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Title: Blood and Urine Cadmium, Blood Pressure, and Hypertension: a Systematic Review and Meta-analysis

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**Abbreviations:**

ABP Ambulatory blood pressure  
ACE antiotensin converting enzyme  
BCd blood cadmium  
 $\beta$ 2-MG beta-2 microglobulin  
DBP diastolic blood pressure  
eNOS endothelial nitric oxide synthase  
HDL high-density lipoprotein  
HTN hypertension  
 $I^2$  heterogeneity test  
MESH medical subject heading  
Mm Hg millimeter of mercury  
MOA mechanism of action  
nM nanomolar  
Nmol/L nanomoles per liter  
SBP systolic blood pressure  
UCd urine cadmium  
 $\mu$ g/g micrograms per gram  
 $\mu$ g/L micrograms per liter  
WOE Weight of evidence

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**Abstract**

**Objectives:** The objective of this systematic review is to update and re-evaluate the evidence regarding the relationships of blood and urine cadmium (BCd and UCd) with blood pressure (BP) and/or hypertension in non-occupationally exposed populations.

**Data Sources/Extraction:** We searched PubMed and Web of Science for articles on BCd or UCd and BP or hypertension in non-occupationally exposed populations, and extracted data from studies sufficiently reporting population, smoking status, exposure, outcomes, and design.

**Data Synthesis:** Twelve articles met inclusion criteria. Eight provided adequate data for comparison, and five for meta-analysis. Individual studies reported significant positive associations between BCd and systolic BP in non-smoking women ( $\beta=3.14$  mmHg per 1  $\mu\text{g/L}$  untransformed BCd; 95% CI=0.14, 6.14) and in pre-menopausal women ( $\beta=4.83$  mmHg per 1 nmol/L log-transformed BCd; 95% CI=0.17, 9.49); and between BCd and diastolic BP in women ( $\beta=1.78$  mmHg comparing BCd in the 90<sup>th</sup> to 10<sup>th</sup> percentiles; 95% CI=0.64, 2.92), and in pre-menopausal women ( $\beta=3.84$  mmHg per 1 nmol/L log-transformed BCd; 95% CI=0.86, 6.82). Three meta-analyses, each of three studies, showed positive associations between BCd and systolic ( $p=0.006$ ) and diastolic ( $p<0.001$ ) BP among women, with minimal heterogeneity ( $I^2=3\%$ ); and a significant inverse association between UCd and hypertension among men and women, with substantial heterogeneity ( $I^2=80\%$ ).

Conclusion: Results suggest positive associations between BCd and BP among females; however, results are inconclusive due to the limited number of population-representative studies of never-smokers. Associations between UCd and hypertension suggest inverse relationships, but inconsistent outcome definitions limit interpretation. Longitudinal study is merited.

## INTRODUCTION

Hypertension and smoking are established risk factors for cardiovascular disease (USDHHS 2000), the leading cause of death worldwide (WHO 2007). The etiology of essential hypertension, however, is unknown (Carretero and Oparil 2000), and cadmium exposure has been inconsistently related to blood pressure. In a recent review of the literature regarding cadmium and health effects, Jarup and Akesson (2009) identified single study-reported associations between cadmium and cardiovascular effects other than hypertension. A review of the literature regarding cadmium exposure and hypertension conducted more than ten years earlier (Nakagawa and Nishijo 1996), found that whereas general population studies had reported positive associations between blood (BCd) and urinary cadmium (UCd) with blood pressure, inverse associations had been reported in studies of residents or workers with known environmental or occupational exposures. The authors interpreted this difference as an effect of low versus high exposures to cadmium (Nakagawa and Nishijo 1996). Nakagawa and Nishijo (1996) identified exposure misclassification as a limitation of studies conducted prior to the 1970s when cadmium measurements were semi-quantitative, and also noted failure to account for the influence of smoking as a concern. Smoking is associated with increased cadmium levels because cigarettes contain cadmium taken up by the tobacco plant (ATSDR 2008). Smokers have approximately twice the cadmium body burden of non-smokers (ATSDR 2008). In non-smokers, however, food is the primary source of exposure (ATSDR 2008). Nakagawa and Nishijo (1996) concluded that additional studies that control for smoking are needed, and several new studies that separated smokers from nonsmokers have been published since their review.

Since 1989, advancements in the technology to analyze cadmium in blood and urine have improved the reliability of human exposure measures (Tsalev 1995); however, the use of biomarkers, i.e., BCd and UCd, has been inconsistent across epidemiological studies of hypertension and blood pressure. UCd is a biomarker for lifetime cadmium exposure in people with lower, non-occupational exposures because, in the absence of episodes of high-level exposure, cadmium-binding sites, primarily in the kidney and liver, are not saturated, and UCd increases in proportion to the amount of cadmium stored in the body (Dillon and Ho 1991). UCd, however, can also reflect recent exposure (ATSDR 2008). BCd is a biomarker of recent exposure, with a half-life of 3 to 4 months, and is also considered a biomarker for longer-term exposure that reflects accumulation in the blood from body stores over the past 10 years (Jarup et al. 1998). A greater percentage of inhaled than ingested cadmium is absorbed into the bloodstream (Jarup et al. 1983,1998). Thus, UCd and BCd levels may provide different information regarding the timing and source of exposure in smokers and non-smokers.

The objectives of the current systematic review and meta-analysis are to update and re- evaluate the state of the evidence regarding the relationships between BCd and UCd, blood pressure and hypertension; and discern the extent that previously reported correlations may be associated with non-smoking-related exposures, as indicated by BCd and/or UCd estimated effects in never-smokers.

## **METHODS**

We conducted an electronic search in PubMed to locate all relevant articles that address BCd and/or UCd and blood pressure in humans, and smoking status. A priori inclusion criteria were the following: UCd and/or BCd levels and systolic (SBP) or

diastolic (DBP) blood pressure or hypertension were evaluated; study population was not restricted to a specific disease, condition or otherwise unique subset; statistical evaluation adjusted for smoking status, age and sex; the difference in mean cadmium values between high blood pressure cases and normotensive controls and/or associations between cadmium levels and blood pressure and/or hypertension were evaluated for statistical significance; and cross-sectional, case-control, or cohort study design was utilized and original analysis conducted. We excluded studies specifically assessing occupationally exposed populations in order to assess general population exposures. The following MESH terms by PICOS (Population, Intervention/Exposure, Comparison, Outcome, Study design) category (Liberati et al. 2009) were used:

Population: Human AND adult AND NOT occupational exposure;

Biomarker of exposure: cadmium/administration and dosage, cadmium/adverse effects or cadmium/blood or cadmium/urine or cadmium/toxicity;

Comparisons: smoking status and gender (no MESH terms specified);

Outcomes: blood pressure or blood pressure monitoring, ambulatory or hypertension;

Study designs: cross-sectional, case-control, cohort; excluding studies limited to occupationally exposed populations (no MESH terms specified).

Additionally, we conducted an electronic “bottom-up” search in Web of Science to find articles that cite results of the PubMed literature search. Studies were limited to those published from 1989 forward based upon evidence of reliability of the technology to measure and analyze cadmium in blood and urine (Tsalev 1995).

We developed a combined approach to weight the evidence of individual studies, (see Supplemental Material, Table 1). Study characteristics that merited higher weight of



evidence (WOE) grades included separation by smoking status, i.e., either results were presented separately for smokers and never-smokers, or the population was restricted to never or non-smokers, control for anti-hypertensive medication use, ambulatory or multiple blood pressure measurements, analysis of both BCd and UCd biomarkers, or samples representative of general populations. WOE codes are indicated in Table 1 and were used to qualitatively guide interpretation of systematic review findings.

