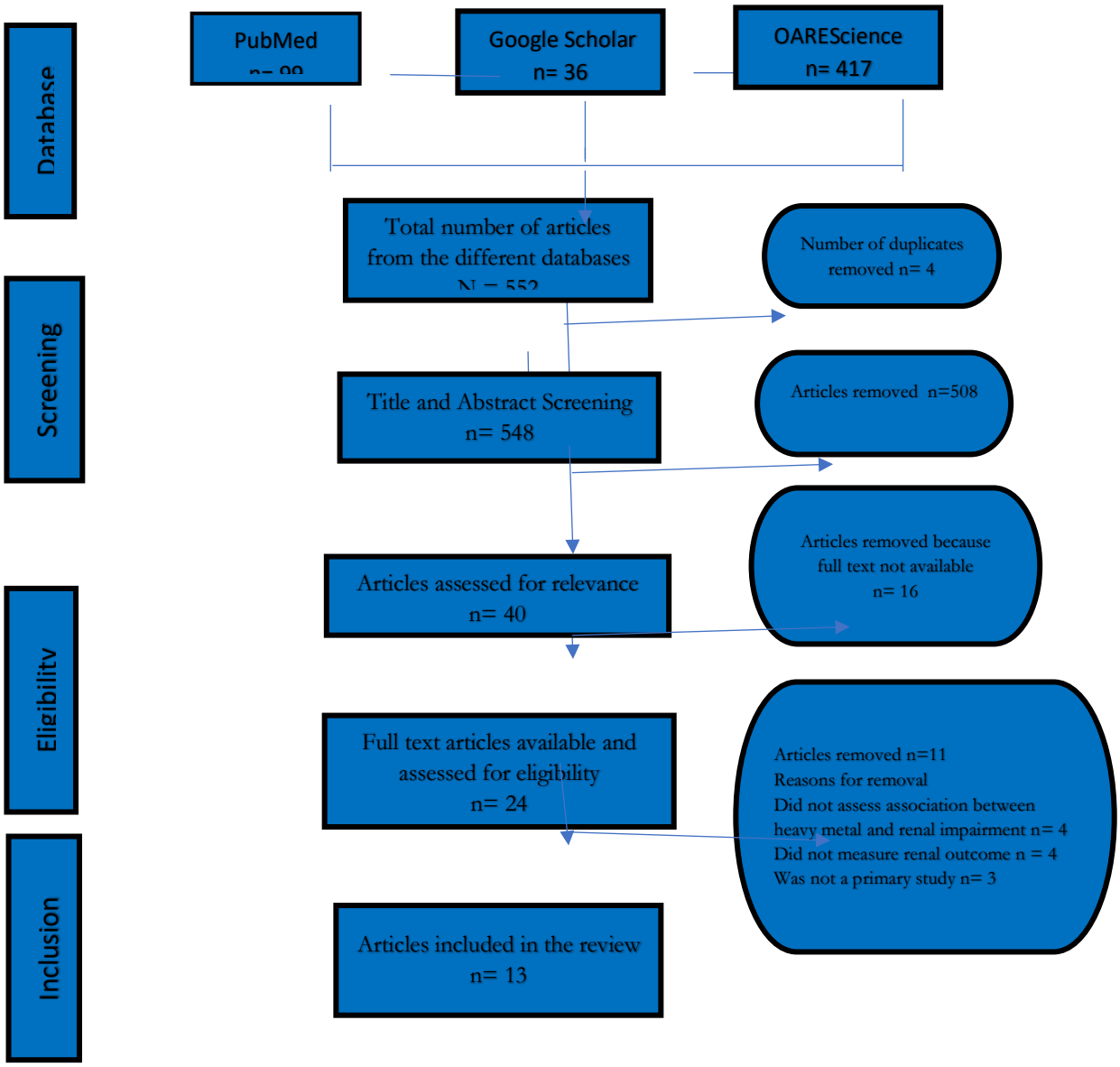

Figure 1: PRISMA flow diagram showing the study selection process

The higher the level of urinary Cd exposure, the higher the occurrence of renal impairment. Attempts should be made by environmental regulatory bodies to stem down heavy metal pollution from man's activities. Also Samir and Aref in Cairo, Egypt conducted a hospital-based cohort study among dental staff as exposed group and non-dental staff as control group to evaluate the occupational risk that may be associated with amalgam as a source of elemental mercury in dental practice.[32] They observed that mean levels of mercury were found to be significantly higher in the exposed group compared to the unexposed group. ($p < 0.001$); In the same vein, indicators of abnormal renal function were significantly higher in the exposed dental staff compared to the control group ($p < 0.001$). This study implies that occupational exposure with mercury as found in this study is positively associated with impaired renal function. Therefore, there should be a safe handling of amalgam during the training and practice of dentists and their assistants to reduce the risk of CKD from heavy metal exposure. Also, there should be routine evaluation of occupationally exposed persons for possible heavy metal exposure.

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Table 1: Summary of data extraction from selected studies

Region/Country	Study setting	Sample size/ Study population	Study design/Sampling method	Heavy metal implicated	Source of heavy metal	Hm assessment method	Renal outcome assessment method	References (Author/Year)
1.Europe/Belgium	Metallurgical refinery (occupational)	122 Company workers	Cross- sectional/ Purposive	Blood Cd Urine Pb	Occupational	Electrothermal (AAS) atomic absorption spectrometry	Not reported	Hambach et al 2013 [28]
