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Toxic metals and chronic kidney disease: A systematic review of recent literature

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Abstract

Purpose of Review—Arsenic (As), cadmium (Cd), and lead (Pb) are ubiquitous toxicants with evidence of adverse kidney impacts at high exposure levels. There is less evidence whether environmental exposure to As, Cd, or Pb plays a role in development of chronic kidney disease (CKD). We conducted a systematic review to summarize the recent epidemiologic literature examining the relationship between As, Cd, or Pb with CKD.

Recent Findings—We included peer-reviewed studies published in English between January 2013 and April 2018 for As and Cd, and all dates prior to April 2018 for Pb. We imposed temporality requirements for both the definition of CKD (as per NKF-KDOQI guidelines) and environmental exposures prior to disease diagnosis. Our assessment included cohort, case-control or cross-sectional study designs that satisfied 5 inclusion criteria. We included a total of 8 articles of which 3, 2, and 4 studies examined the effects of As, Cd, or Pb, respectively.

Summary—Studies of As exposure consistently reported negative impacts on CKD incidence; studies of Pb exposure were mixed. We found little evidence of effects of Cd exposure with CKD. Additional well-designed prospective cohort studies are needed and we present recommendations for future studies.

Keywords

arsenic; cadmium; lead; chronic kidney disease; glomerular filtration rate

Introduction

Arsenic (As), cadmium (Cd), and lead (Pb) are well-established nephrotoxicants (1–3). The relationship between toxic metal exposure and kidney damage was historically characterized in occupational populations with high exposures and in communities exposed to pockets of

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high levels of naturally-occurring environmental metals. However, it has not been established whether these metals cause Chronic Kidney Disease (CKD) at the relatively low environmental exposure levels that are nearly ubiquitous in the global population today (4, 5). The global prevalence of CKD is approximately 11–13%, and according to the Global Burden of Disease Study, is the 12th most common cause of death worldwide (6). Whether low to moderate chronic metal exposures contribute to CKD is a critical public health concern particularly because CKD is a progressive, irreversible disease and environmental risk factors present potential opportunities for interventions in exposure reduction and disease prevention (3, 7, 8).

CKD is a clinical diagnosis, most recently defined according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline (9) as kidney damage (pathologic abnormalities or markers in blood or urine tests) and decreased renal function (glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2) that is persistent for ≥ 3 months. CKD is classified into 5 general stages according to KDOQI guidelines by GFR thresholds, and each stage is subdivided into one of three degrees of damage (measured as proteinuria). Importantly for this review, the case definition of CKD includes a temporality requirement (a diagnosis established over 3 or more months) but it does not include any etiologic specifications. The most common causes of CKD globally are hypertension, hyperlipidemia, diabetes, glomerulonephritis and structural disease.

Chronic Kidney Disease of Unknown etiology (CKDu) has emerged in the medical and environmental health literature in the past 20 years and is generally used to describe a cohort with increased incidence of CKD not associated with known CKD risk factors (10). The case definition for CKDu is not always precisely stated; however, it is assumed to follow the same criteria as CKD diagnosis. CKDu is of particular joint interest to the environmental health and nephrology research communities because of the increased incidence in specific geographic areas and in populations without identified risk factors for CKD.

We conducted a systematic review of epidemiologic studies in an attempt to summarize the state of the science of potential associations of As, Cd, and Pb with CKD. We provide an updated summary of the rapidly growing As and Cd literature focused on CKD and extend the range of publication dates that were previously reviewed for CKD and As or Cd exposures (7, 8). Although some studies have examined CKD association with many different metals, we focus on As, Cd, and Pb, because they are globally pervasive metals that could produce nephrotoxic effects and because they represent the majority of published epidemiologic work on CKD and metals. We present conclusions based on this body of evidence and provide recommendations for future studies.

Methods

Literature Search

Evaluation of the existing epidemiological literature on As, Cd, and Pb and CKD revealed recent systematic reviews on Cd and CKD from 2016 (8), and As and CKD from 2014 (7). Our search aimed to extend those reviews with recent additions published during the past 5 years and to add any epidemiologic literature on Pb and CKD. We conducted searches via

PubMed with the following search criteria for CKD ((“Chronic Kidney Disease” OR “CKDu” OR “Chronic Kidney Insufficiency” [Mesh] OR “Kidney Failure, Chronic” [Mesh] OR “Renal Insufficiency, Chronic”[Mesh] OR “Glomerular Filtration Rate” [Mesh] OR “Proteinuria” [Mesh]) AND human NOT review) and for either As (“Arsenic” [Mesh] OR “Arsenicals” [Mesh]), Cd (“Cadmium” [Mesh]), or Pb (“Lead” [Mesh] OR “Lead Poisoning” [Mesh]). Search criteria for As and Cd and CKD included publication dates from Jan 01, 2013 to April 01, 2018. Search criteria for Pb had no date restriction.