Findings of studies that reported multivariate-adjusted measures of association and 95% confidence intervals and/or standard errors or t-values, are presented in graph format (Figures 1 through 5). In the absence of reported confidence intervals (Staessen et al. 2000; Pizent et al. 2001; Whittemore et al. 1991; Satarug et al. 2005), 95% confidence intervals were calculated as 1.96\* standard error, and thus, represent approximate intervals. Unreported standard error (Satarug et al. 2005) was calculated by dividing the reported coefficient by the reported t-value (Rosner 2006). For results presented in the original article in graph format only, i.e., findings for never-smokers reported by Whittemore et al. (1991), values for estimates and 95% confidence intervals were visually approximated. Mean BCd and UCd values originally reported in nmol/L were converted to  $\mu\text{g/L}$  by dividing by 8.897, and creatinine-adjusted UCd values originally reported as nmol/mmol creatinine were converted to  $\mu\text{g/g creatinine}$  by dividing by 1.006 (Tellez-Plaza 2008). Interpretations of statistical significance are based on an alpha level  $\leq 0.05$ .

Since two studies are a suggested minimum requirement for a systematic review to include a meta-analysis (Littell et al. 2008), we required at least three studies with comparable exposure and outcome measures. Meta-analysis was conducted using random

effects models and inverse variance methods to weight effect estimates. Random effects models were used to account for variation among the studies (Littell et al. 2008). Inverse variance methods were used to give greater weight to studies characterized by greater precision, i.e., relatively narrow confidence intervals (Little et al. 2008). Meta-analysis was performed using Review Manager 5.0 software (RevMan 2008).

## RESULTS

### Literature search

Electronic search results yielded a total of 33 citations, of which only 12 met the inclusion criteria. (See Supplemental Material, Table 2 for citations of excluded articles with reasons indicated).

### *Study characteristics and weight of evidence*

Table 1 summarizes study characteristics and key findings.

*Larger population-representative samples, smoking stratified:* Tellez-Plaza et al. (2008) analyzed data from the 1999-2004 National Health and Nutrition Examination Survey (NHANES) (n=10,991), and Whittemore et al. (1991) analyzed data from the 1976-1988 NHANES II (n=960); both were cross-sectional studies. Tellez-Plaza et al. (2008) defined hypertension as mean SBP  $\geq$  140 mmHg, a mean DBP  $\geq$  90 mmHg, a self-reported physician diagnosis, or medication use, whereas Whittemore et al. (1991) defined hypertension by anti-hypertensive drug use, only. Exposure measures included spot urine samples for both studies; however, Tellez-Plaza et al. (2008) used multivariate adjustment for creatinine to adjust for urine dilution effects, whereas Whittemore et al. (1991) directly adjusted UCd measurements for specific gravity. Tellez-Plaza et al.

(2008) also estimated associations with BCd. Whittemore et al. (1991) estimated associations with continuous, untransformed UCd measures, and Tellez-Plaza et al. (2008) estimated associations for cadmium quartiles (relative to the lowest quartile) and for Cd levels at or above the 90<sup>th</sup> percentile compared with Cd at or below the 10<sup>th</sup> percentile, in addition to estimating associations with log-transformed continuous biomarker measures. The NHANES II database utilized by Whittemore et al. (1991) lacked sample appropriate weights for the subsample with cadmium measurements, so p-values and confidence intervals were calculated based on the assumption that this subsample is a simple random sample of the US population. Tellez-Plaza et al. (2008) adjusted for hypertensive medication use in multivariate analysis, but did not exclude treated hypertensives from analysis of never-smokers, in contrast with Whittemore et al. (1991).

*Smaller studies, limited to non-smokers:* These four studies ranged in sample size from 58 to 267 subjects. Outcome measures included continuous SBP and DBP (Satarug et al. 2005; Pizent et al. 2001); dichotomous SBP and/or DBP, i.e., SBP >140 mmHg and/or DBP >90 mmHg (Vivoli et al. 1989); mean SBP (Satarug et al. 2005), and mean arterial pressure (Lin et al. 1995). Exposure measures included 3-hour log-transformed UCd (Satarug et al. 2005); mean creatinine-adjusted spot UCd (Vivoli et al. 1989); and untransformed BCd (Lin et al. 1995; Pizent et al. 2001). The three cross-sectional studies were limited to nonsmokers (Satarug et al. 2005; Lin et al. 1995; Pizent et al. 2001) and the one case-control study matched cases and controls for smoking status (Vivoli et al. 1989). Treated hypertensive subjects were excluded from all four studies. Study populations were urban (Satarug et al. 2005), clinic-recruited (Lin et al. 1995), rural

(Pizent et al. 2001), and occupation-specific (Vivoli et al.). Findings from Lin et al. (1995) are not depicted in graph format because the outcome measure, i.e., mean arterial blood pressure, was not comparable to those of the other studies. Additionally, findings from Vivoli et al. (1989) are not plotted because this study analyzed the difference in mean cadmium between cases and controls, and did not report comparable measures of association.

*Large studies, not limited to non-smokers:* These three cross-sectional studies utilized sample sizes of 2,853 (Kurihara et al. 2004); 1,902 (Eum et al. 2008); and 1,223 subjects (Menditto et al. 1998). Outcome measures included categorical measures of hypertension, i.e., SBP  $\geq$  140 and/or DBP  $>$  90 or taking anti-hypertensive drugs (Kurihara et al. 2004), SBP  $\geq$  140 or DBP  $\geq$  90 or self-reported hypertension in medical examination (Eum et al. 2008), continuous SBP and DBP (Eum et al. 2008; Menditto et al. 1998), and mean blood pressure, i.e., DBP+pulse pressure/3 (Eum et al. 2008), and DBP+1/3(SBP-DBP) (Menditto et al. 1998). Exposure measures included BCd tertiles, i.e., 0.18-1.28  $\mu\text{g/L}$ ; 1.29-1.86  $\mu\text{g/L}$ ; 1.87-5.52  $\mu\text{g/L}$  (Eum et al. 2008); 84% upper cutoff dichotomized BCd and UCd, i.e., geometric means x geometric standard deviations, as follows: UCd, men: 1.8 x 2.5=4.5  $\mu\text{g/g}$ ; UCd, women: 2.4 x 2.8=6.72  $\mu\text{g/g}$ ; BCd, men: 2.2 x 1.9=4.18  $\mu\text{g/L}$ ; BCd, women: 2.3 x 1.8=4.14  $\mu\text{g/L}$  (Kurihara et al. 2004); and continuous log-transformed BCd (Menditto et al. 1998). Kurihara et al. (2004) used multivariable analysis to control for smoking status, but did not separate former-smokers from non-smokers. Eum et al. (2008) controlled for former, current, and never-smoker, and Menditto et al. (1998) controlled for number of cigarettes smoker/day. Each of these studies statistically adjusted, but did not present results separately for smokers and non-

smokers. Eum et al. (2008) ran separate regression models for low ( $<0.95$  mg/dL), medium ( $\geq 0.95$  &  $< 1.05$  mg/dL), and high ( $\geq 1.05$  mg/dL) serum creatinine to adjust for renal dysfunction, and Kurihara et al. (2004) adjusted for beta-2-microglobulin, a measure of tubular renal dysfunction. The Menditto et al. study (1998) was unique among this group of studies in that treated hypertensive subjects were excluded; however, measures of association were not reported.

*Smaller studies, not limited to non-smokers:* These studies ranged in sample size from 154 to 692 subjects. Outcome measures included SBP and DBP (Schutte et al. 2008; Staessen et al. 2000; Telisman et al. 2001) and 24 hour ambulatory SBP and DBP (Staessen et al. 2000). Exposure measures included 24 hour log-transformed UCd (Schutte et al. 2008; Staessen et al. 2000) and log-transformed BCd (Schutte et al. 2008; Staessen et al. 2000; Telisman et al. 2001). Staessen et al. (2000) conducted a combined cross-sectional and prospective study of 692 residents of two rural areas in Belgium; one with known environmental exposures to cadmium from zinc smelters. The study period included the years 1985 to 1989, and these same participants (less those lost to follow-up) during 1991-1995, after interventions to reduce cadmium exposure had occurred. The Schutte et al. (2008) analysis evaluated cross-sectional data from a sample of 557 subjects from this same study restricted to the years 1991-1994, and included 26 occupationally exposed men. A case-control study (Telisman et al. 2001) restricted participants to 154 non-occupationally exposed men; however measures of association were not presented.

