Cadmium Exposure and Hypertension in the 1999–2004 National Health and Nutrition Examination Survey (NHANES)

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Introduction: Cadmium induces hypertension in animal models. Epidemiologic studies of cadmium exposure and hypertension, however, have been inconsistent.   **Objective**: We aimed to investigate the association of blood and urine cadmium with blood pressure levels and with the prevalence of hypertension in U.S. adults who participated in the 1999–2004 National Health and Nutrition Examination Survey (NHANES) .   **Methods**: We studied participants ≥ 20 years of age with determinations of cadmium in blood (n =10,991) and urine (n =3,496) . Blood and urine cadmium were measured by atomic absorption spectrometry and inductively coupled plasma–mass spectrometry, respectively. Systolic and diastolic blood pressure levels were measured using a standardized protocol.   **Results**: The geometric means of blood and urine cadmium were 3.77 nmol/L and 2.46 nmol/L, respectively. After multivariable adjustment, the average differences in systolic and diastolic blood pressure comparing participants in the 90th vs. 10th percentile of the blood cadmium distribution were 1.36 mmHg [95% confidence interval (CI) , –0.28 to 3.00] and 1.68 mmHg (95% CI, 0.57–2.78) , respectively. The corresponding differences were 2.35 mmHg and 3.27 mmHg among never smokers, 1.69 mmHg and 1.55 mmHg among former smokers, and 0.02 mmHg and 0.69 mmHg among current smokers. No association was observed for urine cadmium with blood pressure levels, or for blood and urine cadmium with the prevalence of hypertension.   **Conclusions**: Cadmium levels in blood, but not in urine, were associated with a modest elevation in blood pressure levels. The association was stronger among never smokers, intermediate among former smokers, and small or null among current smokers. Our findings add to the concern of renal and cardiovascular cadmium toxicity at chronic low levels of exposure in the general population.

Cd: toxic, carcinogenic metal

Primary source: cigarette smoke, food (shellfish, offal, certain vegetables), ambient air in urban/industrial settings.

Cd: induce hypertention in animal model: e.g., Satarug et al., 2006), and nephrotoxic (e.g., Jin et al., 2004)

Cd exposure and blood pressure

-Positive association: (4 refs cited)
-Null/inverse association (4 refs cited)

Small sample size, lack of adjustment for potential confounders, lack of standardization of BP measurements…

Biomarkers of Cd exposure

-Urine Cd: long-term exposure
-Blood Cd: long-term and recent exposure

Methods

Study population: NHANES 1999-2004, representative sample of US population.

Target: 15332 adults>=20 years of age
-833 pregnant women
-1719 no blood Cd
-582 no BP
-100 DBP = 0
-1107 missing other variables of interest

=10991 participants for analyses (blood Cd)
Of them, 3496 participants (urine Cd)

Methods: Cd exposure

-Measured in CDC

-Cd in whole blood: simultaneous multielement atomic absorption spectrometer (Perkin-Elmer model SIMAA 6000) with Zeeman background correction. LOD=2.67nmol/L (1999-2002) and 1.78 (2003-04). NIST standard ref materials used for calibration. Inter-assay CV=4.1% to 9.4%

-Cd in urine: ICP-MS (Perkin-Elmer/SCIEX model 500). LOD=0.53nmol/L. NIST standard ref materials (No.2679) were used for calibration. Inter-assay CV=1.2% to 4.7%.

Samples<LOD = LOD/(2^0.5)

Methods: BP

- Two physicians and two health technologists were trained following the AHA protocol
- 3 to 4 measurements after 5min rest
- All measurements in a same day
- Mean BPs were computed discarding the first reading

Hypertention SBP>=140 mmHg, DBP>=90 mmHg, a self-reported physical diagnosis, or medication use.

