An updated systematic review on the association between Cd exposure, blood pressure and hypertension

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Abstract

\textbf{Background:} Since the first report by Perry et al. (1955), most studies affirmed the hypertensive effects of cadmium (Cd) in humans. Nonetheless, conclusions between studies remain inconsistent.

\textbf{Objective:} The aim of this study was to reevaluate the evidence for a potential relationship between Cd exposure and altered blood pressure and/or hypertension, focusing on studies published between January 2010 and March 2020.

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Declarations of Competing Interest

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

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2020.111636.
Methods: We reviewed all observational studies from database searches (PubMed and SCOPUS) on Cd exposure and blood pressure or hypertension. We extracted information from studies that provided sufficient data on population characteristics, smoking status, exposure, outcomes, and design.

Results: Thirty-eight studies met our inclusion criteria; of those, twenty-nine were cross sectional, three case control, five cohort and one interventional study. Blood or urinary Cd levels were the most commonly used biomarkers.

Conclusions: A positive association between blood Cd levels and blood pressure and/or hypertension was identified in numerous studies at different settings. Limited number of representative population-based studies of never-smokers was observed, which may have confounded our conclusions. The association between urinary Cd and blood pressure and/or hypertension remains uncertain due to conflicting results, including inverse relationships with lack of strong mechanistic support. We point to the urgent need for additional longitudinal studies to confirm our findings.

Keywords
Blood; Blood pressure; Cadmium; Hypertension; Smoking; Systematic review; Urine

1. Introduction
Cadmium (Cd) exposure has been associated with hypertension in humans and several animal models. However, the mechanisms by which Cd induces hypertension have yet to be completely elucidated. Several potential mechanisms include increased oxidative stress, disruption of calcium signaling, kidney damage, interference with the renin–angiotensin system, and dysfunction and impairment of the vascular endothelium (Biagioli et al., 2008; Choudhary and Bodakhe, 2016; Donpunha et al., 2011; Lemaire et al., 2020; Yoopan et al., 2008). However, taking into account that Cd exposures in experimental models are commonly higher than those encountered in real-life-scenarios, it remains unclear, if, and how these mechanisms might be translated to Cd-induced hypertension in humans.

Since 1955, when Perry et al. (1955) first reported on a plausible relationship between Cd exposure and hypertension in humans, numerous studies have addressed this possible association. However, notably in the early 1970s, analyses methods for Cd differed in various reports, and were largely semi-quantitative, constituting an additional factor in the observed differences in the Cd levels in hypertensive patients in that earlier studies (Nakagawa and Nishijo, 1996). The blood pressure response upon Cd exposure may also reflect other causative factors, such as Cd dose, biomarkers (urinary vs. blood Cd), and confounding effects of several factors on this association, including smoking habits, age, and renal tubular function, among others. All these factors might account for the inconsistent results obtained in the most recent studies, which have shown positive, null, or even inverse associations between urinary Cd exposure and blood pressure and/or hypertension (Franceschini et al., 2017; Noor et al., 2018; Park et al., 2017; Roels et al., 1990; Staessen et al., 2000).
Current smoking is the strongest contributor to elevated blood Cd levels (McKelvey et al., 2007), considering that Cd in cigarettes can be volatilized by high temperatures during the burning process, generating particulate matter that is readily inhaled and absorbed (Cuello-Nunez et al., 2018; Piade et al., 2015). Significant associations were noted between the daily number of smoked cigarettes and blood Cd levels (Martins et al., 2020). Furthermore, in cross-sectional data from NHANES (National Health and Nutrition Examination Survey), both mean blood and urine Cd levels were significantly higher in individuals who currently or previously smoked cigarettes as compared to never-smokers (Hecht et al., 2013).

In epidemiologic studies, blood and/or urinary Cd concentrations have served as the most common biomarkers of exposure and internal dose. However, Cd’s half-life differs between blood and urine (Jarup et al., 1998; Roels et al., 1999). Both biomarkers reflect cumulative Cd exposure, since urinary and blood Cd increase relative to the amount of Cd stored in the body, while blood Cd with a half-life of 3–4 months also reflects recent exposure (ATSDR, 2008; Jarup et al., 1998). Cd’s absorption route should also be considered, as inhaled, compared to ingested Cd, is absorbed at a greater proportion by the bloodstream (Jarup et al., 1998). Thus, urinary and blood Cd levels may provide discrete information regarding the timing and the source of Cd exposure among smokers and nonsmokers (Gallagher and Meliker, 2010). In addition, blood Cd concentrations showed a good correlation with urine Cd levels (Gil et al., 2011; Hecht et al., 2016; Sun et al., 2016).

The objective of this study was to reevaluate the evidence for potential relationship between Cd exposure and blood pressure and/or hypertension, and to identify persistent gaps in the literature germane to these associations, focusing on studies published between January 2010 and March 2020. Several reviews were published in this time period addressing the relationship between environmental Cd pollution and adverse health effect, including hypertension (Burroughs Pena and Rollins, 2017; Cosselman et al., 2015; da Cunha Martins et al., 2018; Ghio et al., 2018; Laranjeira et al., 2010; Shakir et al., 2017). In 2010, a systematic review and meta-analysis with a focus analogous to the present review was published (Gallagher and Meliker, 2010). Unlike the former, in our search, we included occupationally Cd-exposed populations as well additional biomarkers. Taken together, our study provides the latest and most comprehensive analysis on the associations between Cd and blood pressure status, and identifies research gaps that have yet to be addressed.

2. Methods

2.1. Search strategy and data abstraction

We aimed to identify observational studies assessing the association between Cd exposure and blood pressure or hypertension end points. Using free text and key words, we searched PubMed (https://www.ncbi.nlm.nih.gov/pubmed/advanced) and SCOPUS (https://www.scopus.com/search/form.uri?display=basic) databases (Appendix). Studies were limited to those published from January 2010 to March 2020 with no language restrictions.

For Cd exposure, we included studies that used blood Cd, urine Cd or other specimens as biomarkers, such as toe nail clippings and hair clippings. As measured endpoints, we
included blood systolic and/or diastolic blood pressure, and/or hypertension. The analyzed studies included primary data on Cd exposure and blood pressure and/or hypertension.

Exclusion criteria were publications containing no original research, studies carried out in species other than humans (experimental animal literature), case reports, case series, studies lacking blood pressure or hypertension outcomes, and studies lacking data on Cd exposure. For studies with multiple publications in the same population, the article with the largest number of cases or the most recent publication were selected. For studies with multiple levels of adjustment, we extracted the measure of association obtained from the model adjusted for the most covariates.

2.2. Statistical methods

Measures of association like odds ratios, hazard ratio, comparisons of means, among others, and their standard errors were abstracted from published data.