*Comparison of Multivariate Adjusted Estimated Effects*

Results from eight studies provided adequate data for comparison of estimated effects. Results from five studies provided sufficient data for meta-analysis, using three studies for each meta-analysis, with one study used in two meta-analyses of different exposures.

*Blood Cadmium and Hypertension:* Figure 1 presents the estimated dose response effects of BCd on hypertension. In multivariable analysis that adjusted for smoking status and use of antihypertensive medications, Tellez-Plaza et al. (2008) estimated associations between hypertension and BCd levels categorized by quartiles, with the first quartile used as the reference group (BCd  $\leq$  0.20  $\mu\text{g/L}$ ); quartile 2= 0.20-0.40  $\mu\text{g/L}$  ; quartile3= 0.40-0.70  $\mu\text{g/L}$ ; and quartile 4=  $>$  0.70  $\mu\text{g/L}$  . Relative to the first quartile (819 cases and 1,689 noncases), subjects in the third quartile (1,452 cases and 1,369 noncases) were 25% more likely to be hypertensive (OR=1.25; 95% CI=0.87, 1.81), but hypertension was not associated with exposures in the second and fourth quartiles. Additionally, the authors compared the 90<sup>th</sup> to 10th percentiles in never-smokers (n=5,486); the nonsignificant effect estimate (OR=1.14; 95% CI=0.89, 1.45) was equivalent to that of the third quartile. Eum et al. (2008) categorized BCd levels into tertiles, with tertile 1 (reference group) ranging from 0.18 to 1.28  $\mu\text{g/L}$ ; tertile 2 from 1.29 to 1.86  $\mu\text{g/L}$ ; and tertile 3 from 1.87 to 5.52  $\mu\text{g/L}$ . Subjects in the highest tertile were 52% more likely to be hypertensive than those in the lowest tertile of BCd (OR=1.52; 95% CI=1.13, 2.05).

*Blood cadmium and systolic and diastolic blood pressure:* Figure 2 shows the relationships between BCd and SBP and DBP in men and women, separately. Tellez-Plaza et al. (2008) reported that, in men, BCd (nmol/L) in the 90<sup>th</sup> relative to the 10<sup>th</sup> percentile was significantly associated with DBP ( $\beta$ =1.81 mm Hg; 95% CI=0.40, 3.22); this relationship, however, was not significant for SBP. In contrast, Staessen et al. (2000)

reported inverse associations of log-transformed BCd (nmol/L) with SBP and DBP among men never on antihypertensive medications; however, this inverse relationship was only significant for DBP ( $\beta=-3.10$  mm Hg; 95% CI=-5.86, -0.34). Because results from a third study were not available, meta-analysis was not performed using these findings for men.

Results were available from three studies of the relation between BCd and SBP in women, so meta-analysis was conducted. Statistically significant positive associations were reported by Pizent et al. (2001) for a 1 unit increase in untransformed BCd ( $\mu\text{g/L}$ ) among non-smoking women ( $\beta=3.14$  mm Hg; 95% CI=0.14, 6.14), and by Staessen et al. (2000) for a 1 unit increase in log transformed BCd (nmol/L) among pre-menopausal women ( $\beta=4.83$  mm Hg; 95% CI=0.17, 9.49). Tellez-Plaza et al. (2008) also reported positive, although insignificant, associations between BCd (nmol/L), comparing 90<sup>th</sup> to 10 percentiles, and SBP among women ( $\beta=1.40$  mm Hg (95% CI=-0.81, 3.61). Overall estimated effects were significantly positive ( $\beta=2.39$  mm Hg; 95% CI=0.69, 4.09;  $p=0.006$ ), with minimal heterogeneity ( $I^2=3\%$ ).

All three studies showed positive relationships between BCd and DBP, with similar effect estimates, in women; however only the findings of Staessen et al. and Tellez-Plaza et al. showed statistical significance ( $\beta=3.84$  mm Hg; 95% CI=0.86, 6.82;  $\beta=1.78$ ; 95% CI=0.64, 2.92). Pizent and colleagues' effect estimate for nonsmoking women was similar to that of Tellez-Plaza for all women ( $\beta=1.40$  mm Hg; 95% CI=-0.15, 2.95). As in the meta-analysis for BCd and SBP, overall associations for BCd and DBP were significantly positive ( $\beta=1.84$  mm Hg; 95% CI=0.95, 2.74;  $p<0.0001$ ), with minimal heterogeneity ( $I^2=3\%$ ).

*Blood cadmium dose response:* Figure 3 compares BCd associations with SBP and DBP by levels of exposure. Among never-smokers, BCd levels in the 90<sup>th</sup> percentile were significantly associated with elevated SBP ( $\beta=2.35$  mm Hg; 95% CI=0.64, 4.05) and DBP ( $\beta=3.25$  mm Hg; 95% CI=1.69, 4.84) relative to the 10<sup>th</sup> percentile (Tellez-Plaza et al. 2008). In the smoking-adjusted analysis, the third quartile of BCd exposure relative to the lowest level showed a larger estimated effect (SBP:  $\beta=1.85$  mm Hg; 95% CI=0.52, 3.19 and DBP:  $\beta=2.01$  mm Hg; 95% CI=0.86, 3.15) than did the second quartile; however, for both SBP and DBP, the effect estimate for the fourth quartile was attenuated relative to that of the third (Tellez-Plaza et al. 2008). For SBP, Eum et al. (2008) reported a positive association with the second tertile of BCd compared to the reference group ( $\beta=1.651$  mm Hg; 95% CI=0.099, 3.203), and a slightly stronger association with BCd exposures in the third tertile ( $\beta=2.204$  mm Hg; 95% CI=0.649, 3.760) relative to the first quartile. For DBP, only the third tertile reached statistical significance ( $\beta=1.671$  mm Hg; 95% CI=0.626, 2.716). Comparisons of 2<sup>nd</sup> and 3<sup>rd</sup> levels across these two studies of lower population mean BCd, 0.42  $\mu\text{g/L}$ , (Tellez-Plaza et al. (2008) and higher population mean BCd, 1.67  $\mu\text{g/L}$ , (Eum et al. 2008) suggest a positive dose response.

*Urine Cadmium and Hypertension:* Figure 4 presents study findings regarding the association between UCd and hypertension. Tellez-Plaza et al. (2008) used a dichotomous measure of UCd obtained from spot urine samples, compared the 90<sup>th</sup> to the 10<sup>th</sup> percentile, and used multivariate adjustment to statistically adjust for urine creatinine; whereas Kurihara et al. used an 84% cutoff (4.5  $\mu\text{g/g}$  for men and 6.72  $\mu\text{g/g}$  for women), and directly adjusted UCd for urine creatinine. The Whittemore et al. study (1991) also measured cadmium from spot urine samples, but adjusted for specific gravity.



Whittemore et al. (1991) used anti-hypertensive drug use to define hypertension; whereas Kurihara used standard blood pressure cutoff measures, and Tellez-Plaza incorporated both definitions, as well as self-report of physician-diagnosed hypertension. Despite these methodological differences, inverse relationships were found between UCd and HTN in men and in women. Odds ratios (ORs) varied considerably across studies, with ORs of 0.62 for men and 0.67 for women in the Kurihara et al. (2008) study, and ORs of 0.34 and 0.94 for never-smoking men and women in the Tellez Plaza et al. (2008) and Whittemore et al. (1991) studies, respectively. Meta-analysis of results from these three studies showed UCd to be significantly negatively associated with hypertension (OR=0.65; 95% CI=0.45, 0.94;  $p=0.02$ ); however, heterogeneity was substantial ( $I^2=83\%$ ).