Other variables:

Age, sex, race/ethnicity, education, smoking, alcohol consumption (self-report), BMI, serum cotinine (measure of smoking), serum creatinine, urine creatinine, glomerular filtration rate（糸球体濾過量）(calculated from creatinine, age, sex, race/ethnicity using the formula of Stevens et al., 2006)

Statistical analysis:

Y: SBP and DBP, prevalence of hypertention
X: quartiles of blood/urine Cd, 10th and 90th percentile of Cd
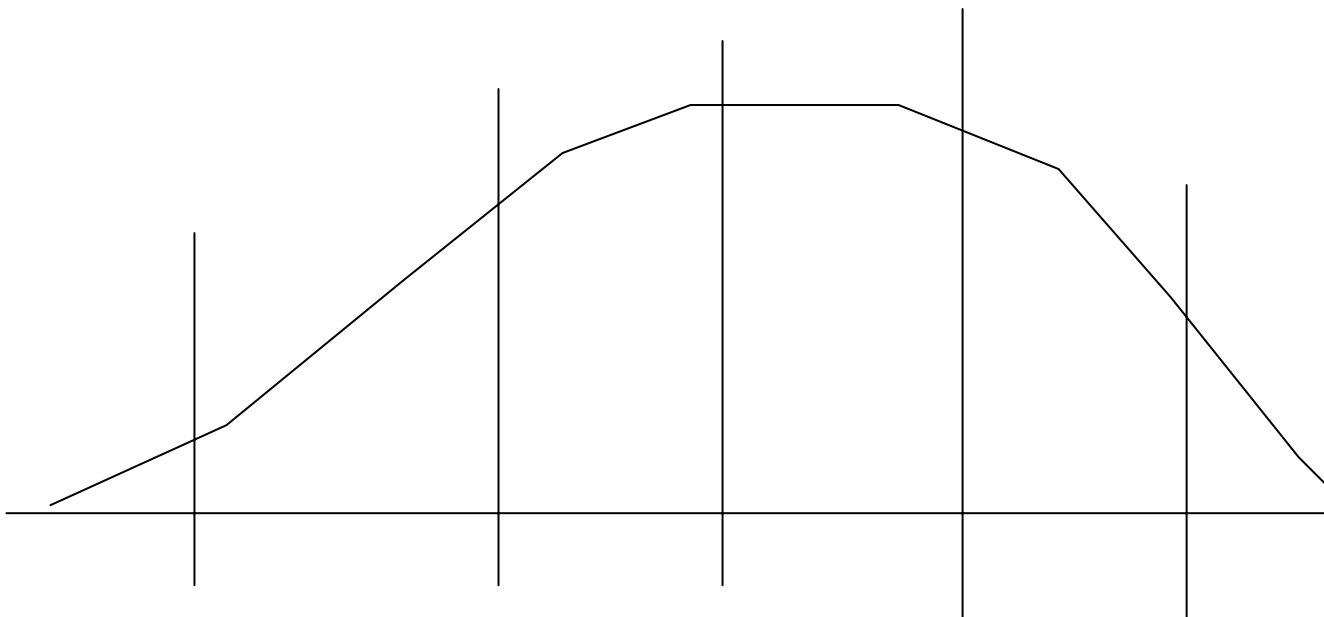
Adjustments:

Model 1: age (years modeled as restricted cubic spline with 5 knots), sex, race/ethnicity, education (< high school, high school, > high school).

Model 2: variables in Model 1 + smoking status (never, former, current), cotinine (log10 nmol/L), alcohol intake (never, former, current), BMI (kg/m2), menopause status (yes, no), antihypertensive medication (yes, no), blood lead (log10 μ mol/L)

Table 1. Participant characteristics by hypertension status.[a]