3. Results

3.1. Selected studies – general characteristics

This systematic review covers more than 160,000 participants from 12 countries, the majority of which were non-occupational populations, with only one study located where the subjects were occupationally exposed to Cd. For this reason, we have focused and discussed only on studies performed in the general population, that is, in subjects not exposed occupationally to Cd.

Fig. 1 shows a schematic depicting the study selection process. Electronic search results yielded a total of 348 studies. Of these, 38 met our inclusion criteria. Twenty-nine studies were cross sectional, three case control, five cohort and one interventional study. One of the studies could not be located online. Requests for a reprint were continuously made in the course of the last several months, but they were met with no response. Another study was excluded as it reported exceedingly high blood Cd values, compared to those reported in all other studies; after several attempts to contact the authors in the course of one month, we failed to get a response.

Of the selected studies, 17 analyzed blood Cd levels and 26 analyzed urinary Cd levels. Seven of the articles reported both blood and urine Cd levels. In two references, Cd levels were measured in scalp hair, and in one study in toenails clippings. In different matrices and populations, thirty studies showed some association between Cd exposure and blood pressure and/or hypertensive end-points (Table 1). However, this number included references that also reported on inverse associations, as well as inconsistent results within the same study, dependent upon the biomarker at hand (e.g. positive and inverse associations with blood and urinary Cd, respectively).

3.2. Blood Cd levels

Blood Cd levels were associated with higher blood pressure in the adult general population in four studies (Chen et al., 2015; Gao et al., 2018; Garner and Levallois, 2017; Lee and Kim, 2012) and with hypertension in five studies (Chen et al., 2013; Lee et al., 2011;
Madrigal et al., 2019; Moon, 2014; Myong et al., 2014). Associations between blood Cd levels and both blood pressure and hypertension in the general population were found in two studies (Lee et al., 2016; Wang and Wei, 2018). In contrast, no association between blood Cd levels and blood pressure and hypertension were found in three studies (Ahn et al., 2018a, 2018b; Boonprasert et al., 2011; Park et al., 2017).

3.3. Urine Cd levels

Eight studies reported an association between urine Cd levels and hypertension (Ikeda et al., 2013; Oliver-Williams et al., 2018; Swaddiwudhipong et al., 2012, 2010b, 2015b; Tangvarasittichai et al., 2015; Van Larebeke et al., 2015; Wu et al., 2019). Two other studies reported an association between urinary Cd levels and an increase in both systolic and diastolic blood pressure (Boonprasert et al., 2018; Franceschini et al., 2017). Urine Cd levels were associated with increase in both blood pressure and hypertension in one study (Wang and Wei, 2018). Associations were found between urine Cd levels and increased diastolic blood pressure (Gao et al., 2018; Huang et al., 2019), and with pregnancy-induced hypertension (Liu et al., 2018). In an adolescent sample, no significant association was found between urine Cd levels and systolic blood pressure (Castiello et al., 2020).

No association was found between urinary Cd and blood pressure in three of the selected articles (Boonprasert et al., 2011; Garner and Levallois, 2017; Shiue and Hristova, 2014), and no association with hypertension was reported in three studies (Boonprasert et al., 2011; Garner and Levallois, 2017; Swaddiwudhipong et al., 2010a). Two studies in children (Skroder et al., 2015; Swaddiwudhipong et al., 2015a) and two studies in adolescents (Ahn et al., 2018a, 2018b; Castiello et al., 2020) also failed to report on an association between urinary Cd and blood pressure.

Inverse associations were found between urine Cd levels and hypertension in four studies (Garner and Levallois, 2017; Noor et al., 2018; Vallee et al., 2020; Wu et al., 2018); the first of these studies found this inverse association in smokers only; and two articles (Gao et al., 2018; Osorio-Yanez et al., 2016) found an inverse relationship between urinary Cd and blood pressure.

3.4. Cd in scalp hair and nails

Afridi et al. (2010a, 2010b, 2011a, 2011b) reported that Cd levels in scalp hair were associated with hypertension. No association was found with blood pressure, where Cd concentration in toenail clippings was used as a biomarker (Mordukhovich et al., 2012).

4. Discussion

This timely review showed mixed results; several studies have found evidence for raised systolic blood pressure and/or diastolic blood pressure and/or hypertension, whereas other studies have found inverse, or no association. The associations varied by the marker of Cd levels (mainly blood vs. urine) and differed by subpopulations, considering sex, age and smoking status. Our findings highlight the urgent need for future studies to address the relationship between Cd exposure and blood pressure.
4.1. Strength of association, consistency, and temporality

In a large and cross-sectional study, positive associations were found between blood Cd levels with elevated blood pressure among never smoker women (Garner and Levallois, 2017). In another set of large and cross-sectional studies with smoking-adjustments, blood Cd was strongly associated with elevated blood pressure and/or risk of hypertension (Gao et al., 2018; Lee et al., 2011, 2016; Lee and Kim, 2012; Madrigal et al., 2019; Moon, 2014). Other large studies have found these associations with blood Cd only in women (Wang and Wei, 2018) or men (Myong et al., 2014). No such associations were found in two other large studies (Ahn et al., 2018a, 2018b; Park et al., 2017).

It follows, that a relationship between blood Cd levels and blood pressure and/or hypertension exists, irrespective of smoking adjustment or stratification methods. Our findings also showed that an association between blood Cd levels and blood pressure was observed in populations with different geographic, ethnic, and socioeconomic background. From a toxicokinetic point of view, both erythrocytes and metallothioneins in human blood accumulate circulatory Cd (Gibson et al., 2017; Rahman et al., 2017; Zalups and Ahmad, 2003), suggesting the suitability of whole blood as a biomarker to assess exposure. However, temporal interpretations were limited in scope, given that all the large studies performed with blood as a potential biomarker of Cd exposure, were of cross-sectional design. Furthermore, in several of these studies, the definition of hypertension was inconsistent. As noted in Table 1, most of the studies in the present review classified the participants as hypertensive, if they used antihypertensive medications and had elevated systolic and/or diastolic blood pressure. However, the use of antihypertensive medications as one of the criteria was not observed in six of these studies. In addition, only “history of hypertension” was considered in the classification of hypertension in four of these studies, and two of them failed to inform on which criteria were used.

While blood Cd is influenced to a greater extent by recent exposures, and systolic and diastolic blood pressure are concurrent measures, previous evidence suggests a relationship between blood Cd levels and short-term effects (Gallagher and Meliker, 2010). In the study by Gao et al. (2018), urinary Cd excretion decreased with declining renal function, however blood Cd levels did not change.