2.Asia/Japan	Community based study	828 Adults residents 40-59yrs	Cross sectional/Stratified	Urine Cd	Environmental	U-Cd graphite-furnace AAS using a Hitachi Model Z-8100	Urine analysis of creatinine	Suwazono et al. 2012.[29]
3.Asia/Sri Lanka	Community based study	877 Adults males and females	Comparative cross-sectional/ Multistage	Urine Cd Ars Pb	Environmental	Inductive coupled plasma mass spectrometry (MS) /electrothermal AAS	Not reported	Jayatilake et al. 2013[30]
4.Asia/South Korea	Community	Adults>20yrs	Cross sectional/ Stratified systematic	Pb, Hg, Cd	Environmental	Graphite furnace atomic absorption spectrophotometry (GFAAS) using AAnalyst 600 (PerkinElmer, Turku, Finland) and blood Hg levels, gold-amalgamation process using DMA-80 (Milestone, Milano, Italy)	Urinary albumin (turbidimetric assay using a Hitachi Automatic Analyzer 7600 (Hitachi, Koka-city, Japan) and serum creatinine (enzymatic colorimetric method). eGFR (Modification of Diet In Renal Disease (MDRD) formula	Kim et al 2015[20]
5.Asia Japan	Community study	828 Adults 40- 59 years	Cross sectional/ Stratified sampling	Urine Cd	Environmental	Graphite-furnace AAS using a Hitachi Model Z-8100	Creatinine determined by the Jaffe reaction method	Uno et al 2005[31]
6.Africa/ Egypt	Hospital based study	69 (32 exposed, 37 control dental Staff	Cohort study	Urine Hg	Occupational	Cold vapor atomic absorption technique using mercury evaporation kit) and Absorption Cell-Standard spectrophotometer cells 10-cm long having quartz windows.	Quantitative analyses of proteins were performed using a Behring BN II nephelometer.	Samir and Aref, 2011.[32]
7.Asia/Sri lanka	Community based	134 Adults(>18yrs) and children(10-18yrs)	Comparative cross sectional/ Purposive for	As Cd Pb	Environmental /Drinking water	Inductively coupled	A semi-quantitative urinalysis (using Siemens microalbustix	Rango et al 2015,[33]