Inclusion and exclusion criteria

Two authors (AS and EM) selected the eligible publications using predefined search criteria. Five criteria broadly defined eligibility: (1) The population was occupationally or environmentally exposed to As, Cd or Pb. (2) Eligible publications had a full report published in peer-reviewed journals. Proceedings, abstracts and non-peer-reviewed publications were not eligible. (3) The publications included measurements of As, Cd, or Pb exposure at the individual level (biological monitoring; personal sampling; measurements/estimates in food or drinking water) carried out at least once. Exposure temporality was important for inclusion in this review. We required that exposures were measured prior to outcome assessment OR, if measured concurrently, applied an exposure assessment method that reasonably reflected past exposures (household water or biomonitored hair, nail, or bone matrices). (4) Eligible studies considered the temporality of outcome measures and either enrolled participants with clinical CKD diagnosis (with diagnoses established over 3 or more months’ follow-up) or included a follow-up such that there were at least two measurements of the renal outcome over time. The specific timing interval of the prospective measurements was not considered an eligibility criterion but it was considered in the study appraisal. Both prospective and historical prospective cohort studies were eligible. Ecological studies were not eligible because individual exposure measurements are not available. Isolated cross-sectional studies were included if participants were selected based upon an established CKD diagnosis and the exposure assessment reflected past exposure. (5) The renal outcome determining eligibility for inclusion was CKD according to the CKD Work Group 2013; “abnormalities of kidney structure or function, present for ≥3 months, with implications for health” (9). Included measures of kidney function were GFR, estimated GFR (eGFR) and/or proteinuria. The approach chosen for assessing GFR (measured GFR (mGFR), eGFR, creatinine clearance), or the choice of the serum marker (creatinine, beta-2 microglobulin (B2MG), cystatin C or urea) was not an eligibility criterion but was considered in the study appraisal. Studies with inclusion of clinically diagnosed CKDu patients were included. Studies based on structural abnormalities or imaging were not included. Studies based exclusively on markers of tubular function such as tubular phosphate reabsorption, serum chloride, urinary B2MG or kidney injury molecule-1 (KIM1) were not eligible. Studies of ESRD incidence or hemodialysis initiation (as an indicator of CKD progression) were included, but studies in ESRD patients on hemodialysis were excluded.

All studies that met search criteria were reviewed in detail (Figure 1). Data were abstracted for summary tables, reported findings were reviewed, and studies were evaluated for quality and bias. We evaluated the quality of evidence from each individual study according to the criteria outlined in the PRISMA checklist (11). The bias of individual studies was assessed

based on study design and methodology. Sources of bias due to study design included small sample size, inability to establish temporality, inappropriate selection of controls, limited or unclear definition of CKD. Sources of bias due to statistical methodology included no adjustment for covariates, no correction for multiple comparisons, and selection of statistical test. The quality of the data was evaluated and summarized and further research needs were identified.

Results

We identified and summarized a total of 8 epidemiologic studies, of which 3, 2, and 4 examined As, Cd, or Pb and their association with CKD, respectively. One study examined more than one metal and its association with CKD (12). It should be noted that some studies also measured other metals such as mercury, but the published findings regarding additional toxicants with CKD or kidney function are not reported herein; we direct the reader to the original article for these details. All studies that met inclusion criteria were published in English. Seven studies were conducted in general populations and one in occupational populations. Two case-control studies were included whose exposure assessments reflected past exposure: hair and fingernail As (13), and tooth Pb (14).

Epidemiologic evidence for the association between arsenic exposure and CKD

We identified 3 studies that assessed the association between As exposure and CKD and met the search outlined above (13, 15, 16) (Table 1). Two studies were considered high quality with low bias and met temporality requirements with prospective design and outcome measure of CKD incidence (15, 16). One additional study measured associations between As and prevalent CKD and was considered to have high (13) bias due to cross-sectional design and lack of statistical adjustment for confounders. Exposure assessment methods for As varied between studies. Zheng *et al.* assessed exposure via total urinary As and metabolites (15), appropriately adjusted for urinary creatinine. Hsu *et al.* measured As exposure via well water sample at participants' homes, a measure that can be confounded by variation in the amount of water consumed or used for cooking at the individual level (16). Diyabalange *et al.* measured As exposure in hair and nails (13), which may better reflect a chronic exposure to inorganic As exposure yet can be susceptible to external contamination of the hair or nails (17, 18).