The value of urine as a Cd biomarker for the assessment of associations with blood pressure and hypertension was addressed in a comprehensive and cross-sectional study in never-smoker females, and in non-smokers in the population-at-large. Both studies reported increased prevalence of hypertension as urinary Cd levels increased (Swaddiwudhipong et al., 2010b; Wu et al., 2019). Analogous findings were reported among light- and never-smokers and blood pressure (Franceschini et al., 2017). In a case control study, this association was found in non-smokers, but not in smokers (Wu et al., 2019). In a large cohort of smoking-adjusted study, a positive relationship was found between urinary Cd levels and SBP and DBP (Oliver-Williams et al., 2018). The same relationship between urinary Cd levels and hypertension (Van Larebeke et al., 2015) and with pregnancy-induced hypertension (Liu et al., 2018), was found in both cross-sectional studies. A longitudinal decrease in urine Cd was documented upon decreased exposure to environmental sources with a significant decrease in DBP (Huang et al., 2019). No association between urinary Cd
levels and high blood pressure was found in one large and cross-sectional study (Shiue and Hristova, 2014).

However, the relationship between urinary Cd and blood pressure and hypertension remains uncertain. Several studies showed an inverse association between urinary Cd, a biomarker of long-term exposure, and hypertension (Gao et al., 2018; Garner and Levallois, 2017; Noor et al., 2018; Vallee et al., 2020; Wu et al., 2018). Inverse associations were found in a review performed with studies published through 2010, where an inverse association between urinary Cd and hypertension was also evident in both high- and low- Cd exposure populations (Gallagher and Meliker, 2010). A plausible hypothesis for the inverse associations noted in these studies may be the lack of consideration of renal function as an effect modifier on these associations, where urinary Cd excretion might be affected secondary to altered renal function (Gao et al., 2018). In agreement, a recent publication described a decline in glomerular filtration rate (GFR) upon low-level environmental exposure to Cd (Satarug et al., 2020), showing that the renal excretory capacity is impaired (Weaver et al., 2016). While kidney damage per se affects blood pressure (Roels et al., 1991), it may also be a consequence of hypertension, among many other factors (George et al., 2019).

Two of the studies used in the present review have adjusted the data for estimated glomerular filtration rate (eGFR) and found a positive relationship between urinary Cd and blood pressure (Franceschini et al., 2017; Oliver-Williams et al., 2018), the last one to report findings in light (mean 10.8 pack-years)- and never-smokers. However, inverse associations between urinary Cd and blood pressure were found in never-smokers in the studies by Noor et al. (2018) and Gao et al. (2018); in the latter study, this inverse association was modified in the stratified analysis by renal function. Other studies noted an inverse association between urinary Cd levels and blood pressure only among smokers (Garner and Levallois, 2017; Vallee et al., 2020). The latter study over-adjusted this relationship, including an indicator of chronic kidney disease in regression models, but this inclusion did not appear to significantly alter this relationship.

Still, another hypothesis for the inverse association with urine Cd levels advances the argument that urinary Cd levels reflect Cd concentrations that accumulate in the kidney with increased age, whereas blood Cd levels reflect recent, rather than chronic exposure (Jarup and Akesson, 2009; Nordberg et al., 2007). Accordingly, the positive association found with blood, but not urinary Cd levels, may be attributable to a short-term effect of Cd on blood pressure (Gallagher and Meliker, 2010). Again, this may indicate that blood pressure is affected by recent, rather than long-term Cd exposure; alternatively, it is possible that blood Cd reflects biologically active Cd to a greater extent than urinary Cd (Tellez-Plaza et al., 2008). Indeed, a positive association between blood pressure with blood Cd was found, but systolic blood pressure was inversely associated with urinary Cd levels (Gao et al., 2018). In another study, an association was found between blood Cd levels, but not urine Cd levels, and blood pressure (Tellez-Plaza et al., 2008). However, Akerstrom et al. (2013a, 2013b) noted that urine Cd concentrations reflect normal renal physiology, establishing an additional concern regarding urinary Cd as an appropriate biomarker.
The inconsistencies observed in the hypertension classification criteria discussed previously, are also inherent to the studies where urinary Cd levels were used as a biomarker of exposure.

The associations between Cd exposure and blood pressure and hypertension described in this review in non-smokers provide stronger evidence than the associations reported in smoking-adjusted studies, because instead of adjusting statistically, the effects of current and ever-smoking are absent in the former (Gallagher and Meliker, 2010). The influence of smoking on Cd levels both in blood and urine is well established (Eum et al., 2008; Hecht et al., 2013; Kim et al., 2019; Mansouri et al., 2020; Martins et al., 2020). Urinary Cd levels may be influenced to a greater extent by smoking duration, while in current smokers, blood Cd levels may be influenced to a greater extent by the smoking dose (Hecht et al., 2016). Despite the inverse association between urinary Cd and hypertension found in the total population, when the sample was stratified, smokers showed a positive association between urinary Cd levels and hypertension (Noor et al., 2018). In contrast, Tellez-Plaza et al. (2008) did not observe an association between urinary Cd levels and blood pressure, and when stratified by smoking status, blood Cd and blood pressure levels were stronger among never smokers, intermediate among former smokers, and small or null among current smokers. Explanations advanced by the same authors for these differences include markedly different sources, routes, and patterns of Cd exposure for smokers vs. nonsmokers, and co-exposures by smoking status, among others.

On the other hand, Hecht et al. (2013) advanced the hypothesis that Cd exposure may explain, at least in part, why smokers have increased risks of cardiovascular diseases. Being a component of cigarettes, and considering the propensity of Cd to persist in the vessel wall for decades, this metal may initiate endothelial damage, and perpetuate the proinflammatory and prothrombotic events necessary to accelerate the atherosclerotic process. In summary, smoking status is a strong confounding variable in the assessment of the relationship between exposure to Cd and blood pressure, and studies in non-smokers should be considered as more appropriate for deciphering this relationship.

In the present review, Cd levels in scalp hair were associated with hypertension (Afridi et al., 2011a, 2011b, 2010a, 2010b) same results were obtained when comparing normo- and hypertensive postmenopausal women (Gonzalez-Munoz et al., 2010). However, no correlations have been reported between hair Cd levels and blood pressure in non-smoking men (Hermann et al., 1989), neither in women with pre-eclampsia, compared to the normotensive women (Maduray et al., 2017). Collection of hair is noninvasive and allows for easy long-term storage; however, due to highly variable intra-hair growth rates and potential for external contamination (Slotnick and Nriagu, 2006), this matrix should be viewed with caution as predictive of Cd exposure. In addition, reference values for Cd in hair have shown a significant variation in a systematic review (Mikulewicz et al., 2013).