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			cases and random for controls			plasma–mass spectrometer (ICP–MS) calibrated using serial dilutions.	reagent strips) used to measure albumin and creatinine	
8.Europe/Bulgaria	Community base	201 adults 102/99 (cases/controls) offsprings of parents with BEN	Comparative cross-sectional/Purposive for exposure group and matched for control	U-Cd Pb-B U-Ars	Environmental	Perkin-Elmer AAS (Bodenseewerk Perkin-Elmer, Ueberlingen, Germany)	Total protein, albumin, urine creatinine, serum creatinine and serum urea were quantified with the photometric colorimetric optical system	Karmaus et al; 2008.[34]
9. Asia /Taiwan	Hospital based	354 Adults (125 cases /229 control)	Case control study/Consecutive recruitment of cases	Total Urine Ars:	Environmental	Inorganic arsenic and its metabolites were quantified by using hydride generator–AAS	creatinine levels (micrograms per gram of creatinine) by colorimetric assay automatically determined by the Roche Modular P800 instrument (Roche Inc, Mannheim, Germany).	Hsueh et al, 2009.[35]
10.Asia/Korea	Community survey	1909 Adults	Cross-sectional study/multistage sampling	Blood Cd Blood Pb	Environmental	Graphite furnace AAS (model SpectrAA-800, with Zeeman correction; Varian Instruments, Agilent Technologies, Mulgrave, Australia).	serum creatinine was measured with a kinetic Jaffé method using an auto-analyzer (model 747; Hitachi, Tokyo, Japan), then used the MDRD Study equation to estimate eGFR	Hwangbo et al, 2011.[36]
11. Avonmouth (southwest England)/Europe	Community survey	180 Adults	Comparative cross sectional/ Stratified	Urine Cd	Occupational exposure	Inductively coupled plasma mass spectrometry,	Fixed time incubation (uNAG)Enzyme linked Absorbent Assay (urinary RPB)Non-competitive immunoAssay (U-AIM)	Thomas et al., 2009[37]
12. North America /Pennsylvania	Community survey	361 persons (6months-75yrs)	Comparative cross sectional/ Random sampling	Urine Cd	Environmental	Graphite furnace atomic absorption spectrometry	AAP (automated Jung and Scholz Method;NAG(Leaback and Walker method); Albumin (Enzyme immunosorbent assay); β2-microglobulin (Pharmacia	Noonan et al,2002[38]

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13. Asia/ China	Community survey	6103 Adults	Comparative cross sectional/ Multi stage sampling	Urine Cd	Environmental	Graphite furnace atomic absorption spectrometry with peak area evaluation	Diagnostics Phadebas β2-Microglobulin Test Kits (Uppsala, Sweden) Radio-immunoassay (RIA) (Pharmacia β2-micro-RIA, Pharmacia Diagnostics AB, Sweden)	Ke et al, 2015[39]

Table 2: Association between heavy metal exposure and renal impairment

Region/Country	Heavy metal implicated	Reported Concentration	Outcome measure/parameters	Summary measures of Association	References (Author/Year)
1.Europe/Belgium	Cd Pb	0.1 µg/l for Cd and 1 µg/l for Pb	Abnormal renal biomarkers {Microalbumin (µ-Alb), beta-2-microglobulin (β2-MG), retinol binding protein (RBP), N-acetyl-β-d-glucosaminidase (NAG), intestinal alkaline phosphatase (IAP)}	Pb increases the impact of Cd exposure on early renal damage (Pb-B;Cd-B/NAG P=0.02: Pb-B ,Cd-B/ IAP p=0.01 (Pb-B;Cd-U/NAG P=0.001	Hambach et al 2013[28]
2.Asia/Japan	Cd	Geometric mean U-Cd (0.6-1.1µg/g creatinine, or 1.0-1.6µg/24h in men 1.5- 2.2µg/g creatinine or 1.4- 2.0µg/24h in women	Abnormal renal biomarkers {µ-Alb), β2-MG), (RBP), NAG), IAP), urinary creatinine}	Urinary cadmium (U-Cd) and markers of renal effects by gender and age were statistically significant p<0.05	Suwazono et al. 2012. [29]
3.Asia/Sri Lanka	Cd	1.039µg/g creatinine.	Chronic Kidney Disease (CKD) {Persistent albuminuria (ACR ≥30 mg/g in initial and repeat urine sample) and estimated glomerular filtration rate (eGFR)	Dose–response analysis showed that Cd exposure is a risk factor for the development of CKDu: P = 0.019 for stage 3 and P = 0.024 for stage 4.	Jayatilake et al. 2013[30]
4.Asia/South Korea	Pb Hg Cd	Mean blood Pb, 2.37±1.02 µg/dL Hg, 4.35±3.33 µg/L, Cd 1.17±0.68 µg/L	CKD {eGFR ((mL/min/1.73 m2) =175×SCr-1.154×age-0.203×0.742 (if female) ×1.21)}	No association detected between environmental heavy metal exposure and CKD in adults.Blood Pb (OR, 1.05; 95% CI, 0.85-1.30, P=0.644), Hg (OR, 1.02; 95% CI, 0.97-1.07, P=0.479), and Cd level (OR, 1.09; 95% CI, 0.81-1.47, P=0.577)	Kim et al 2015[20]