The two prospective cohort studies we identified that were considered high quality (15, 16). Hsu *et al.* studied 6,093 adults in Taiwan over the age of 40 at recruitment and demonstrated a positive dose-response association between home well water As and CKD incidence after an average 14-year follow-up was reported (16). Strengths of this study include the large sample size, standard ICD-9 codes for CKD diagnosis, prospective design, and adjustment for important covariates. Zheng *et al.* studied 3,119 American Indian adults and reported a positive association between total urinary As and CKD incidence after a mean follow-up of 7 years; comparing the 75^{th} to the 25^{th} percentile yielded a hazard ratio of 1.2 (95%CI: 1.0, 1.14). The hazard ratio for incident CKD was borderline significant for arsenic metabolites methylarsonic acid (MMA) (HR: 1.2, 95%CI: 1.0, 1.3), dimethylarsinic acid (DMA) (HR: 1.2, 95%CI: 1.0, 1.4), and arsenobetaine (HR: 1.1, 95%CI: 1.0, 1.2) but was not significant

for inorganic As (HR: 1.0, 95%CI: 0.9, 1.2) (15). The strengths of this study included a large population size, with 502 incident cases of CKD, and adjustment for important covariates; however incident CKD was defined by a single follow-up eGFR measurement ≤60 mL/min/1.73m^2 or presence of kidney transplant or dialysis at either follow-up visit, rather than by standard clinical definition.

One case-control study of As met inclusion criteria and had medium-high bias, and reported negative results. Participants included 79 biopsy-confirmed CKDu cases between the ages of 16 and 89 in Sri Lanka and 30 age-matched controls. The results showed significantly lower mean hair As in cases vs controls but no significant difference between nail As in cases and controls (13). Strengths of this study include well-described exposure assessment methods, but methodological limitations included a small number of local age-matched controls, lack of adjustment for important covariates, and unclear timing of exposure (nail and hair samples reflect past exposure but likely recent past and it is not certain when exposures occurred relative to disease development). In addition, the chemical analysis included 18 metals without any discussion of controlling for multiple comparisons.

Overall, our review of the recent literature on As and CKD found two high quality epidemiologic studies (15, 16) to add to the moderate strength of the literature as presented by Zheng *et al.* (7). One of these studies identified a positive association between As and CKD and the other reported a borderline significant association. Zheng *et al.*, reported in their 2014 review there was some evidence in support of an association between As and specific CKD outcomes including albuminuria and mortality, and noted that some of this evidence was from populations with high exposures from drinking water as well as populations with low exposures.

Epidemiologic evidence for the association between cadmium exposure and CKD

There were 2 studies that assessed the relationship between Cd exposure and CKD and met the search criteria above (12, 19) (Table 2). Both study designs were prospective and considered of high quality with low bias (12, 19). Cd exposure was assessed in blood samples (12) or with dietary estimates (19).

In a large, high quality prospective cohort of 74,307 adults 45–83 years of age in Sweden, dietary Cd levels were not associated with incidence of CKD after 13 years of follow-up in men or women (19) (Table 1). This study included the largest population size reviewed herein, with 852 incident CKD cases as defined by ICD10: N18, and sufficient adjustment for a number of covariates, however, the conclusions are limited to dietary Cd exposure which may not reliably predict biomarker levels of Cd (20, 21). Although biomonitoring of blood or urinary levels was not performed, the authors adjusted for smoking status which is critical since tobacco products are the major source of Cd among smokers (22). In a historical prospective case-control study of 118 incident ESRD cases and 378 sex and age-matched controls in Sweden, with increasing erythrocyte blood Cd levels there was an elevated but not significant odds (OR: 1.15, 95%CI: 0.99, 1.34) of developing ESRD (12). Strengths included prospective design, with banked samples from registries analyzed for Cd, moderate sample size (for cases), appropriate selection of controls, and adjustment for covariates.