Toenail samples are also convenient for collection and storage, grow more slowly than hair, and are generally more protected from external contaminants (Mordukhovich et al., 2012). In the present review, no association was found between toenail clippings and blood pressure (Mordukhovich et al., 2012). Accordingly, no difference was obtained between Cd levels in
nails and blood pressure in the preeclampsia group compared to normotensive group (Soobramoney et al., 2019). Although toenails are validated biomarkers for arsenic, and are thought to reflect exposures that have occurred over the past 6–12 months (Slotnick and Nriagu, 2006), the validity of this biomarker for Cd exposure has been questioned, since Cd levels in toenails did not vary by smoking status (Mordukhovich et al., 2012), which is a major Cd source. Besides, no correlation with urinary Cd was found (White et al., 2018).

It is also important to consider that the study populations inherent to the various reports markedly differed with respect to age, ranging from children to elderly, in addition to Cd exposure levels, ranging from low to high, both in studies that used blood or urine as a biomarker. It is known that age is an important determinant in the prevalence of high blood pressure and hypertension; the increase in blood pressure with aging has been extensively documented in adults (Barba et al., 2008). However, this is not the case for children for whom the increase in blood pressure is predominantly related to excess body weight (Theodore et al., 2015). In our review, studies that were carried out in children (Skroder et al., 2015; Swaddiwudhipong et al., 2015a) and in adolescents (Ahn et al., 2018a, 2018b; Castiello et al., 2020), showed no association between Cd exposure and blood pressure. Cd exposure levels in the reviewed articles ranged from low (Ahn et al., 2018a, 2018b; Noor et al., 2018; Park et al., 2017; Shiuie and Hristova, 2014; Skroder et al., 2015) to high (Afridi et al., 2010a, 2010b; Chen et al., 2013; Swaddiwudhipong et al., 2010b), which may also affect the findings. These differences in Cd levels obtained in the different studies discussed in this review, may also be attributed to study location, as this would reflect differential diet, an important source of Cd in various populations (Martins et al., 2020). Cd has a high soil-to-root translocation and may be readily taken up by several cultivars (Wiseman et al., 2014).

It is also important to assess Cd exposure in light of exposure to other metals and/or metalloids, which may impact the results. Studies suggest that cumulative exposures to heavy metals as mixtures, including Cd, are associated with chronic conditions such as hypertension (Moon, 2014; Park et al., 2017; Wang et al., 2018). Considering the causal relationship between lead exposure with hypertension (Navas-Acien et al., 2007), adjustments for other covariates such as lead in blood or urine have been made in some studies in this review (Liu et al., 2018; Swaddiwudhipong et al., 2015a; Wang and Wei, 2018). Thus, the inconsistencies noted in the studies analyzed herein may, in part, also be attributed to exposures to mixtures containing other metals (or other xenobiotics), which might concomitantly affect the blood pressure.

A limited number of studies evaluated the role of genetic polymorphisms and susceptibility to Cd health effects. Findings from gene-Cd interaction analyses indicated that polymorphisms in metalloproteinase-2 (MMP-2) have modifying effects on the hypertensive effect of Cd, likely secondary to the former’s role in mediating biological processes such as inflammation and oxidative stress (Jacob-Ferreira et al., 2009; Wu et al., 2019). An additional study provided a potential mechanistic explanation for the association between polymorphisms in the SLC39A8 gene (encodes a transmembrane protein that acts as a transporter of several divalent cations) and Cd-induced increased blood pressure, which is likely mediated by increased intracellular Cd accumulation (Zhang et al., 2016a, 2016b). Polymorphisms in glutathione S-transferases, involved in biotransformation and
detoxification, were also associated with blood Cd levels, influencing individual susceptibility to Cd toxicity (Khansakorn et al., 2012). Therefore, the possible modifying effects of gene polymorphisms should also be considered in the context of exposure and Cd-induced alterations in blood pressure.

4.2. Dose-response, biologic plausibility and experimental data

Dose–response analyses of Cd levels in quartiles, or other comparisons, were not restricted to never-smokers, and therefore interpretations regarding Cd’s exposure–response effects independent of smoking are limited in scope.

Despite the inconsistencies in the reported findings, there are a number of mechanisms that may explain the relationship between Cd exposure and increased blood pressure. Both in vivo and in vitro studies provided evidence for Cd’s propensity to (1) adversely affect endothelial function, causing impaired nitric oxide bioavailability and increased vasoconstriction (Gokalp et al., 2009; Yoopan et al., 2008), (2) promote plaque inflammation and atherosclerosis, characterized by a dysfunctional interplay between the immune apparatus and lipids (Choi et al., 2020; Fagerberg et al., 2016; Lin et al., 2020; Stoll and Bendszus, 2006), (3) increase oxidative stress (Almenara et al., 2013; Donpunha et al., 2011; Ferramola et al., 2011) and inflammation (Angeli et al., 2013; Chen et al., 2016), (4) modify vascular responses to neurotransmitters (Angeli et al., 2013; Washington et al., 2006) and changes in calcium signaling (Biagioli et al., 2008), (5) interfere with the renin-angiotensin system (Choudhary and Bodakhe, 2016), and (6) alter renal function (Lemaire et al., 2020).

For the general population, the most frequently reported effect of Cd exposure is injury to tubular epithelial cells that actively reabsorb Cd from the glomerular filtrate (Satarug et al., 2017). Boonprasert et al. (2018) showed that exposure to Cd is a predictor of urinary 20-hydroxyeicosatetraenoic acid (20-HETE) levels; 20-HETE levels, in turn, are associated with increased odds of hypertension and tubular dysfunction. As noted above, renal function may modify the association between urinary Cd levels with blood pressure (Gao et al., 2018). Indeed, the effect of Cd on blood pressure has been reported to be markedly stronger with decreased kidney function (Eum et al., 2008). Again, being a component of cigarettes, smoking may initiate endothelial dysfunction (Hecht et al., 2013).

4.3. Limitations and strengths

Limitations inherent to this systematic review include the inconsistency in the definition of hypertension in the studies, and the cross-sectional design of most of the selected studies. Hence, we cannot rule out the possibility that the positive association observed between Cd exposure and hypertension reflects dietary or behavioral attitudes (e.g. exercise) due to the diagnosis of hypertension (i.e. reverse causation). In addition, as already discussed, substantial heterogeneity between studies might reflect outcome misclassification and measurement discrepancies. Furthermore, inadequate adjustment for confounders or sample size, may have resulted in over or under estimation of the true association between Cd exposure and hypertension. However, most of the studies included in this review have made adjustments for relevant confounding factors in addition to age and sex, such as smoking habits, body weight, and kidney function, among others, and they were performed with
diverse statistical methodologies. Finally, the included studies have been carried out in North American, European and Asian populations; the lack of studies from other regions, especially developing countries, represents a major gap in the literature. Relevant studies in these regions are timely and of research priority.