Characteristic	Hypertension ($n = 4{,}669$)	No hypertension ($n = 6{,}322$)	All ($n = 10{,}991$)
Age (years)	56.4 (0.36)	40.9 (0.25)	46.5 (0.27)
Sex (% male)	48 (0.93)	51 (0.56)	50.0 (0.45)
Race/ethnicity (% white)	76 (1.8)	73 (1.6)	74 (1.6)
Education (% > high school)	48 (1.1)	58 (1.2)	54 (1.0)
BMI (kg/m^2)	29.9 (0.15)	26.9 (0.10)	28.0 (0.10)
Smoking			
Former smoker (%)	33 (0.90)	21 (0.84)	25 (0.7)
Current smoker (%)	19 (0.74)	28 (1.0)	25 (0.7)
Cotinine[b] (nmol/L)	2.23 (1.84–2.70)	4.36 (3.52–5.61)	3.48 (2.87–4.24)
Alcohol intake			
Former drinker (%)	12 (0.97)	7 (0.53)	9 (0.6)
Current drinker (%)	54 (1.8)	69 (1.5)	63 (1.6)
Glomerular filtration rate (1 mL/min/1.73 m^2)	84.5 (0.53)	95.6 (0.51)	91.7 (0.46)
Blood lead[b] (µmol/L)	0.088 (0.085–0.091)	0.074 (0.072–0.076)	0.079 (0.077–0.081)
Blood cadmium[b] (nmol/L)	3.99 (3.85–4.12)	3.66 (3.49–3.83)	3.77 (3.63–3.92)
Urine cadmium[b,c] (nmol/L)	2.75 (2.58–2.93)	2.32 (2.18–2.47)	2.46 (2.35–2.59)
Urine cadmium[b,c] (nmol/mmol creatinine)	0.34 (0.32–0.36)	0.24 (0.23–0.25)	0.27 (0.26–0.28)

To convert serum cotinine from nmol/L to ng/mL, divide by 5.68; blood lead from µmol/L to µg/dL, divide by 0.0483; and blood and urine cadmium from nmol/L to µg/L, divide by 8.897. To convert urine cadmium from nmol/mmol creatinine to µg/g creatinine, divide by 1.006.
[a]Hypertension defined as mean systolic blood pressure ≥ 140 mmHg, mean diastolic blood pressure ≥ 90 mmHg, self-reported physician diagnosis, or medication use. [b]Geometric mean (95% CI); other results in the table are arithmetic means or percentages (SE). [c]Subsample (hypertension = 1,515; no hypertension=1,981; all = 3,496).

Figure 1. Blood and urine cadmium median (interquartile range) levels by participant characteristics. Points represent medians; horizontal lines represent interquartile ranges; and the dotted vertical line represents the median for the overall study sample.

	Blood cadmium		Urine cadmium
Never smoker	5,486		1,731
Former smoker	2,999		975
Current smoker	2,506		790
Never smoker: men	2,274		723
Former smoker: men	1,859		604
Current smoker: men	1,493		480
Never smoker: women	3,210		1,008
Former smoker: women	1,140		371
Current smoker: women	1,013		310
Cotinine < 0.57 μmol/L	5,782		1,823
Cotinine 0.57–56.8 μmol/L	2,323		763
Cotinine 56.8–852 μmol/L	1,134		352
Cotinine ≥ 852 μmol/L	1,752		558
Never alcohol drinker	3,382		1,078
Former alcohol drinker	1,219		426
Current alcohol drinker	6,390		1,992