Overall, while Cd exposure may contribute to CKD, data from prospective cohort studies are extremely limited. A number of large cross-sectional studies did not meet our inclusion criteria yet report mixed associations between Cd exposure and kidney function (23–34). In general, these studies coupled with the literature summarized above support the notion that there is a need for better-conducted prospective cohorts with respect to Cd exposure.

Epidemiologic evidence for the association between lead exposure and CKD

There were 4 studies that assessed the relationship between Pb exposure and CKD and met the search criteria in this study, published between 1989 and 2018 (12, 14, 35, 36) (Table 1). Three prospective studies were considered high quality; two studies were considered to have significant bias. The US Environmental Protection Agency and the World Health Organization's monitoring and action levels are published as blood lead level (BLL), and it is the most commonly used exposure biomarker in published studies. Three studies that met inclusion criteria assessed BLL or erythrocyte Pb (approximately 2x the levels in whole blood) and one study measured tooth and bone Pb. These measures, including tooth Pb and erythrocyte Pb, are difficult to compare directly with other measures due to complex toxicodynamics and issues of reproducibility (37). Bone Pb, measured by x-ray fluorescence is used to assess lifetime exposure, and is a well-validated measure.

A large cohort of Swedish workers with occupational exposure to Pb found no association between Pb exposure and end stage renal disease (ESRD) after 20-year follow-up (36). The population included 10,303 workers from a national occupational cohort, compared with an age, sex and calendar-period adjusted expected incidence based on data from the Swedish renal registry. The study had the advantage of a large sample size, long follow-up period, well-documented serial BLL measures, and reliable diagnosis of kidney disease. The median of the maximum BLL of the participants was 23.8 μg/dL, compared to an average of 1–2 μg/dL in the general Swedish population. They did not report association of Pb exposure with non-ESRD CKD risk. A smaller prospective case-control study in Sweden of 118 incident ESRD cases and 378 sex and age-matched controls, discussed above, reported a positive association between erythrocyte Pb and risk of ESRD (12). Strengths included prospective design, with banked samples from registries analyzed for Pb, moderate sample size (for cases), appropriate selection of controls, and adjustment for covariates. Next, a prospective case-control study in Taiwan of 121 patients with chronic renal insufficiency and without diabetes showed increased risk for progression of renal insufficiency with increased BLLs (35). Baseline body Pb burden and BLL were the most important risk factors to predict progression of renal insufficiency over 4 years. The dose-dependent result was adjusted for important confounders but the study was limited by a small sample size and the interpretation is limited to the progression of kidney disease and cannot be extrapolated to the development of chronic kidney disease.

One case-control study was included with positive results (14, 32, 33). A small case-control study in children measured Pb in deciduous teeth and blood, and reported a significant association between tooth Pb and CKD (14). Interpretation is limited by the small sample size of 22 CKD cases, of which 17 had congenital kidney disease, which likely has different etiology than incident CKD.

Overall, there was a paucity of high quality prospective data on the possible association between Pb exposure and CKD incidence. The two large prospective Swedish cohort studies we included reported conflicting findings on the association of Pb exposure with ESRD incidence, but did not examine CKD incidence. A third study reported a positive association between Pb exposure and progression of CKD, which may in fact point toward a second hit hypothesis but does not provide insight into the development of CKD.

Discussion

There is a small, growing body of literature examining the relationship between toxic metal exposure and CKD; however after assessment of the potential for bias there remains little high quality data on which to support a conclusion that exposure to Cd or Pb may cause CKD in the general population. The evidence that As is associated with CKD is moderately stronger. Our review found two high quality epidemiologic study showing a positive association between As and CKD to add to the moderate strength of the literature as reviewed by Zheng *et al.* (7). The evidence assessing association between Cd and CKD is weak and requires additional study. The published findings for Pb are mixed, and when taking into account the potential bias of each study and the strength of the conclusions that can be made from each of the studies, no conclusion on the association between Pb and CKD can be reached at this time. While there are a large number of descriptive and cross-sectional studies of exposures to As, Cd, and Pb and CKD that report mixed results, these study designs cannot be interpreted to draw conclusions about causation and were therefore not included in this review (23–34, 38–53). Below we provide recommendations for future studies.

Recommendations for Future Directions

There are considerable challenges in this field and many research gaps remain. The timing and magnitude of exposure for disease risk is not understood, yet the challenge of long-term prospective data collection is significant. Further challenges to harmonizing the data include selection of CKD outcome criteria and implementing appropriate statistical models and tests. While it may be difficult to systematically address all of these issues in studies on metals and CKD, the role of each should be taken into consideration when designing new prospective cohorts.