5. Conclusions and future needs

This timely review of the latest literature supports a positive relationship between blood Cd levels and blood pressure and/or hypertension, irrespective of smoking adjustment or stratification methods. However, considering the limited number of representative population-based studies of never-smokers and prospective cohorts, additional studies are needed to confirm these findings. Further research is also needed to establish dose–response gradients in never-smokers.

The association between urinary Cd and blood pressure and/or hypertension remains uncertain due to conflicting results. The inverse relationships between urine Cd and blood pressure reported in the present review lack strong mechanistic support, and should be further investigated as to establish the biological significance of urinary Cd levels as a biomarker of long-term Cd exposure in populations exposed to low-moderate Cd levels. These concerns are reinforced by the fact that urinary Cd concentrations may not take into account changes in renal physiology that are unaccounted for by Cd exposure, thus, overestimating the adverse effects of Cd on kidney function especially at low-level Cd exposures (Akerstrom et al., 2013a, 2013b). In summary, findings from the present review provide evidence that Cd exposure remains a risk factor for high blood pressure even at low exposure levels, having important implications for public health, and mandating further reduction in Cd exposure in the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Flow diagram of study selection process.
Table 1

Characteristics of epidemiological studies of cadmium (Cd) exposure included in the systematic review.

| Authors, date and country | Study design | Study population | Setting | Sample size or n° cases/noncases | Mean age/age range (years) | Male sex, n (%) | Hypertension definition | Outcome(s) | Adjustment variables | Cd exposure/Matrix | Cd concentration/matrix of association | Conclusions |
|--------------------------|--------------|------------------|---------|---------------------------------|---------------------------|----------------|------------------------|-------------|----------------------|------------------|------------------------------------------|-------------|
| Vallee et al., 2020       | Cross-sectional | General adult population | Cases: 659 Noncases: 1446 | 47.2 ± 14.6 | 44.9 | SBP/DBP ≥ 140/90 mmHg or use of antihypertension medication | Blood pressure, hypertension | Age, gender, smoking, antihypertensive drugs, BMI, alcohol consumption, Fruits and vegetables consumption, diabetes mellitus, hypercholesterolemia, CKD | Urine (μg/g creatinine) | Mean (SE): Cases: 0.42 (0.01) Noncases: 0.40 (0.01) OR 95% CI*: HPT: 0.91 (0.78–1.04) HPT among smokers: 0.78, (0.64–0.92) HPT among chronic kidney function: 0.68 (0.75–0.97) Comparison: Quartiles | No correlation between Cd, BP and hypertension was observed in overall population. In smokers, inverse association was found with hypertension |
| Castillejo et al., 2020   | Cohort        | Adolescents      | 133     | 15–17                           | 100 | SBP/DBP ≥ 2080 mmHg | Blood pressure and serum hormone levels | Urinary creatinine, age, serum triglycerides, HDL and LDL, BMI, and metals simultaneously | Urine (mg/g creatinine) | GM (range): 0.04 (0.01–0.55) OR 95% CI: SBP = 1.10 (0.74–1.55) DBP = 1.07 (0.82–1.07) Comparison: per each 5% increase in Cd concentrations | Urinary Cd was associated with slight elevations in SBP |
| Wu et al., 2019           | Case-control  | Chinese population | Cases: 497 Controls: 497 | Cases: 57.06 Controls = 56.33 | 56.2 | SBP/DBP ≥ 140/90 mmHg, or a diagnosis by a physician, or the current use of antihypertensive medication | Hypertension | Urinary creatinine, age, sex, BMI, smoking and drinking status, smoking pack-years, income and education | Urine (μg/L) | Median (25%-75%): Cases = 0.93 (0.51–1.64) Controls = 0.80 (0.44–1.35) OR (95% CI): Non-smokers 1.25 (1.09–1.43) Overall: 1.19 (1.06–1.33) Comparison: < 0.54 vs. > 1.07 | Urinary Cd were positively associated with hypertension risk |
| Authors, date and country | Study design | Study population | Hypertension definition | Outcome(s) | Adjustment variables | Cd exposure/measure of association | Conclusions |
|--------------------------|-------------|-----------------|------------------------|------------|---------------------|----------------------------------|-------------|
| Madrigal et al., 2019 United States | Cross-sectional | NHANES (2007–2012) | Cases: 5651 Noncases: 6926 | SBP/DBP ≥ 140/90 mmHg, or self-reported diagnosis by a physician, or antihypertensive medication use | Kidney function | Blood (μg/L) | GM (95% CI): Cases = 0.38 (0.37–0.39) Noncases = 0.34 (0.32–0.35) | Significant association between blood Cd levels and hypertension was found |
| Huang et al., 2019 China | Interventional | General population | Intervention group (a): consume of rice from non-polluted soil Non-intervention group (b): continue to consume rice from polluted soil control group (c): continued eating low-Cd rice they have been eating for years | SBP/DBP ≥ 140/90 mmHg, self-reported physician diagnosis or use of antihypertensive medication | Blood pressure, β2-microglobulin, N-acetyl-β-D-glucosaminidase | Urine (μg/g creatinine) | GM (SD): Intervention group = 1.46 (0.36) Non-intervention group = 1.76 (0.87) Control group = 1.42 (0.87) | Short-term changes in Cd exposure can positively impact blood pressure levels, especially DBP |
| Oliver-Williams et al., 2018 United States | Cohort | Strong Heart Study, American Indians communities | 2853: BP analyses 2865: hypertension (HPT) analyses | SBP/DBP ≥ 140/90 mmHg or antihypertension medication | Blood pressure, hypertension | Urine (μg/g creatinine) | Median (IQR) = 1.1 (0.7–1.6) BP: HR = 1.10 (1.01–1.20) HPT: HR = 1.17 (0.97–1.40) Comparison: One-unit increase in log-transformed urinary Cd was associated with 10% hypertension risk | Positive relationship was found between urinary Cd level and SBP and DBP, but not statistically significant with hypertension. |
| Noor et al., 2018 United States | Cross-sectional | General population NHANES (2001–2014). With and without metabolic Syndrome (MS) | Male: 1996 Female: 1985 | SBP/DBP ≥ 130/85 mmHg, or treatment for hypertension | Metabolic syndrome, hypertension | Urine (μg/L) | GM ±GSD: Men case (with MS): 0.29 (0.26–0.31) noncase (without MS): 0.22 (0.20–0.23) Women: case (with MS): 0.33 (0.30–0.32) | Among never smokers, an inverse association was observed between urinary Cd levels and hypertension. |