Left axis (nmol/L): 1.5 5.6 9.8 14

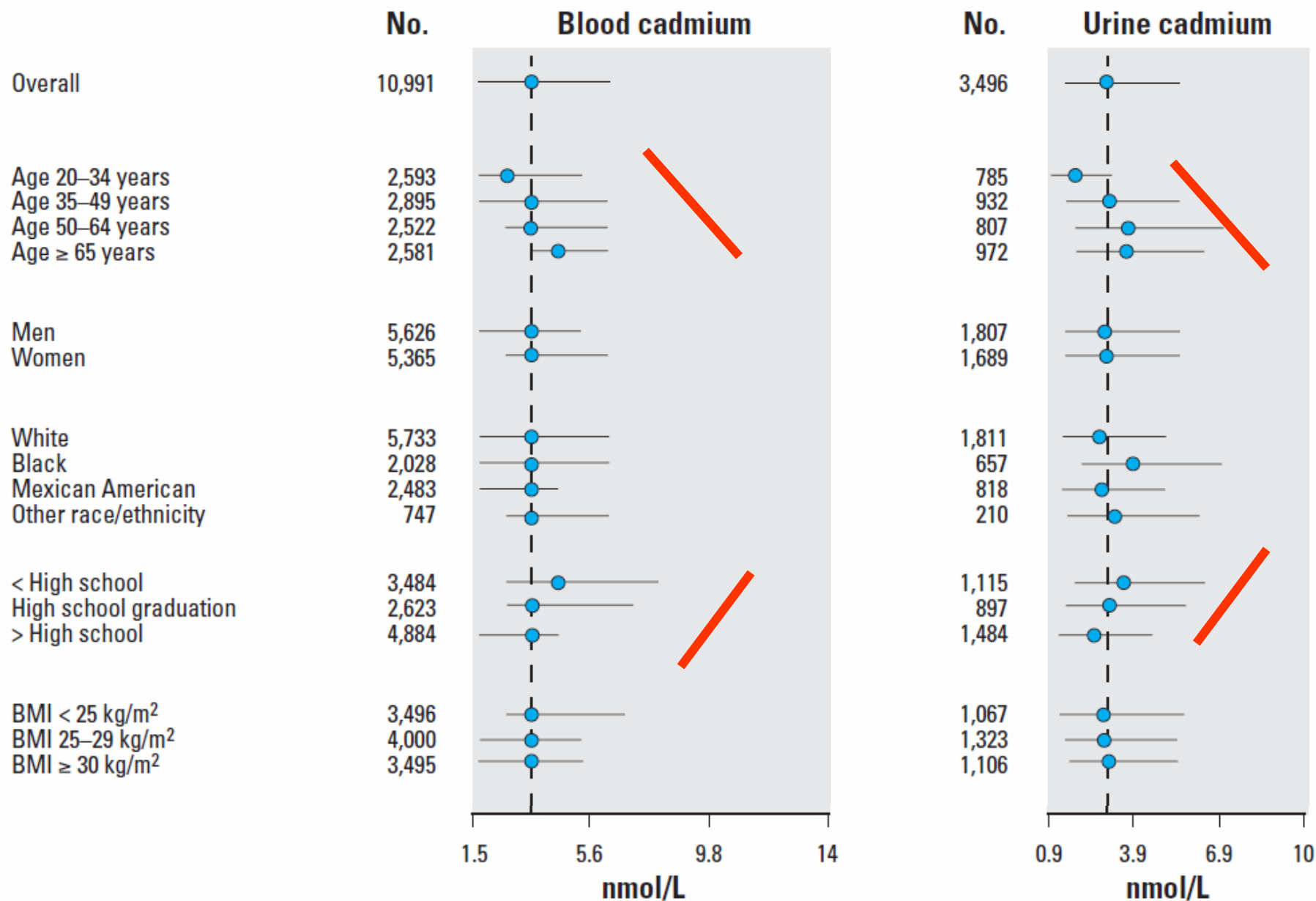Right axis (nmol/L): 0.9 3.9 6.9 10

Figure 1. Blood and urine cadmium median (interquartile range) levels by participant characteristics. Points represent medians; horizontal lines represent interquartile ranges; and the dotted vertical line represents the median for the overall study sample.