Timing and Serial Monitoring—Prospective studies including exposure measures prior to the development of CKD and serial assessments of kidney function are needed to better characterize the associations between metal exposures and CKD risk. Timing of outcome measures is always important in establishing causality, but in the case of CKD, which requires multiple measures of kidney function over time to establish a diagnosis, the problem is compounded. The inclusion criteria for this review was ≥ 2 kidney function measures. However, we recommend that prospective studies include baseline measures as well as ≥ 2 follow-up measures to establish CKD diagnosis. Many different factors including acute illness, dehydration, exertion, and medications can cause temporary increases in serum creatinine (and decrease in eGFR) that are reversible without permanent kidney damage. The

feasibility of such studies is a challenge as they can be very expensive, but without such design conclusions about the etiology of CKD are limited and cannot establish causation.

Ascertainment of exposure—Exposure assessment is difficult to compare across historical studies, as technological advances have changed practice over the years. Ongoing studies will ideally select biomarkers of exposure that best reflect the current state of technologic and mechanistic knowledge to provide reliable results. For example, As exposure assessment should include measurement of total As exposure, as well as speciated As. While blood and urine are routinely assessed as biomarkers of metal exposure, the development of more reliable longitudinal biomarkers of exposure is clearly needed since impaired renal function affects toxicant excretion. This is likely particularly true for As and Cd (46, 54–57). Moreover, newer biomarkers that reflect cumulative or historic exposure hold promise for studies of CKD, such as deciduous teeth that allow for more precise determination of historical exposure (58, 59). These markers of internal dose over time will represent a major shift in the ability assess exposures over time, but will require harmonization with other historical exposure assessment methods. Documentation and reporting of the reasons for the choice of biomarker, as well as of high standards of laboratory practice are important for ensuring high quality, low bias, and reproducibility of published studies.

Environmental exposures do not occur in isolation and certainly CKD is likely a result of multiple insults over time. In the field of environmental health, there is a growing interest in the exposome, the totality of human exposure throughout the lifespan. While this field is still relatively underdeveloped, newer untargeted assays can now screen for thousands of chemicals in a single biological sample. Understanding the complex milieu of environmental exposures measured by these assays is the great challenge of this next stage of environmental health research and holds the possibility of more complete understanding of disease risk in the real world. Rather than negating the need for further single-exposure studies, the promise of exposome research will depend on a foundation of high quality epidemiology. This is an exciting age of discovery in nephrology and advances in understanding both the primary and multiple contributing factors in disease development will lead to better interventions to reduce disease risk. Replication of studies in diverse populations, including CKDu cohorts and populations with exposure to naturally occurring As and Cd will add further dimensions to this growing body of research, with the goal of offering population-specific protective public health interventions.

CKD outcome definition—In addition to addressing concerns regarding limited sample size, appropriate selection of controls, and lack of detailed methods, there was considerable heterogeneity in reported CKD outcome definitions that precluded meta-analyses. Future studies will benefit from clearer and more consistent CKD outcome definitions. With the publication of the new KDOQI guidelines, this should streamline studies going forward, but comparison with older studies of CKD is difficult. In our group of 8 studies reviewed, each had a different method of CKD outcome definition. These ranged from ICD-9 or ICD-10 codes and clinical diagnosis by KDOQI guidelines to interview and medical record review.

While a uniform definition is not always possible, we recognize the importance of clear definitions for comparability and interpretation of results.

While debate remains whether CKDu and CKD represent the same disease processes, inclusion of CKDu in our review is important because at the time of this review, clinical diagnosis of CKDu is defined by the same laboratory criteria as CKD. There is a need for well-designed epidemiologic studies in different CKDu cohorts, the results of which will help define the risk factors for CKDu as well as help define the disease relative to CKD.