*Urine cadmium and systolic and diastolic blood pressure:* Figure 5 presents partial regression coefficients (adjusted for covariates in multivariable analysis) and 95% confidence intervals for the relationship of UCd with SBP and DBP, evaluated separately for women and men. Statistically significant inverse relationships for a one-unit increase in log-transformed 24 hour UCd (nmol/L) with SBP ( $\beta=-5.55$  mm Hg; 95% CI=-11.04, -0.06) and DBP ( $\beta=-4.80$  mm Hg; 95% CI=-8.19, -1.41) were reported for men who were never on anti-hypertensive drugs (Staessen et al. 2000). Although Whittemore et al. (1991) reported positive relationships of untransformed UCd ( $\mu\text{g/L}$ ) with SBP and DBP in both male and female never-smokers, associations were not statistically significant. Satarug et al. (2005) observed a statistically significant positive relationship of log-transformed 3 hour UCd (nM) with SBP ( $\beta=0.31$  mm Hg; 95% CI=0.05, 0.57) among

male non-smokers not on anti-hypertensive medications; however, the estimated effect size was small, and findings were null for women. Overall, these results are inconsistent, which may be attributable, in part, to different units of exposure measures, variations in sample sizes, and/or differences in smoking status and anti-hypertensive drug use.

## **DISCUSSION**

### *Synthesis of findings using a causal inference framework:*

Causal inference criteria provide a framework useful to interpret the strength and limitations of the evidence regarding an association between BCd and/or UCd with blood pressure. Hill (1965) and contemporaries (Kundi et al. 2006; Rothman and Poole 2007) caution against using epidemiological causal inference criteria as a checklist. Noting these cautionary concerns, it is informative to qualitatively group these criteria as follows: strength of association, consistency among studies, and temporality; and dose-response, epidemiologic coherence, and biologic plausibility.

*Strength of association/ Consistency/ Temporality:* Positive associations between BCd with elevated SBP and DBP were found among non-smokers (Pizent et al. 2001) and never-smokers (Tellez-Plaza et al. 2008). Statistically significant relationships between BCd, SBP and DBP among non- and never-smokers are interpreted as providing stronger evidence than associations from smoking-adjusted studies because the effects of current and ever-smoking, respectively, are removed, rather than statistically adjusted for. Meta-analysis supported strength of association, and the relationship between BCd and blood pressure was evident across three studies of women (Staessen et al. 2000; Pizent et al. 2001; Tellez-Plaza et al. 2008), regardless of smoking-adjustment or stratification

methods. In the only prospective study, Staessen et al. (2000) found that BCd was positively related to SBP and DBP in premenopausal women. Moreover, a longitudinal decrease in BCd was documented after environmental remediation, and decreased BCd was associated with decreased DBP in women (Staessen et al. 2000). Because BCd is more influenced by recent exposure, and SBP and DBP are concurrent measures, the evidence suggests a temporal relationship between blood cadmium and recent effects. BCd may also reflect accumulation of cadmium with age; however all studies adjusted for or matched on age.

BCd was less consistently associated with hypertension. This may be due to the disparate definitions of hypertension. Studies similar in terms of adjustment for measures of renal dysfunction and populations with relatively high BCd levels reported discrepant findings; specifically, Eum et al. (2008) reported positive associations between BCd, blood pressure and hypertension in a sample with a geometric mean  $> 2.0 \mu\text{g/L}$ , whereas Kurihara et al. (2004) reported no association between BCd and hypertension in a sample with similarly high BCd= $1.67 \mu\text{g/L}$ . BCd means for both of these samples were greater than that of the NHANES sample ( $0.42 \mu\text{g/L}$ ) (Tellez-Plaza et al. 2008), and BCd was positively associated with blood pressure in this low exposure population, as well as in the Eum et al. (2008) study of a high exposure population. Thus, the results of the current review do not support Nakagawa and Nishijo's review conclusions (1996) that general populations with low exposures show positive associations between cadmium and blood pressure, whereas populations with kidney dysfunction and high exposures show inverse associations. Of note, the only study reviewed in both the current and original review was the Staessen et al. (2000) study; however, Nakagawa and Nishijo (1996) referenced

earlier versions (Staessen et al. 1984, 1991), and thus, did not include the more recent findings of a positive association between BCd and blood pressure in women (Staessen et al. 2000).

Several studies showed an inverse association between UCd, a biomarker of long-term exposure, and hypertension. This inverse relationship was evident in both high- and low-exposure populations, so again, does not support the earlier systematic review's interpretation that inverse associations between cadmium and blood pressure are characteristic of populations with higher exposures and associated renal dysfunction (Nakagawa and Nishijo 1996). Specifically, both the Tellez-Plaza et al. (2008) study of a low-exposure population (mean BCd=.42  $\mu\text{g/L}$  and mean UCd=.28  $\mu\text{g/L}$ ) and the Kurihara et al. (2004) study of a high-exposure population (geometric mean BCd between 2.2 and 2.3  $\mu\text{g/L}$  and geometric mean UCd between 1.8 and 2.4  $\mu\text{g/g creatinine}$ ) found statistically significant inverse relationships between UCd and hypertension. Staessen et al. (2000) evaluated SBP and DBP averaged over 15 readings taken during the period from 1985-1995; this time-integrated analysis also showed an inverse relationship between UCd and long-term DBP in men..

A limitation common to all studies, and thus, to the meta-analysis of the relation between UCd and hypertension, is that the outcome of hypertension was not consistently defined across studies. Although meta-analysis findings support an inverse relationship, the finding of substantial heterogeneity might reflect outcome misclassification. Thus, while causal inference criteria support the interpretation of a positive association between BCd and higher SBP and DBP, the relationship between UCd, blood pressure and hypertension remains uncertain.

*Dose-response/ Epidemiologic coherence/ Biologic plausibility:* Dose response analyses of BCd tertiles and quartiles were not restricted to never-smokers, so interpretations regarding cadmium's exposure-response effects independent of smoking are limited. It is notable in the Tellez-Plaza et al. study (2008), however, that for the outcomes of SBP and DBP, never-smokers show the largest effect estimates when comparing the 90<sup>th</sup> to 10<sup>th</sup> percentile of BCd exposures, and that, in the smoking-adjusted analysis of dose response in this same study, the fourth quartile of cadmium exposure shows a smaller effect estimate compared to the third quartile. Some studies show that smokers have lower blood pressure than non-smokers (Green et al. 1986; Primatesta et al. 2001; Stolarz et al. 2003), and Lee (2008) found that smoking was a risk factor for masked hypertension, i.e., normal clinic blood pressure but elevated ambulatory blood pressure, suggesting that effect estimates in the upper range of cadmium exposure may be confounded by cigarette smoking. This hypothesis warrants investigation.

Based upon animal and in vitro studies, cadmium may increase blood pressure through vascular effects. A hypothesized mechanism of action (MOA) for cadmium in humans is inhibition of endothelial nitric oxide synthase (eNOS) protein in blood vessels, which suppresses acetylcholine-induced vascular relaxation to induce hypertension (Yoopan et al. 2008). On the other hand, serum cotinine, a metabolite of nicotine, has been inversely related to blood pressure in smokers (Benowitz and Sharp 1989), and Ghasemi et al. (2010) reported a significantly positive correlation between serum nitric oxide and the number of cigarettes smoked per day, suggesting a possible MOA for how smoking might confound the relationship between cadmium and blood pressure.