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5.Asia Japan	Cd	Urine Cd were 1.9 µg/g cr for men and 4.3 µg/g cr for women	Renal impairment {Protein, µg/l: β2-MG, U/l : NAG, µg/l and Creatinine g/l}	There is a significant association between urinary Cd excretion and renal impairment (ORs for Urinary Cd excretion were significantly > 1 for all the observed markers).	Uno et al 2005[31]
6.Africa/ Egypt	Hg	10.02 + 1.36 ug Hg/gm creatinine.	Abnormal renal function {Albuminuria and alpha-1 microgloblin}	Mean levels of Hg were found to be significantly higher in the exposed group compared to controls. (7.74+1.03 versus 4.79+0.84 mg/L)p<0.001 Iindicators of abnormal renal function were significantly higher in the exposed dental staff compared to controls. P<0.001	Samir and Aref, 2011.[32]
7.Asia/Sri lanka	Cd Ars Pb	As is 2.7-313 µg/L (mean: 39.5 ± 40.2);Cd below DL to 2.3 µg/L (mean: 0.49 ± 0.44) Pb below DL to 8.8 µg/L (mean: 1.4 ± 1.5)	CKD {Albumin and Creatinine}	The results suggest that CKDu cannot be clearly linked with the presence of Heavy metal contamination in drinking water	Rango et al 2015[33]
8.Europe/Bulgaria	Cd Ars Pb	Urine-Cd 0.6-0.7 µg/L Urine-Ars 2.9-3.1 µg/L Pb-B 85-90.9 µg/L	Renal impairment. {Total protein, albumin, urine creatinine, serum creatinine and serum urea}	Heavy metals (Cd,Ars,Pb) do not play a role in the etiology of Balkan Endemic Nephropathy	Karmaus et al; 2008.[34]
9. Asia /Taiwan	Ars	Total arsenic (ug/g creatinine). Cases :31.95 ± 2.59 Controls:2 0.71 ±1.10 P<0.001	CKD {eGFR for cases (28.4-1.41 mL/min/1.73m^2/ for controls 80.17-1.21mL/min/1.73m^2;p=0.001}	High urinary total arsenic level is associated positively with CKD	Hsueh et al, 2009.[35]
10.Asia/Korea	Cd Pb	Mean blood Cd: 1.57 µg/L in men and 1.49 µg/L in women mean blood Pb: 2.98 µg/dL in men and 2.31 µg/dL in women	CKD {eGFR}	High blood Cd was associated with lower eGFR in women and higher bld Cd level was associated with higher eGFR in men with high blood Pb levels	Hwangbo et al, 2011[36]
11. Europe / Southwest England	Cd	U-Cd 0.22 nmol/mmol creatinine (non-smoking 0.18/smoking 0.40) and 0.34 nmol/mmol creatinine (nonsmoking 0.31/smoking 0.46) in non- exposed and exposed men and women, respectively	Early renal damage {NAG (U-NAG), RBP (U-RBP), and A1M (U-A1M)}.	Higher urine Cd levels was associated with higher prevalence of uNAG, a biomarker for renal damage.	Thomas et al., 2009[37]