Selection of appropriate statistical tests and models—Our systematic search found some evidence of reporting bias in the overall body of literature. We identified a large number of descriptive studies that characterized exposure levels (environmentally or in biomonitored samples), but did not report tests for association. We speculate that this is due to multiple reasons, but reasons were not discussed in such papers. The studies may have been small and lacked power to test differences between groups, could have had null findings or critical methodological concerns as discussed above. Of studies that did meet inclusion criteria, over half were severely limited by small sample size (4 of the 8 studies included had sample sizes with fewer than 150 CKD cases). Particularly among the Cd and As literature, a number of studies could not be included in this review due to a lack of statistical tests for association (and thus did not meet our inclusion criteria). Additionally, as technology allows for detection of lager numbers of analytes, it is important to clearly define the statistical approach and to consider adjustments for multiple hypothesis testing in the settings of large numbers of possible predictors. Covariate adjustment is another critical issue, and careful consideration of the covariates used as well as the quality of the covariate measure is especially important. In addition to age, gender, smoking status and BMI, the most important clinical risk factors for development of CKD in US adults are hypertension, dyslipidemia and diabetes (60). We observed adjustment for hypertension in 4 of 8 studies, adjustment for dyslipidemia in one study and adjustment for diabetes status in only two studies.

None of the studies reviewed herein considered genetic (61) or medical history of early life risk factors related to CKD development (62). Despite evidence that the *in utero* environment, including shorter gestation or low birth weight, may program later-life renal disease (63, 64) and recent guidelines recommending special consideration of these factors (62), few environmental studies of CKD explicitly considered the potential effect of environmental nephrotoxic chemical exposure as a modifier of known risk factors. Similarly, genetic risk factors such as variants in apolipoprotein-L1 (APOL1) are important to consider (61). Future studies must design appropriate tools to assess whether susceptibility to environmental nephrotoxic exposures exists within these subpopulations and examine whether exposures modify the association between fetal growth/prematurity with CKD in populations.

Conclusions

This systematic review of the recent literature suggests evidence that As exposure may be associated with CKD, but additional well-designed prospective epidemiologic studies are

clearly needed. Studies of As exposure were mixed, but the highest quality studies reported negative impacts of As on kidney function and CKD incidence, in agreement with previous literature. Studies of Pb exposure were mixed. There does not appear to be strong unbiased evidence of a relationship between Cd and CKD. Despite evidence from descriptive studies that environmental and biomonitored Cd levels are elevated among some CKD populations, the epidemiologic findings are limited. Overall, these studies contribute to growing evidence that low-level exposure toxic metals may contribute to increased nephrotoxicity with far-reaching public health significance. Yet, further work in this area is needed and will have the potential to inform future public health policy for the protection of public health.

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Abbreviations:

As	Arsenic
BLL	Blood lead level
BMI	Body mass index
BP	Blood Pressure
Cd	Cadmium
eGFR	estimated Glomerular Filtration Rate
Pb	Lead
SBP	Systolic blood pressure
CKDu	Chronic Kidney Disease of Unknown etiology
ESRD	End Stage Renal Disease