The inverse relationships observed between UCd and blood pressure raise the question of whether cadmium might have depressor effects. Experimental findings suggest that cadmium binds to calcium-binding sites on the regulatory protein calmodulin, and like calcium, cadmium can increase dopamine synthesis in the brain that lowers blood pressure (Sutoo and Akiyama 2000). Further research is merited to investigate this hypothesized MOA in humans.

Hypertension is a disease of differential physiological characterization. Approximately one fourth of hypertensive subjects, particularly those with renovascular hypertension, show high levels of angiotensin II, a vasoconstrictor (Malpas 2010). Angiotensin II receptor binding sites are located in the brain at sites involved with sympathetic nerve activity via baroreflex regulation (Malpas 2010). Research on rats showed that cadmium inhibited angiotensin converting enzyme (ACE) at low, medium and high doses without a dose response effect, yet paradoxically induced hypertension (Puri and Saha 2003). The authors postulated that cadmium's vascular effects predominated over its central effects in hypertensive rats (Puri and Saha 2003). Cadmium's central versus vascular effects in humans, however, are unknown. It has been shown however, that the ACE inhibitor, valsartan, is more effective in preventing cardiac failure in hypertensive men than women (Zancheti et al. 2006). In light of meta-analysis findings of an association between BCd and elevated blood pressure in women, perhaps future research into cadmium's mechanisms of action may lead to improved gender-specific therapeutic interventions.

Staessen et al. (2000) found an inverse association between BCd and blood pressure in men never on anti-hypertensive drugs. This finding and the meta-analysis finding of UCd's inverse association with hypertension, yet UCd's positive associations with heart

failure (Peters et al. 2010), seem counterintuitive, as hypertension is an established risk factor for cardiovascular disease. In as many as 33% of hypertensive heart disease patients, however, heart failure is unrecognized because as this condition develops, the left ventricle becomes too weak to raise DBP (Riaz 2010). Further, masked hypertension, is prevalent in 10-20% of the adult population (O'Brien 2008). The extent to which undiagnosed and untreated hypertensive disease is associated with cadmium exposure has not been evaluated.

*Methodological critique of individual studies:* Cross-sectional analysis and inadequate specification of the duration of hypertension limit temporal interpretations.

Misclassification bias may result from the inconsistent measurement of hypertension across studies. Even the measurement of blood pressure may be biased by the phenomenon of masked hypertension, which has been associated with cardiac and arterial target organ damage comparable to that of sustained hypertension (Kotsis et al. 2008). Hypertensive heart failure is of even greater prevalence (Riaz 2010), and thus, non-measurement may be an additional source of outcome misclassification.

Sample selection considerations and exposure measurement error are additional limitations in these studies. Staessen et al. (2000) included men with known occupational exposures, as did Schutte et al. (2008); thus limiting interpretations of findings in men. Further, industrial exposures to cadmium emissions may have uniquely influenced dietary cadmium intake for subjects who consumed food grown in cadmium-contaminated soil. Of the six studies, that separated smokers from non-smokers, the four smaller studies used specific samples that limited generalizability of findings, and the Whittemore et al. 1991 study was not a probability sample. Treated hypertensives were

either analyzed separately or excluded in all smoking-stratified studies except the Tellez-Plaza et al. study (2008). Further, the use of spot urine samples in the Tellez-Plaza et al. (2008), Whittemore et al. (1991), Vivoli et al. (1989), and Kurihara et al. (2004) studies may limit the accuracy of exposure assessment due to variable urinary dilution effects throughout the day (Barr et al. 2005). Urine specific gravity and creatinine correction were used to address this limitation, however, and Berlin et al. (1985), reported a correlation between cadmium levels measured in spot and 24 hour samples from occupationally exposed subjects.

*Limitations of meta-analysis:* The small number of studies precluded quantitative bias assessment, as well as meta-analysis of the relation between BCd with SBP and DBP among men. Further, Menditto et al. (1998) and Kurihara et al. (2004) did not report statistics for null findings regarding the relation between BCd and blood pressure, so meta-analysis may be subject to positive reporting bias. On the other hand, Lin et al. (1995) and Vivoli et al. (1989) found positive relationships between BCd and blood pressure, but did not report comparable measures of association, which may have subjected the meta-analysis to negative reporting bias. Meta-analysis of SBP and DBP utilized both continuous (Staessen et al. 2000; Pizent et al. 2001) and 90:10<sup>th</sup> percentile exposure measures (Tellez-Plaza et al. 2008). Similarly, meta-analysis of hypertension utilized both continuous (Whittemore et al. 1991) and high: low UCd exposure measures (Tellez-Plaza et al. 2008; Kurihara et al. 2004). Further, units of measure varied across studies. Thus, there were substantial differences in exposure measures that limited inter-study comparisons of effect estimates.



*Conclusion and recommendations:*

The body of evidence relating BCd to blood pressure suggests a positive relationship, especially in females, but in the absence of dose-response gradients in never-smokers, is inconclusive. The inverse relationships between UCd and blood pressure reported in the meta-analysis lack strong mechanistic support. Our findings offer new insights, however, because these paradoxical relationships were evident in both high and low exposure populations, as indicated by mean population cadmium exposure levels, and thus, contradict earlier assumptions that this inverse association only reflected higher cadmium exposures. In light of this review's evidence of an association between BCd and higher blood pressure, an established risk factor for cardiovascular disease, and recent evidence of a prospective association between long-term cadmium exposure and cardiovascular mortality (Menke et al. 2009), cadmium merits further epidemiologic inquiry. The European Food Safety Authority (EFSA 2009) recognized that cadmium has been associated with myocardial infarction (Everett and Frithsen 2008) and alterations in cardiovascular function (Schutte et al. 2008). More rigorous investigation of both short and longer-term effects of non-smoking cadmium exposures may shed insights regarding susceptibility to hypertension and cardiovascular disease by identifying cadmium dose response relationships over time.

This line of research would benefit from both physiological studies of cadmium's MOA, and longitudinal epidemiological studies of never-smoking, general populations, i.e., non-occupationally and non-industrially-exposed, to evaluate the relationship between BCd and UCd with SBP, DBP and sustained hypertension. Sufficient power

would be needed to examine effects in the never-smoking general population, with subset analyses by gender,

A longitudinal study would help tease out temporally relevant influences, such as menopausal status and hormonal effects. Cadmium has been shown to suppress progesterone production (Paksy et al. (1997), and has also been associated with increased serum levels of follicle-stimulating hormone (Gallagher et al. 2010). Insights regarding gender differences in cadmium toxicokinetics may be gained by measuring iron levels, as iron competes with cadmium for binding sites on the metal transporter DMT1 (Nishijo et al. 2004). Because cadmium has been associated with peripheral arterial disease (PAD) (Navas-Acien et al. 2004), and zinc and UCd were inversely associated in patients with PAD (Tsai et al. 2004), zinc intake also merits consideration. Further, Guallar et al. (2006) found that BCd partially explained the relationship between elevated homocysteine levels and PAD. Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in homocysteine metabolism, and MTHFR gene polymorphisms were associated with essential hypertension (Ilhan et al. 2008).

An increasing body of evidence suggests that cadmium is a risk factor for cardiovascular morbidity and mortality, as well as a contaminant of concern in our food supply (EFSA 2009; Reuben 2010). Findings from this meta-analysis indicate a positive association between BCd and increased blood pressure, particularly in women, and identify gaps in research regarding the association of cadmium exposure with hypertension. Longitudinal studies are merited to evaluate the relationships between cadmium exposures, more rigorous measures of hypertension, physiological indicators of

cadmium's central, cardiac and vascular effects, hormonal and nutritional factors, genetic susceptibilities, and cardiovascular disease among never-smokers.

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Table 1. Individual study characteristics, key findings, and weight of evidence codes.