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12. North America /USA	Cd	0.23 µg/g creatinine	Early kidney damage {AAP, NAG, Albumin and β2-MG}	For children(6mo-17yrs) low levels of Cd exposure was not associated with evidence of renal damage whereas in adult it was associated with renal damage	Noonan et al,2002[38]
13. Asia/ China	Cd	Male(4.82 (0.08–56.99 (µg/g cr) All regions Female 4.87 (0.05–57.27 (µg/g cr)	Renal damage {Urinary β2-MG (Uβ2-MG) levels}	The BMD for Cd exposure in females were lower compared to that of males. Therefore females may be relatively more sensitive to Cd exposure than males	Ke et al, 2015[39]

Cadmium (Cd), Lead (Pb). Mercury (Hg), Arsenic (Ars), microgram/litre (ug/L), Blood lead (Pb-B), Urinary Cadmium (U-Cd), Urinary Arsenic (U-Ars), Microalbumin (µ-Alb), beta-2-microglobulin (β2-MG), retinol binding protein (RBP), N-acetyl-β-d-glucosaminidase (NAG), intestinal alkaline phosphatase (IAP), Urinary creatinine(U-Cr)

Table 3: Newcastle-Ottawa Quality Assessment Scale

		Selection				**Comparability**	**Outcome**		
Source	Title	Representative of the Sample [a]	Sample size [b]	Non-Respondents [c]	Ascertainment of the Exposure [d]	Subjects in different outcome groups are comparable [e]	Assessment of the Outcome [f]	Statistical test [g]	Quality [h]
Hambach, 2013.[28]	Co-exposure to lead increases the renal response to low levels of cadmium in metallurgy workers	*		*	*	**	**	*	Good
Suwazono et al. 2012[29]	Application of hybrid approach for estimating the benchmark dose of urinary cadmium for adverse renal effects in the general population of Japan	*		*	**	**	**	*	Very good
Jayatilake et al. 2013.[30]	Chronic kidney disease of uncertain aetiology: prevalence and causative factors in a developing country	*		*	**	**	**	*	Very good
Kim et al 2015. [20]	Environmental Heavy Metal Exposure and Chronic Kidney Disease in the General Population	*		*	**	**	**	*	very good

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Uno et al 2005. [31]	Health effects of cadmium exposure in the general environment in Japan with special reference to the lower limit of the benchmark dose as the threshold level of urinary cadmium	*	*	*	**	**	**	*	very good
Samir and Aref, 2011.[32]	Impact of occupational exposure to elemental mercury on some anti-oxidative enzymes among dental staff	*	*	*	**	**	**	*	very good
Rango et al 2015.[33]	Nephrotoxic Contaminants in Drinking Water and Urine, and Chronic Kidney Disease in Rural Sri Lanka			*	**	**	**	*	Very good
Karmaus et al; 2008.[34]	Metals and kidney markers in adult offspring of endemic nephropathy patients and controls: a two-year follow-up study	*			**	**	**	*	Good
Hsueh et al, 2009.[35]	Urinary Arsenic Species and CKD in a Taiwanese Population: A Case-Control Study	*		*	**	**	**	*	Very good

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Hwangbo et al, 2011.[36]	Blood Cadmium and Estimated Glomerular Filtration Rate in Korean Adults	*	*	*	**	**	**	*	Very good
Thomas et al., 2009.[37]	Early Kidney Damage in a Population Exposed to Cadmium and Other Heavy Metals	*			**	**	**	*	Good
Noonan et al,2002[38]	Effects of Exposure to Low Levels of Environmental Cadmium on Renal Biomarkers	*		*	**	**	**	*	Very good
Ke et al, 2015.[39]	Estimation of the benchmark dose of urinary cadmium as the reference level for renal dysfunction: a large sample study in five cadmium polluted areas in China	*		*	**	**	**	*	Very good

Quality: we assigned stars to evaluate study quality, with 9-10 stars indicating "very good" quality, 7-8 stars indicating "good' quality, 5-6 stars indicating "satisfactory" quality, and 0-4 stars indicating "unsatisfactory" quality.

From Table 3, the risk of bias assessment for all studies was low and the quality of the studies using the Newcastle-Ottawa Quality Assessment Scale were mainly very good (10 studies) and good (3 studies).