| Study design | Study population | Hypertension definition | Outcome(s) | Adjustment variables | Cd exposure/measure of association | Conclusions |
|--------------|------------------|-------------------------|------------|---------------------|----------------------------------|-------------|
| Cross-sectional | Residents in contaminated areas | Cases: 110 Noncases: 115 | 33–55 | SBP/DBP ≥ 140/90 mmHg, physician diagnosis or prescription of antihypertensive medications | 20-HETE levels, blood pressure | Age, BMI, blood pressure, biomarkers of kidney effects | AM±SD: Blood Case= 3.16 ± 2.6 Control= 4.06 ± 3.9 Urine: Case= 0.52 ± 0.39 Control= 0.64 ± 0.54 | Among current smokers, higher urinary Cd levels were associated with increased odds of hypertension |
| Cross-sectional | General population KNHANES 2010-2016 | 1776 | 10–18 | SBP/DBP ≥ 140/90 mmHg Prehypertension: DBP of at least 80 mmHg (but below 90 mmHg), or a SBP of at least 120 mmHg (but below 140 mmHg) | Hypertension, Prehypertension | Sex, age, residence area, smoking status, drinking status, BMI, year of measurement, physical activities, hemoglobin, and serum creatinine | GM (95% CI) = 0.317 (0.306–0.328) OR (95% CI): Female 0.223 vs. 0.471 Male 0.225 vs. 0.441 | In non-smokers, no association between urinary Cd and blood pressure was found. In smokers, moderate association was found |
| Cross-sectional | General population NHANES (1999–2010). | 9258 | ≥20 | SBP/DBP ≥ 140/90 mmHg Participants that intake antihypertensive medications were excluded. | Blood pressure, renal function | Sex, race, age, educational attainment, household income, alcohol drinking, BMI, total energy intake, or Smoking status. For urine was added: ever told had CVD | Blood (μg/L) Urine (μg/g creatinine) | Blood < 0.20, 0.20–0.38, 0.38–0.60, ≥0.60 (quartiles) Urine < 0.16, 0.16–0.29, 0.29–0.52, ≥0.52 (quartiles) | Both SBP and DBP were positively associated with blood Cd. DBP was positively associated to urinary Cd whereas SBP was inversely associated with urinary Cd among never smokers. |
| Authors, date and country | Study design | Study population | Hypertension definition | Outcome(s) | Adjustment variables | Cd exposure/measure of association | Conclusions |
|---------------------------|--------------|------------------|-------------------------|------------|---------------------|----------------------------------|-------------|
| Wang and Wei, 2018 United States | Cross-sectional | General population NHANES (1999–2014) | SBP/DBP ≥ 140/90 mmHg | Blood pressure, hypertension | Age, BMI category, educational, marital status, poverty index, alcohol consumption, smoking status and serum contents of sodium, potassium, calcium, creatinine, phosphorus, total protein, total cholesterol, glucose, and iron and blood concentration | Blood (μg/L) Urine (μg/L) | Cd exposure was associated with elevated blood pressure and hypertension in women |
| Wu et al., 2018 China | Case-control | Chinese population with and without hypertension | SBP/DBP ≥ 140/90 mmHg, use of antihypertensive medication | Hypertension | Gender, BMI, status of smoking and drinking, and levels of education and income | Urine (μg/g creatinine) | Urinary Cd levels were inversely associated with hypertension risk |
| Liu et al., 2018 China | Cross-sectional | Pregnant women with and without pregnancy-induced hypertension | 28.5 ± 3.7 | 0 | medical records | Urinary creatinine, age, pregnancy BMI, parity, annual household income, gestational weight gain, iron and | Urine (μg/g creatinine) | Urinary Cd levels were positively associated with PIH. |
| Authors, date and country | Study design | Study population | Hypertension definition | Outcome(s) | Adjustment variables | Cd exposure/measure of association | Conclusions |
|---------------------------|--------------|------------------|-------------------------|------------|---------------------|----------------------------------|-------------|
| An et al., 2017 South Korea | Cross-sectional | Workers in a copper smelter | Cases: 33 Noncases: 277 | SBP/DBP ≥ 140/90 mmHg or self-reported current use of antihypertensive medication | Blood pressure, age, body mass index, diabetes, alcohol drinking Habit, smoking status, exercise habit, and family history of hypertension | Blood (μg/L) | Associations were found between blood Cd levels and elevations in SBP and DBP. |
| Garner and Levallois, 2017 Canada | Cross-sectional | Canadian Health Measures Survey (CHMS), General population | Cases: 2898 Noncases: 7201 | SBP/DBP ≥ 140/90 mmHg, self-reported doctor-diagnosed high blood pressure or use of antihypertensive medications | Blood pressure, hypertension, age, sex, smoking status, antihypertensive medications, BMI, alcohol consumption status, diabetes, chronic kidney Disease, exposure to second hand smoke, Indicator(s) for CHMS cycle. | Blood (μg/L) Urine (μg/g creatinine) | Adjusted GM (SE) SBP/DBP Cases: 0.43 (0.02)/0.46 (0.03) Noncases: 0.41 (0.01)/0.40 (0.01) Hypertension Cases: 0.40 (0.01) Noncases: 0.40 (0.01) OR (95% CI) (smokers): 0.61 (0.44–0.85) Comparison: unit change in natural logarithm transformed blood/urine Cd | Associations between blood Cd levels and blood pressure were found. Negative associations were noted in smokers between urinary Cd and hypertension. Associations between blood Cd levels and hypertension were found among women, particularly among never smokers. |
| Park et al., 2017 United States | Cross-sectional | General population NHANES (2003–2004) | Cases: 3385 Noncases: 5790 | SBP/DBP ≥ 140/90 mmHg, physician diagnosis of hypertension, use of blood pressure, hypertension, gender, race/ethnicity, smoking status and education | Age, BMI, creatinine, smoking status and education | Blood (μg/L) Urine (μg/L) | GM (SD): blood = 0.37 (2.22) urine = 0.24 (2.77) OR (95% CI) (blood): 1.17 (0.79–1.74) | No association between blood Cd levels and blood pressure and hypertension was found. |
| Authors, date and country | Study design | Study population | Hypertension definition | Outcome(s) | Adjustment variables | Cd exposure/measure of association | Conclusions |
|--------------------------|--------------|------------------|-------------------------|------------|---------------------|-----------------------------------|-------------|
| Franceschini et al., 2017 United States DBP: light- and never-smokers (SBP = 0.94, p = 0.004) | Cross-sectional | Strong Heart Study, American Indians communities | Cases: 1429 Noncases: 2285 | SBP/DBP ≥ 140/90 mmHg or use of antihypertensive medication | Blood pressure, Age, sex, geographic area, body mass index, smoking and kidney function | Urine (μg/g creatinine) | Associations between urinary Cd and higher SBP and DBP among light- and never-smokers were found. No association with DBP among only never-smokers. |