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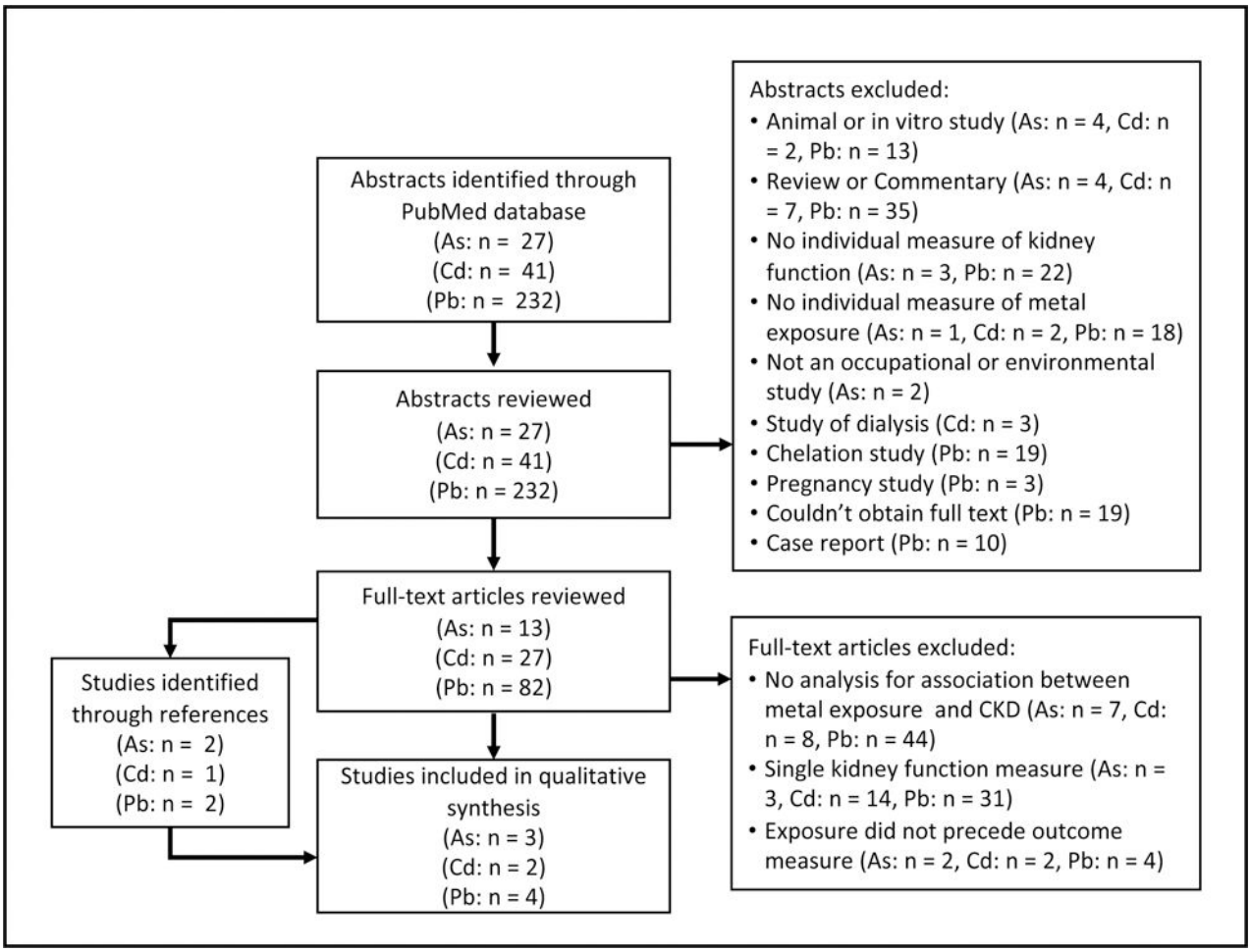

Fig. 1.
Flow diagram for studies of As, Cd, Pb assessed in this systematic review.

Table 1.

Epidemiological studies of arsenic, cadmium and lead exposure and CKD.

Authors & Year	Study design	Location	Sample size	Exposure Measure [Reported level]	Outcome Measure	Bias	Confounders	Major Finding
Arsenic and CKD Studies, 2013–2018								
Hsu *et al.* 2017 (16)	Prospective cohort	Taiwan	6,093 adults	Household well water As [3.5, 28.0, 92.8, 295.7, and 525.0 mg/L for the 25th, 50th, 75th, 90th, and 95th percentiles, respectively]	447 incident cases of CKD (ICD9 code: 585) over 14 years	Low - meets temporality requirement, covariate adjustment, large sample size, no internal biomarker of exposure	Age, sex, education, BMI, cigarette smoking, alcohol consumption, and analgesic use	Increased well water As associated with increased CKD incidence among adults HR 1.12 (95% CI, 0.88–1.42), 1.33 (95% CI, 1.03–1.72), and 1.33 (95% CI, 1.00–1.77) for water As concentrations of 10.1 to 49.9, 50.0 to 149.9, and ≥150.0 mg/L, respectively (P for trend = 0.02).
Zheng *et al.* 2015 (15)	Prospective cohort	USA	3119 adults ages 45–74 years	Total urinary As [median (IQR): 9.7 (5.8, 15.7) μg/L]	Incident CKD was defined as eGFR ≤ 60 or presence of kidney transplant or dialysis at either follow-up visits	Low - meets temporality requirement, large sample size, covariate adjustment	Age, sex, location, education, smoking status, BMI, hypertension medication, SBP, baseline eGFR, diabetes status and fasting glucose	Borderline, but not significant association of As with CKD (OR: 1.2 [1.0, 1.14])
Diyabalange *et al.* 2017 (13)	Case-control	Sri Lanka	76 adult cases ages 16–87 years, age matched controls	Hair As [mean: 0.037 μg/g cases, 0.054 μg/g controls]. Fingernail As [mean: 0.0.79 μg/g cases, 0.088 μg/g controls]	Biopsy proven CKDu cases	High - small sample size, no covariate adjustment, multiple hypothesis testing	None	Decreased mean hair As in CKDu cases compared to controls (p=0.039). No significant difference in fingernail As between cases and controls.
Cadmium and CKD Studies, 2013–2018								
Thomas *et al.* 2014 (19)	Prospective cohort	Sweden	74,307 adults 45–83 years	Dietary Cd assessed as baseline with FFQ [Mean: 13 μg/day among women; Mean: 19 μg/day among men]	852 incident cases of CKD (ICD10: $N18^2$) over 13 years	Low/Medium - meets temporality requirement, large sample size; no biomarker measured	BMI, HTN, smoking status, alcohol consumption, aspirin use, education, and dietary iron. Age standardized	Comparing highest to lowest tertile, increased dietary Cd, was not associated with CKD incidence among men HR 0.97 (0.77, 1.21) or among