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From this review, most studies reported a positive association between heavy metal exposure and renal impairment ($p<0.05$) Jayatilake et al determined the risk factors and prevalence of chronic kidney disease among adult men and women in Sri Lanka.[30] The authors observed a positive association between chronic kidney disease of unknown aetiology and environmental cadmium through the food chain. ($p<0.05$). However, other infective causes of CKD such as HIV and glomerulonephritis were not properly excluded. Exclusion was based on the assumption that HIV was not prevalent in Sri Lanka and so blood HIV tests were not done. Also, glomerulonephritis was simply excluded by past medical history and renal biopsy was not done. These limitations may have biased the positive finding on the association of cadmium exposure from food sources and chronic kidney disease. Similarly, Suwazono et al in a community based cross-sectional study in Japan, reported the association between urinary Cadmium and markers of renal dysfunction among 828 adult men and women (410 men, 418 women).[29] The researchers observed that there was a statistically significant association between urinary cadmium (U-Cd) levels and biomarkers of renal function after controlling for confounders such as gender and age. ($p<0.05$). This connotes that the renal effect of Cadmium is not age or gender-dependent. Therefore, cadmium-renal damage can affect all persons irrespective of age or gender. Efforts should be made to ensure that people are protected from all forms of heavy metal exposure in the environment. In the same vein, Hsueh et al., carried out a case-control study in Taiwan to determine the association between urinary arsenic level and CKD among patients with CKD and those without CKD.[35] The researchers found out that chronic renal disease was significantly associated with total urinary arsenic level. Again, this implies that people with higher environmental arsenic exposure are at risk of developing chronic kidney disease. Though, a case-control study, sample size was small and this could influence the outcome of the study. It was also difficult to establish if CKD in these patients was as a result of arsenic exposure or that the CKD had already occurred resulting in impaired urinary excretion of arsenic. The implication of this finding lies in that prolonged environmental exposure to arsenic may lead to renal damage. This calls for regular environmental monitoring of heavy metals especially through the common routes of exposure such as water and food. Corroborating with the above studies is a cross-sectional study led by Hwangbo in Sri-Lanka which determined the association between blood cadmium and glomerular filtration rate (GFR) in a certain adult population.[36] The researchers observed a positive association between elevated blood cadmium levels and lower eGFR in women, which supports the role of cadmium as a risk factor for chronic kidney disease. However, in men, higher blood Cd levels was associated with higher eGFR in men who had higher blood Pb levels but there was no association between higher blood Cd levels and lower eGFR in men with low blood Pb levels. The authors opined that the association between blood cadmium and eGFR was modified by blood lead levels in men (p-value = 0.048). This implies the possibility of gender effect on Cadmium toxicity in men, making women more at risk to cadmium toxicity than men. Similarly, Thomas et al., in South West London conducted a comparative cross-sectional study to determine the association between urine cadmium and early renal damage in a certain adult population who were stratified based on smoking status in order to control for its confounding effect.[37] They observed that higher urine Cd levels was associated with higher urinary biomarker (NAG) for renal damage. The findings of this study may have been influenced by their small sample size. This again supports the finding that cadmium exposure is a strong risk factor of renal damage. Additionally, a comparative cross-sectional study was carried out by Noonan et al., in the US among residents living in a community contaminated with heavy metals from past zinc smelting as exposed group and residents living in a community located about 10 miles from the defunct smelting facility as a comparison group.[38] They determined whether biologic measures of cadmium exposure were associated with biomarkers of early kidney damage. The authors observed that in children 6months-17 years, low urinary Cd exposure levels was not associated with evidence of renal damage (NAG, AAP and albumin) while in adults, low urinary Cd levels was associated with early kidney damage (increased NAG, AAP but not with Albumin) after controlling for possible confounders. This may imply that albuminuria may be a later finding in early kidney damage. It also implies that children exposed to low urinary Cd are protected from early kidney damage compared to adults who are similarly exposed. The findings of this study suggests that renal damage can still occur at low exposure levels of cadmium in adults. In agreement with the above findings, Shen Ke et al., conducted a study to estimate the benchmark dose of urinary cadmium as the reference level for renal dysfunction in five cadmium polluted areas in China.[39] They observed that the BMD for Cadmium exposure was slightly lower in females compared to males. This shows that females may be relatively more sensitive to Cd exposure than males. This implies that females may be prone to more renal damage compared to males when exposed to similar Cd levels.