| Osorio-Yañez et al., 2016 United States | Cohort | Pregnant women in prenatal care clinics | 653 33.0 ± 4.4 0 | SBP/DBP ≥ 140/90 mmHg | Preeclampsia, hypertension | Maternal age, ethnicity, parity, smoking, prenatal vitamin use, family history of hypertension, GDM status, and physical activity | Urine (μg/g creatinine) | Inverse association between urinary Cd and mean blood pressure was found in preeclampsia |
| Lee et al., 2016 South Korea | Cross-sectional | General population KHNANES 2008-2013 | (a) control: 5772 (b) pre-hypertensive: 3051 (c) hypertensive: 3156 | SBP/DBP ≥ 140/90 mmHg or self-reported current use of an antihypertensive medication | Blood pressure and hypertension | Sex, age group, residence area, smoking status, drinking status, education level, hypertensive status | Blood (μg/L) | Blood Cd was strongly associated with elevated blood pressure and risk of hypertension |
| Tangvarasittichai et al., 2015 Thailand | Cross-sectional | Residents in Cd polluted villages and unexposed noncases | Cases: 258 Noncases: 277 | BP ≥ 140/90 mmHg or taking antihypertensive medications or diagnosed with hypertension | Hypertension, diabetes | CKD, U-Protein/g creatinine, U-Cal/g creatinine, BMI, drinking, smoking, age and gender | Urine (μg/g creatinine) | Elevation of Cd exposure is associated with increased risk for hypertension and diabetes |
| Chen et al., 2015 China | Cross-sectional | Residents living in a cadmiunum- | 441 Women= 58.4 Men= 60.9 | SBP/DBP ≥ 140/90 mmHg or current | Hypertension | Hypertension, sex | Blood (μg/L) | Association between blood Cd levels and |
| Authors, date and country | Study design | Study population | Hypertension definition | Outcome(s) | Adjustment variables | Cd exposure/ measure of association | Conclusions |
|---------------------------|-------------|------------------|-------------------------|------------|---------------------|-------------------------------------|-------------|
| Skroder et al., 2015 Bangladesh | Cross-sectional | Preschool-aged children (1356) | antihypertensive treatment | Blood pressure, renal function | Sex, birth weight, season of birth, age at outcome measurement, weight for age z-score, maternal BMI | Urine (μg/L) | Blood pressure and hypertension was found |
| Swaddiwudhipong et al., 2015a Thailand | Cross-sectional | Children living in contaminated areas (cases) and non-contaminated areas (noncases) (Cases: 301, Noncases: 293) | β2-microglobulin, blood pressure | Age, sex, and blood lead levels | Blood (μg/L) Urine (μg/g creatinine) GM (GSD): Blood cases: 2.42 (1.80) noncases: 1.54 (2.12) Urine cases: 0.70 (1.98) noncases: 0.41 (2.44) | GM±SD: cases: 2.96 ± 2.46 noncases: 0.60 ± 2.19 | No significant associations between Cd exposure and blood pressure |
| Swaddiwudhipong et al., 2015b Thailand | Cross-sectional | Residents in Cd-contaminated (cases) and non-contaminated rural areas (noncases) (Cases: 751, Noncases: 682) | BP/DDBP ≥ 140/90 mmHg, or current use of antihypertensive medication | Hypertension, Renal dysfunction, Metabolic disorders, Bone density | Not informed | Urine (μg/g creatinine) | Higher prevalence of hypertension was associated with higher urinary Cd. |
| Van Larebeke et al., 2015 Belgium | Cross-sectional | FLEHS General population: (a) follow up study (2011) (b) previous study (2004-2005). (a): 973 (b): 608 | History of hypertension | Blood pressure, diabetes | BMI, exercise in minutes per week, level of education, glasses alcoholic beverages per week, and others | Urine (μg/g creatinine) | Positive association between urinary Cd and hypertension was found |
| Myong et al., 2014 South Korea | Cross-sectional | General population KNHANES (2008-2010) | SBP ≥ 120 mmHg and antihypertensive treatment | Hypertension | Survey year, age, and urinary cotinine concentration | Blood (μg/L) | Blood Cd levels among men were significantly associated with SBP |
| Shike and Hristova, 2014 United States | Cross-sectional | General population | SBP/DBP ≥ 140/90 mmHg | Blood pressure | Urine creatinine, age, sex, body mass index | Urine (μg/L) | No association was found between |
| Authors, date and country | Study design | Study population | Hypertension definition  | Outcome(s) | Adjustment variables | Cd exposure/matrix | Cd concentration/measure of association | Conclusions |
|---------------------------|-------------|------------------|--------------------------|------------|---------------------|------------------|----------------------------------------|-------------|
| Ikeda et al., 2013 Japan  | Cross-sectional | Women from non-polluted areas | Cases: 289 Noncases: 867 | 20–89 | 0 | Hypertension history | Tubular dysfunction markers, urinary Cd | None | GM: Cases= 2.0 Noncases= 1.8 | history of hypertension may be associated with elevation in urinary Cd levels and high BP |
| Chen et al., 2013 China  | Cross-sectional | Population living in Cd contaminated area | Cases: 115 Noncases: 66 | 58.2 ± 10.8 | 39 | SBP/DBP > 160/95 mmHg or antihypertensive treatment | Blood pressure | Age and BMI | Blood (μg/L) | GM: Men/women SBP< 140 2.95, 3.77 SBP > 160 3.77, 4.84 | blood Cd level was associated with BP, especially for women. Higher prevalence of hypertension was observed with the increasing blood Cd levels both in men and women |
| Lee and Kim, 2012 South Korea | Cross-sectional | General population KNHANES 2008–2010 | 5919  ≥20 | 49.96 | SBP/DBP ≥ 140/90 mmHg or self-reported use of antihypertensive medication | Hypertension | Sex, age, residence area, education level, smoking and drinking status, serum creatinine, hemoglobin, BMI, and diabetic status | Blood (μg/L) | GM (IQR) | Women: normal pressure: 1.023 (0.632–1.407) hypertensive: 1.106 (1.009–1.812) Men: normal: 0.841 (0.547–1.223) hypertensive: 0.945 (0.721–1.487) OR (95% CI)/comparison: SBP: women: 3.201 (1.284–5.117) 0.734 vs. >1.571 men: 3.872 (1.843–5.902) 0.621 vs. >1.331 hypertensive men: 1.826 (1.325– | Significant association between blood Cd levels and elevated blood pressure were found. For hypertension, the association was significative for men |
| Authors, date and country       | Study design  | Study population | Hypertension definition                                      | Outcome(s)                                                                 | Adjustment variables                                      | Cd exposure/Matrix | Cd concentration/ measure of association | Conclusions                                                                 |