Study population	Exposure measure: BCd=blood cadmium; UCd=urine cadmium	Covariates	Outcome measure: HTN=Hypertension; SBP=systolic, DBP=diastolic blood pressure	Key findings: +: significant positive association; -: significant inverse association o: null association	Study design/ Weight of Evidence Codes: 1. Association 2. Environmental Equivalence 3. Population Equivalence 4. Bias	Reference
Larger population-representative samples, with smoking-stratified findings						
U.S. men + women age 20+; N=10,991; Mean BCd: 0.42 µg/L; UCd: 0.28 µg/L	BCd; Spot UCd w/o direct dilution adjustment	Age, sex, race, education, cotinine, alcohol, BMI, menopause, anti-HTN drug use, blood lead; and urinary creatinine for UCd	HTN=mean SBP >= 140 mmHg, mean DBP >= 90 mgHg, self-reported MD diagnosis, or drug use; SBP, DBP 3-4 measures	Never-smokers: BCd + SBP BCd + DBP BCd o HTN UCd - HTN	Cross-sectional (NHANES 1999-2004), Cadmium-weighted sample/  1. A 2. A 3. A/B 4. B	Tellez-Plaza et al. (2008)
U.S. men + women age 20-74; Mean UCd: Men: 1.1 µg/L Women: 1.3 µg/L N=960	Spot UCd, adjusted for specific gravity	Age, sex, race, Quetelet's index, family history HTN, and anti-HTN drug use. Never-smokers exclude HTN drug use.	HTN=anti-HTN drug use; SBP, DBP, 3 measures	Never-smokers: UCd o SBP UCd o DBP UCd o HTN	Cross-sectional (NHANES II 1978-1979), cadmium-unweighted sample/  1. B 2. A/B 3. A 4. B	Whittemore et al. (1991)
Smaller studies, limited to non-smokers						
Adults age 16-60 yrs, near Bangkok, Thailand, no occupational exposures/	3 hour UCd	Age, BMI, urine Pb; Excluded: subjects on anti-hypertensive drugs	SBP DBP MBP	Male never-smokers: UCd + SBP Female never-	Cross-sectional/  1. B	Satarug et al. 2005

N=100 female + 53 male never-smokers UCd mean, Female: 3.5 nM/3 hr urine Male: 2.7 nM/3hr urine		or any medication on a regular basis		smokers: UCd o SBP	2. B 3. A 4. C	
Never-smoking women age 31-77 yrs, from routine & HTN clinics, Taiwan, near Cd-polluted area; 1) N=24 no HTN 2) N=24 untreated essential HTN 3) N=10 non-essential HTN; Mean BCd: 1) 0.88 µg/L 2) 1.69 µg/L 3) 0.92 µg/L;	BCd UCd: 24 hr, Creatinine-adjusted	Age, BMI; Excluded: Smokers & occupational exposure history, proteinuria, hematuria, low creatinine-clearance	MBP, Averaged from 3 different visits on 3 different days	BCd + MBP UCd + MBP	Cross-sectional/  1. B 2. B 3. A 4. C	Lin et al. 1995
“Peasant” women age 40-85 yrs from rural Croatia, all non-smokers (included former smokers) N=267 Median BCd: .6 µg/L	BCd	Area of residence (high vs low calcium intake), age, alcohol, BMI, serum lead. Excluded: subjects on drugs that could affect BP	SBP DBP	BCd + SBP BCd + DBP	Cross-sectional/  1. B 2. B 3. A/B 4. C	Pizent et al. 2001
Male bankers from Modena, Italy; mean age 37-38 yrs; epidemiological screening/ BCd mean hyper-/normotensive: .58/.44 µg/L; UCd_cr mean hyper-/normotensive: 1.36/1.23 µg/g; N=63 HTN + 63 non-HTN	BCD; Spot UCd, creatinine adjusted	Matched for age, smoking, anthropometrics, work conditions. Exclude: taking drugs for hypertension	SBP>140 and/or DBP >90; 2 readings	Mean BCd, cases= .41 µg/L; controls= .25 µg/L (p<.01); no significant difference in UCd between cases and controls	Case-control/ 1. A 2. B 3. A 4. C	Vivoli et al. 1989
Larger studies, not limited to non-smokers						
Non-occupationally exposed, age 50 yrs +; from 3 “unpolluted” rural	BCd, Spot UCd,	Age. smoking (non-smoker, including ex-	HTN=SBP≥140 and/or DBP>90 or	BCd o HTN UCd - HTN	Cross-sectional/ 1. B	Kurihara et al. 2004

areas, Japan; N=1140 men and 1713 women; Geometric Mean BCd, men: 2.2 µg/L Women: 2.3 µg/L; Geometric Mean, UCd, creatinine adjusted: men: 1.8 µg/g women: 2.4 µg/g.	creatinine- adjusted	smoker, and current smokers) alcohol intake, serum creatinine. BMI, β2-MG.	taking anti- hypertensive drugs.		2. C 3. B/C 4. C	
Korean men and women age 20 yrs +; N=958 men and 944 women; Mean BCd=1.67 µg/L	BCd Tertile T1: 0.18- 1.28 µg/L (ref) T2: 1.29- 1.86 µg/L T3.: 1.87- 5.52 µg/L	Age, sex, education smoke (never, ex, current), alcohol intake, BMI, self-reported hypertension, family hypertension, blood lead; Also stratified by serum creatinine	HTN=SBP>=140 or DBP>=90 or self- report. SBP DBP MBP=DBP+pulse pressure/3	BCd T2 + SBP BCd T3 + SBP BCd T3 + DBP BCd T3 + MBP BCd T3 + HTN Effect of BCd on BP strengthened with renal dysfunction.	Cross-sectional/ (KHANES 2005) 1. B 2. A/B 3. B/C 4. B	Eum et al. 2008
Men age 55-75 yrs from Rome, Italy; excluded treated hypertensives. N=1,223 Mean BCd: 0.62 µg/L	BCd	Age, alcohol consumption, # cigarettes sper day, BMI, HDL-cholesterol, nonHDL-cholesterol, serum lead, heart rate, driving minutes/day, skin-fold thickness	SBP DBP MBP=DBP + 1/3 (SBP-DBP)	BCd o SBP BCd o DBP BCd o MBP	Cross-sectional/ (New Risk Factors Project, 6/89-12/90) 1. B 2. B 3. A/B 4. B	Menditto et al. 1998
Smaller studies, not limited to non-smokers						
Men + women age 20+ yrs; 2 rural areas Belgium, 1 near 3 zinc smelters. Arithmetic mean BCd for high/low exposure areas=.98/.08 µg/L Geometric mean 24 hr UCd for high/low exposure areas=9.8/7.1	BCD 24 hr UCd	Sex, age, BMI, γ- glutamyl-transferase, blood glucose, current smoker versus nonsmoker, anti- hypertensive treatment,	SBP DBP MBP=DBP+1/3 pulse pressure, Average of 5 consecutive readings.	UCd – SBP BCd o SBP BCd o DBP BCd o MBP	Cross-sectional (1991-1994)/ 1. A 2. C 3. B/C 4. B	Schutte et al. 2008

nmol/24 hrs; N=557, including 41 male + 37 female smokers, 26 occupationally exposed men.		total cholesterol, HDL				
Same as above, except included time period prior to interventions to reduce exposure levels. Baseline geometric mean BCd for men/women= 1.26/1.23 µg/L. Baseline geometric mean 24 hr UCd for men/women= 11.8/8.8 nmol/24 hrs. N=336 men + 356 women.	BCd 24 hr UCd	SBP DBP Average of 5 consecutive readings. Time-integrated analysis of SBP and DBP averaged over 15 readings, 1985-1995. 24 hour ambulatory blood pressure.	Age at baseline, change in BMI, γ-glutamyl-transferase, urinary Na:K, anti-hypertensive drugs, smoking (no change, quit, acquired), oral contraceptive use	BCd – DBP in men never on anti-HTN drugs. BCd + SBP, DBP in premenopausal women. Longitudinal BCd + DBP in women. UCd – SBP, DBP in men never on anti-HTN drugs. UCd – 24 hr SBP in peri/postmeno-pausal women	Cross-sectional (CadmiBel 1985-1989 and Prospective PheeCad compared 1991-1995 to 1985-89)/ 1. A 2. C 3. B/C 4. B	Staessen et al. 2000
Croatian males age 20-54 yrs, andrology clinic; exclude occupationally exposed, treated hypertensives, renal or other disease that could affect BP. Median BCd=.83 µg/L. N=154.	BCd	SBP DBP	BMI, blood lead, alcohol, blood copper, smoking	BCd o SBP BCd o DBP	Case-control/ 1. B 2. C 3. B 4. B	Telisman et al. 2001

## Figure Legends

Figure 1: Blood Cadmium (BCd) Dose Response Comparisons:

Hypertension (HTN)

Odds Ratios and 95% Confidence Intervals

Tellez-Plaza et al. (2008); Eum et al. (2008)

Tellez-Plaza: HTN=mean SBP  $\geq$ 140, mean DBP $\geq$ 90 mmHg, self-report MD diagnosis or anti-HTN drug use.