In contrast, A South Korean cross-sectional study led by Kim aimed at measuring the association between environmental heavy metal exposure and CKD among adults (≥ 20 years).[20] They observed that after adjusting for the confounding effects of age, sex, BMI,

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smoking, hyperlipidemia, hypertension, diabetes, and other metals, there was no association between blood Pb, Cd level and CKD. This connotes that CKD has a multi-etiological mechanism in its pathogenesis. This could also mean that at lower or normal heavy metal concentrations in the presence of chronic health conditions such as hypertension, obesity and diabetes, CKD may be prevalent. Therefore, there is need for early detection and improved care and management of chronic medical conditions which are precursors for chronic kidney diseases irrespective of heavy metal exposure. Another discordant finding on the association between heavy metal exposure and renal impairment is a community survey done by Rango et al in Sri lanka.[33] They aimed to determine the relationship between CKD and heavy metal exposure from drinking water sources in the community. Urinary heavy metals among the controls (non-CKD cases) were significantly higher than that of the CKD cases. The authors reported that CKDu cannot be clearly linked with the presence of the heavy metals in drinking water sources. This implies that other environmental sources of heavy metal may be implicated in the pathogenesis of CKD in this study. However, urinary albumin and creatinine levels were higher among the cases compared to the controls. This implies that the renal function of the CKD cases could have been compromised. Also, in a comparative cross-sectional study by Karmaus et al in Bulgaria investigating the association between heavy metal exposure and Balkan Endemic Nephropathy (BEN) (a nephropathy with familial clustering commonly seen in Balkan countries.[34] The authors observed this association among children of parents with BEN as the exposed group and those whose parents did not have BEN as a control group. The study reported that heavy metals (Cd, Ars, Pb) did not play a role in the etiology of BEN. This implies that although some studies have reported a significant association between heavy metal exposure and renal impairment, this study shows that some other factors are more significant in the aetiology of renal impairment. In this study, the offspring of BEN patients were younger and degenerative kidney disorders often occur in older people. Hence, it is possible, that the researchers underestimated the effect of the metals.

Implications of the Study: Chronic kidney disease and its link with heavy metal exposure is a growing area of research that needs to be encouraged by relevant stakeholders.[48,49] More comprehensive and prospective studies on heavy metal exposure and kidney disease are needed in sub-Saharan Africa. This will help to establish the true burden of heavy metal-related CKDs in the continent. The findings from the studies can serve as an advocacy tool for a more coordinated action by relevant stakeholders in kidney care such as persons living with kidney disease, their clinicians, professional associations and policy makers. It is also important for clinicians who are involved in the care and management of patients who have kidney disease to have an increased level of suspicion and explore other possible risk factors for CKD such as environmental heavy metal exposure.[49,50] The findings from this review underscore the importance of policy formulation and implementation on workplace and environmental monitoring of exposure to heavy metals and the need for routine and regular health screening.

Limitations: A dearth of literature exists on the association between heavy metal exposure and renal impairment. Also included studies were cross-sectional in design and as such cause-effect relationship was difficult to establish. Although, the nature of the exposure and outcome of interest makes it appropriate for this kind of study to be observational because of the ethical issues that are involved in human exposure to toxicological substances.

Conclusion

The weight of evidence in this review showed a positive association between heavy metal exposure and renal impairment. Environmental sources were the major routes of heavy metal exposure. This underscores the importance of environmental pollution from crude oil and other pollutants which are significant sources of heavy metals in countries in Sub Saharan Africa. There was a dearth of these studies in Africa as majority of the studies were done in Asia. This highlights the need for more studies in Africa on the effect of heavy metal exposure on renal function, considering the burden of chronic kidney disease.

Declarations

Authors' contribution: EI conceptualized this study. EI and CK conducted the literature searches, collated articles and drafted this review. CT AND BO reviewed, edited, and contributed to the final version of the manuscript.

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