|--------------------------------|---------------|------------------|--------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------|-------------------|----------------------------------------|--------------------------------------------------------------------------------|
| Mordukhovich et al., 2012      | Cohort        | Veterans Administration Normative Aging Study (NAS)         | SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or antihypertensive medication use  | Blood pressure                                                        | Age, cigarette smoking, pack-years, BMI, alcohol intake, race/ethnicity, education, and season and year of clinical visit | Toenail clippings (µg/g) | Median (IQR): 0.02 (0.02) OR (95% CI): 1.01 (0.95, 1.06) | Comparison: IQR increase in Cd levels were not found. Blood Cd levels and blood pressure were not significantly associated. |
| Swaddiwudhipong et al., 2012   | Cohort        | Residents in Cd contaminated rural areas: reducing exposure group (a) and continuing exposure group (b) | SBP/DBP ≥ 140/90 mmHg, or current antihypertensive medication | Hypertension, diabetes and urinary stone disease | Not informed | Urine (µg/g creatinine) | GM±SD: (a): year 2005 (baseline)=9.6±1.7 year 2010=8.8±1.6 (b): year 2005 (baseline)=9.3±1.6 year 2005=8.90±1.7 | No association between urinary Cd and hypertension. Significant increases in the prevalence of hypertension, even after Cd exposure reduction, were found. |
| Afridi et al., 2011a, 20011b   | Cross-sectional | Pakistan: 1.6 ± 0.25 Irish: 0.62 ± 0.13 | Cases: 128 Hypertensive and non-hypertensive groups | Blood pressure                                                        | Age, education level, household income, smoking status, alcohol, BMI, waist circumference, family history of hypertension, and blood lead | Blood (µg/L) | GM (SE): Cases: 1.67 (0.03) Noncases: 1.49 (0.02) OR (95% CI): 1.29 (1.09–1.52) | Comparison: IQR increase in blood Cd was associated with an elevated risk of hypertension. |
| Lee et al., 2011 South Korea    | Cross-sectional | KHANES (2005) | Cases: 481 Noncases: 1427 | SBP/DBP ≥ 140/90 mmHg, self-reported physician diagnosis, or use antihypertensive medication | Ischemic heart disease, stroke, and hypertension | Blood (µg/L) | GM (SE): Cases: 1.67 (0.03) Noncases: 1.49 (0.02) OR (95% CI): 1.29 (1.09–1.52) | Comparison: IQR increase in blood Cd was associated with an elevated risk of hypertension. |
| Authors, date and country | Study design | Study population | Hypertension definition | Outcome(s) | Adjustment variables | Cd exposure/measure of association | Conclusions |
|---------------------------|--------------|------------------|-------------------------|------------|---------------------|-----------------------------------|-------------|
| Boonprasert et al., 2011 Thailand | Case control | Residents in Cd-contaminated rural areas | Cases: 154 | Control: 154 | SBP/DBP ≥ 140/90 mmHg, clinical diagnosis of hypertension | Hypertension, Renal dysfunction biomarkers and genetic polymorphism | Blood (μg/L) Urine (μg/g creatinine) | No evidence was found between Cd exposure and high blood pressure |
| Swaddiwudhipong et al., 2010a Thailand | Cross-sectional | Residents in Cd-contaminated rural areas with urinary Cd < or ≥ 5 (cases and noncases, respectively) | Cases: 484 | Noncases: 311 | SBP/DBP ≥ 140/90 mmHg, or current antihypertensive medication | Hypertension, diabetes and urinary stone disease | Urine (μg/g creatinine) OR (95%CI): 1.00 (0.97–1.02) Comparison < 5 vs. ≥5 | No significant association between urinary Cd and hypertension was found |
| Swaddiwudhipong et al., 2010b Thailand | Cross-sectional | Subjects living in Cd-contaminated villages | cases: 1571 | noncases: 3702 | SBP/DBP ≥ 140/90 mmHg or receipt of current antihypertensive medication | Hypertension, diabetes | Adjusted for age, alcohol consumption, BMI, diabetes | GM (±SD) Males: 2.0 (2.2) Females: 2.4 (2.3) OR (95% CI) Never smokers: Males = 1.043 (0.953–1.140) Females = 1.055 (1.020–1.091) Smokers: Male:1.052 (1.012–1.094) Female: 1.704 (1.019–1.133) Comparison (male): < 1.36 vs. ≥ 2.89 (female): < 1.72 vs. > 3.65 | The prevalence of hypertension significantly increased as urinary Cd levels increased |
| Afridi et al., 2010a, 2010b Pakistan | Cross-sectional | Patients from basic health | Cases: 457 | Noncases: 369 | SBP/DBP ≥ 160/90 mmHg or use of hypertension medication | Hypertension | Smoking, weight, BMI, LDL, cholesterol, blood pressure, Cd, Pb, Ni, Zn | Mean Cases (hair, blood, urine): Non-smokers 2.86 ± 0.43, 5.97 ± 1.3, 4.69 ± 0.46 Smokers 7.3 ± 0.69, 8.9 ± 0.46 | Cd levels were significantly higher of both smoker and nonsmoker patients with hypertension |
| Authors, date and country | Study design | Study population | Hypertension definition | Outcome(s) | Adjustment variables | Cd exposure/Matrix | Cd concentration/measure of association | Conclusions |
|--------------------------|-------------|------------------|------------------------|------------|---------------------|-------------------|----------------------------------------|-------------|
|                          |             |                  |                        |            |                     |                   | 1.3, 5.86 ± 2.12                       | than in referents |
|                          |             |                  |                        |            |                     |                   | Noncases (hair, blood, urine):         |             |
|                          |             |                  |                        |            |                     |                   | Non-smokers: 1.24 ± 0.3, 4.24 ±        |             |
|                          |             |                  |                        |            |                     |                   | 1.27, 3.2 ± 0.9 Smokers: 1.99 ± 0.54, 5.36 ± |             |
|                          |             |                  |                        |            |                     |                   | 1.4, 3.98 ± 1.22                       |             |

Abbreviations: AM, arithmetic mean; BP, blood pressure; BMDL; benchmark dose lower (response of 10%); BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; EGFR, estimated glomerular filtration rate; FLEHS, Flemish Environment and Health Survey; GM, geometric mean; GSE, geometric standard error; 20-HETE, 20-hydroxyeicosatetraenoic acid; HPT, hypertension; HR, hazard ratio; IQR, interquartile range; KHANES, Korea National Health and Nutrition Examination Survey; NHANES, National Health and Nutrition Survey; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

For studies that categorized Cd exposure, we report the HR or OR (with 95% CI) comparing the highest with the lowest Cd category.