BCd (ug/L) quartiles: Q1(ref):  $\leq$ 0.20; Q2: 0.20-0.40; Q3: 0.40-0.70; Q4:  $\geq$ 0.70.

Eum: HTN=SBP $\geq$ 140, DBP $\geq$ 90 mmHg, or self-report of HTN. BCd (ug/L) tertiles: T1 (ref): 0.18-1.28; T2: 1.29-1.86; T3: 1.87-5.52.

All data for men and women, combined. Size of different point estimate symbols for quartiles and tertiles reflect increasing BCd levels.

Figure 2: Blood Cadmium (BCd): Systolic (SBP) & Diastolic (DBP) Blood Pressure

Women, Men, separately

Partial Regression Coefficients and 95% Confidence Intervals

Staessen et al. 2000; Pizent et al. 2001; Tellez-Plaza 2008

Staessen, women, pre-menopause, SBP

Pizent, nonsmoking women never on anti-hypertensive drugs, SBP

Tellez-Plaza, women, SBP



Meta-analysis, women, SBP, beta=2.39; 95% CI=(0.69, 4.09)

{p=0.0006; I<sup>2</sup>=3% }

Staessen, women, pre-menopause, DBP

Pizent, nonsmoking women never on anti-hypertensive drugs, DBP

Tellez-Plaza, women, DBP

Meta-analysis, women, DBP, beta=1.84; 95% CI=(0.95, 2.74)

{p<0.0001; I<sup>2</sup>=3% }

Staessen, men never on anti-hypertensive drugs, SBP

Tellez-Plaza, men, SBP

Staessen, men never on anti-hypertensive drugs, DBP

Tellez-Plaza, men, DBP

Staessen: BCd (nmol/L)=continuous log-transformed; 95% CI=coefficient +/- 1.96\*standard error.

Pizent: BCd (ug/L)=continuous untransformed; 95% CI=coefficient +/- 1.96\*standard error. Tellez-Plaza: BCd (nmol/L): 90<sup>th</sup> to 10<sup>th</sup> percentile.

SBP and DBP (mmHg); Size of point estimate symbols vary to identify different studies without quantitative or qualitative ranking.

Figure 3: Blood Cadmium Dose Response Comparisons:

Systolic (SBP) & Dastolic (DBP) Blood Pressure

Partial Regression Coefficients and 95% Confidence Intervals

Tellez-Plaza (2008); Eum (2008)

Tellez-Plaza: BCd (ug/L) quartiles: Q1 (ref):  $\leq 0.20$ ; Q2: 0.20-0.40; Q3: 0.40-0.70; Q4:  $\geq 0.70$ .

Eum: BCd (jg/L) quartiles: T1 (ref): 0.18-1.28; T2: 1.29-1.86; T3: 1.87-5.52.

All data for men and women, combined. SBP and DBP (mm Hg). Size of different point estimate symbols for quartiles and tertiles reflect increasing BCd levels.

Figure 4: Urinary Cadmium (UCd) and Hypertension (HTN)

Odds Ratios and 95% Confidence Intervals

Kurihara et al. 2004

Tellez-Plaza et al. 2008

Whittemore et al. 1991

Kurihara: HTN=SBP $\geq 140$  or DBP  $> 90$  mmHg, UCd (ug/g)=84% upper limit: lower; spot urine sample, creatinine-adjusted.

Tellez-Plaza: HTN=mean SBP $\geq 140$ , mean DBP  $\geq 90$  mmHg, self-report MD diagnosis, or anti-HTN drug use.

UCd (nmol/L)=90<sup>th</sup>:10<sup>th</sup> percentile; spot urine sample, statistical model adjusted for creatinine.

Whittemore: HTN=anti-HTN drug use. UCd (ug/L)=continuous untransformed; spot urine sample, specific gravity-adjusted.

Size of different point estimate symbols vary to identify different studies without quantitative or qualitative ranking.

Figure 5: Urinary Cadmium (UCd): Systolic (SBP) & Diastolic (DBP) Blood Pressure

Women, Men, separately

Partial Regression Coefficients and 95% Confidence Intervals

Whittemore et al. (1991); Staessen et al. (2000); Satarug et al. (2005)

Whittemore, women, never-smokers not on anti-HTN drugs, SBP

Staessen, women never on anti-HTN drugs, SBP

Whittemore, women, never-smokers not on anti-HTN drugs, DBP

Staessen, women never on anti-HTN drugs, DBP

Whittemore, men, never-smokers not on anti-HTN drugs, SBP

Staessen, men never on anti-HTN drugs, SBP

Satarug, men, never on anti-HTN drugs, SBP

Whittemore, men, never-smokers not on anti-HTN drugs, DBP

Staessen, men never on anti-HTN drugs, DBP

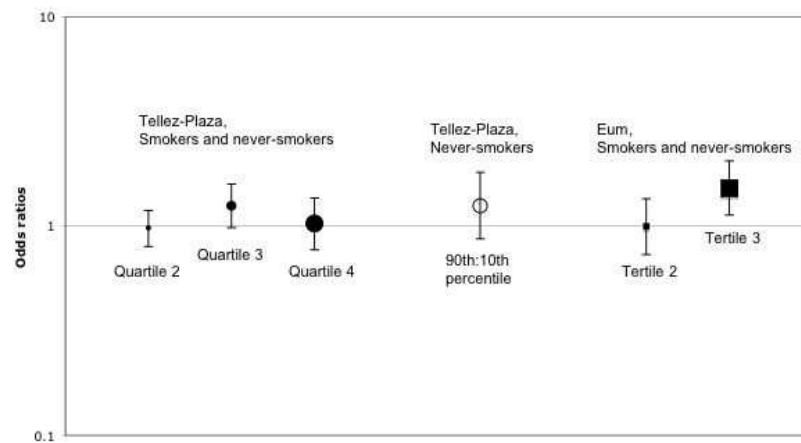
Whittemore: spot UCd (ug/L) Adjusted for specific gravity, untransformed; 95% CI visually estimated from author graphs.

Staessen: 24 hour UCd (nmol) Log transformed; 95% CIs calculated as  $1.96 \times$  standard error

Satarug: 3 hour UCd (nM) Log transformed; 95% CIs estimated from coefficient and t-value

Blood pressure: mm Hg; HTN=hypertensive; Size of different point estimates vary to identify different studies without quantitative or qualitative ranking.

Figure 1: Blood Cadmium (BCd) Dose Response Comparisons:  
Hypertension (HTN)  
Odds Ratios and 95% Confidence Intervals  
Tellez-Plaza et al. (2008); Eum et al. (2008)



Tellez-Plaza: HTN=mean SBP $\geq$ 140, mean DBP $\geq$ 90 mmHg, self-report MD diagnosis or anti-HTN drug use.  
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All data for men and women, combined. Size of different point estimate symbols for quartiles and tertiles reflect increasing BCd levels.