Authors & Year	Study design	Location	Sample size	Exposure Measure [Reported level]	Outcome Measure	Bias	Confounders	Major Finding
							FFQ. Stratified by sex.	women 0.74 (0.53, 1.04).
Sommar *et al.* 2013 (12)	Historical prospective cohort	Sweden	118 CKD cases, 378 matched controls	Erythrocyte Cd and Pb (erythrocyte Pb levels are approx 2x Pb levels in whole blood). Cd: [geometric mean (GM): 66.2 μg/L among cases; 55.0 μg/L among controls] Pb: Erythrocyte Pb [geometric mean: 66.2 μg/L among cases; 55.0 μg/L among controls]	118 incident cases of ESRD, defined by enrollment in the Swedish Renal Registry (GFR <10–15 ml/min)	Medium - Meets temporality requirement, moderate sample size, covariate adjustment	Erythrocyte Pb and Hg, smoking, BMI, diabetes, and hypertension	Increased erythrocyte Cd (one IQR increase) was associated with an elevated but not significant odds of developing ESRD (OR: 1.15, 95%CI: 0.99,1.34). One μg/L increase in erythrocyte Cd was not significantly associated with odds of ESRD progression (OR: 1.11; 95%CI: 0.78, 1.57) Increased erythrocyte Pb (one IQR increase) was associated with an increased risk of developing ESRD (OR: 1.54; 95%CI: 1.18, 2.00)
Lead and CKD studies, 1980–2018								
Evans *et al.* 2017 (36)	Historical prospective cohort	Sweden	10,303 occupationally exposed adults	Blood Pb, max Pb achieved [median (IQR): 23.8 μg/dL (14.5–36.2 μg/dL)]	30 incident ESRD cases defined as start of dialysis or kidney transplantation	Low- Meets temporality requirement, large sample size	Age, sex and calendar year	No association between max achieved blood Pb and ESRD incidence: SIR was 0.79 (95%CI: 0.54, 1.13). Among those who achieved the highest blood Pb (>41.4 μg/dL), the SIR was 1.01 (95%CI: 0.44, 1.99).
Sommar *et al.* 2013 (12)	See above							
Yu *et al.* 2004 (35)	Prospective cohort	Taiwan	121 adults with chronic renal insufficiency (serum creatinine 1.5 mg/dL-3.9 mg/dL)	Blood Pb [mean: 4.2 ± 2.2 μg/dL] and body Pb burden by EDTA mobilization test [mean 99.1 ± 83.4 μg]	Increase in serum creatinine to double baseline value after 48 months or HD initiation	Medium - temporality requirement met, covariate adjustment; small sample size, no control group	Age, sex, BMI, hyperlipidemia, hypertension, smoking, ACE use, baseline serum creatinine	Each increase of 1 μg/dL in BLL reduced GFR by 4 (p=0.01) over 48 months.

Authors & Year	Study design	Location	Sample size	Exposure Measure [Reported level]	Outcome Measure	Bias	Confounders	Major Finding
Scharer *et al.* 1991 (14)	Case-control	Germany	22 children with chronic renal failure, 36 controls	Pb in deciduous teeth [mean: 2.81 μg/g in cases, 1.72 μg/g and 1.45 μg/g in control groups] Blood Pb [mean: 2.9 μg/dL in cases, 4.7 μg/dL in controls]	CKD cases (no case definition) vs controls	High – case-control design, small sample size, no covariate adjustment	None	Mean dental Pb was significantly ($p < 0.05$) higher in the patients (2.81 μg/g tooth, range 1.4–5.4) than in C1 (1.72 μg/g, range 1.1–2.5) and in C2 (1.45 μg/g, range 0.8–2.2) ($p<0.05$). No difference in blood Pb levels between cases and controls.