Figure 2: Blood Cadmium (BCd): Systolic (SBP) & Diastolic (DBP) Blood Pressure

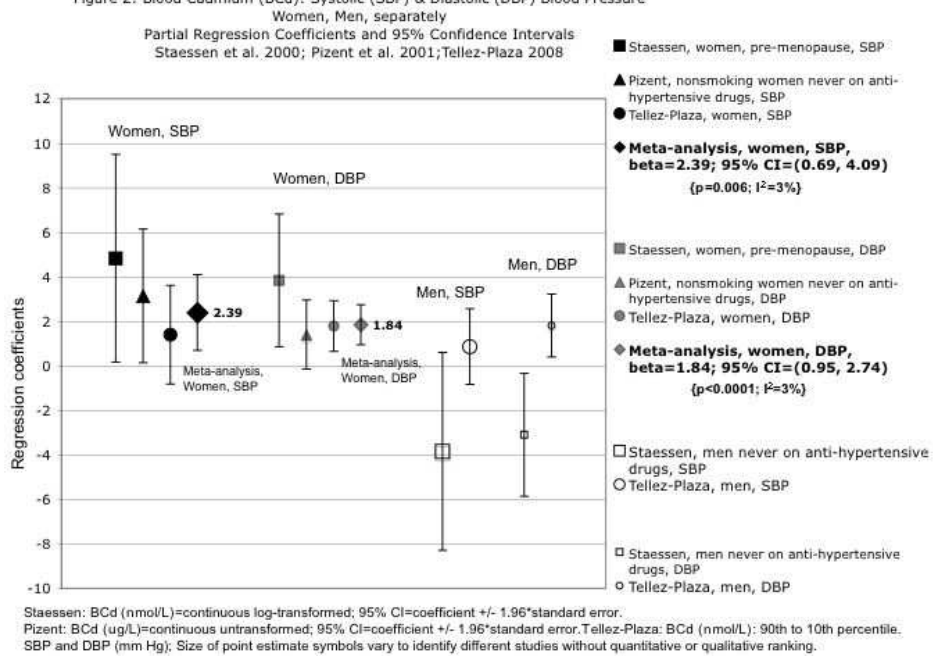


Figure 3: Blood Cadmium Dose Response Comparisons:  
 Systolic (SBP) & Diastolic (DBP) Blood Pressure  
 Partial Regression Coefficients and 95% Confidence Intervals  
 Tellez-Plaza (2008); Eum (2008)

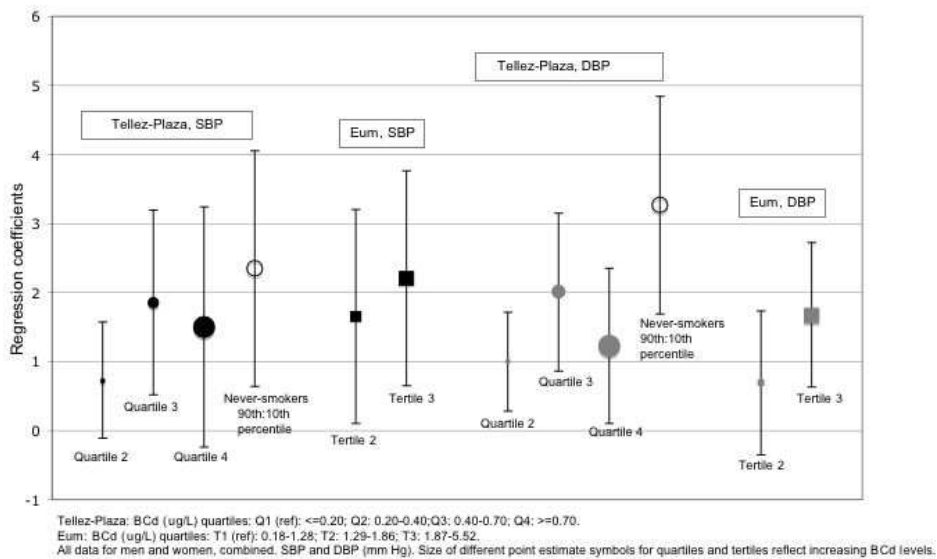
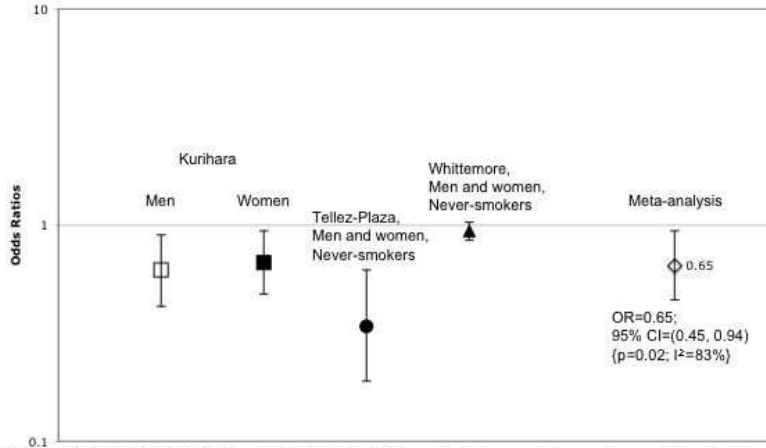


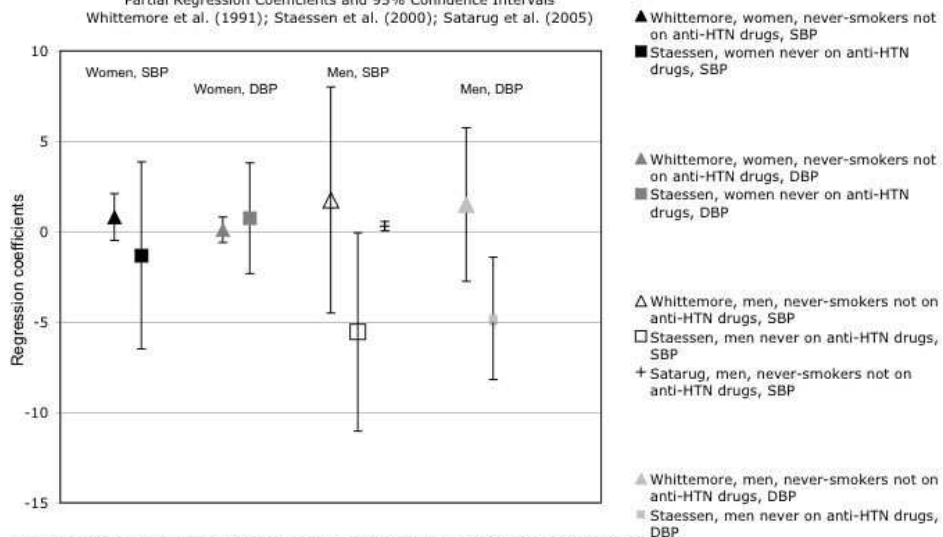
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 Kurihara et al. 2004  
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Kurihara: HTN=SBP $\geq$ 140 or DBP $\geq$ 90 mmHg, UCd (ug/g)=84% upper limit; lower; spot urine sample, creatinine-adjusted.  
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 UCd (nmol/L)=90th:10th percentile; spot urine sample, statistical model adjusted for creatinine.  
 Whittemore: HTN=anti-HTN drug use, UCd (ug/L)=continuous untransformed; spot urine sample, specific gravity-adjusted.  
 Size of different point estimate symbols vary to identify different studies without quantitative or qualitative ranking.



Figure 5:  
Urinary Cadmium (UCd): Systolic (SBP) & Diastolic (DBP) Blood Pressure  
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