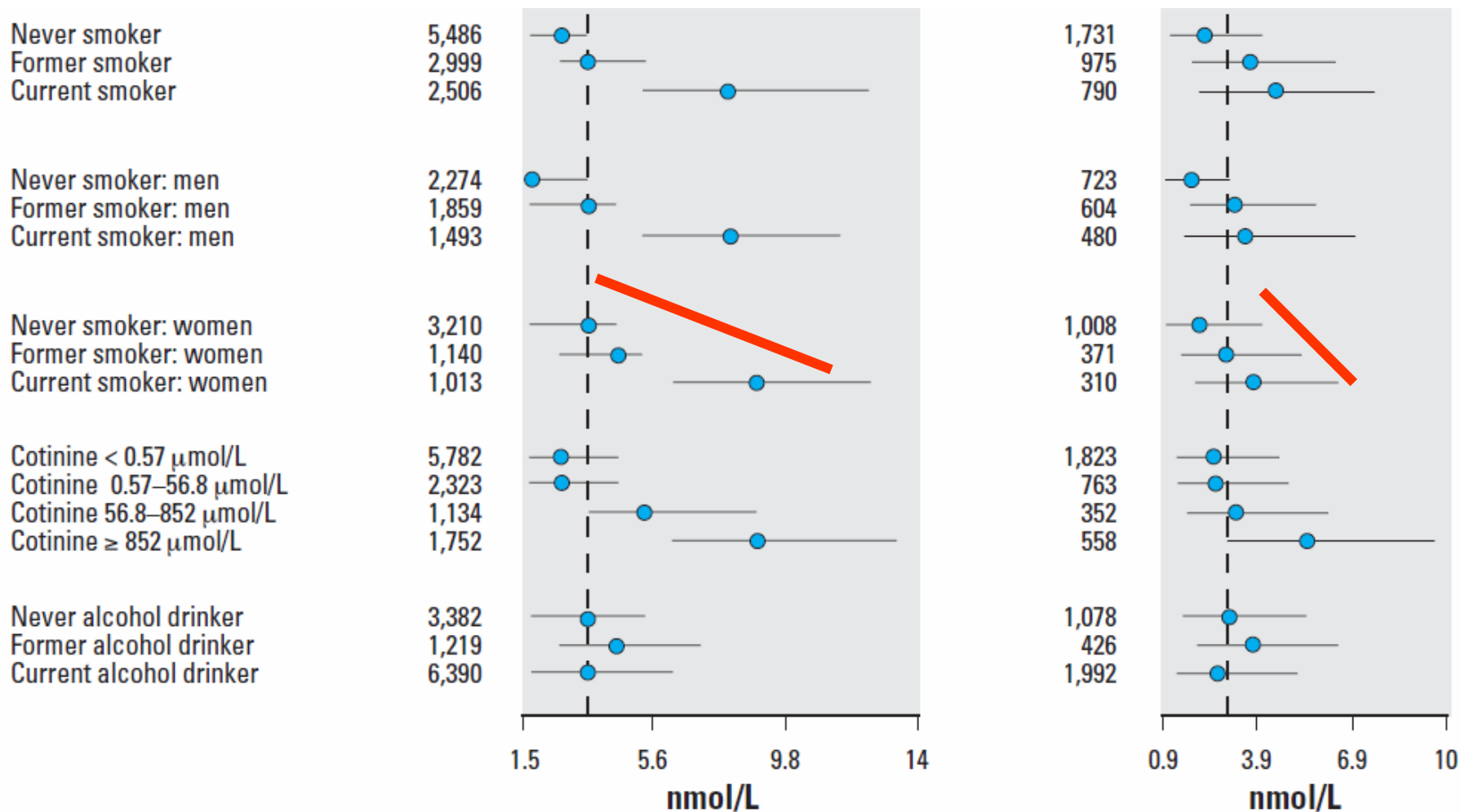
Table 2. Change (95% CI) of <u>systolic blood pressure</u> levels by blood cadmium and urine cadmium levels (nmol/L).

| | No. | Systolic blood pressure (mmHg) | |
		Model 1	Model 2
Blood cadmium			
Quartile 1 (≤ 1.78)	2,508	0.00 (reference)	0.00 (reference)
Quartile 2 (1.78–3.56)	3,394	0.21 (−0.63 to 1.06)	0.72 (−0.11 to 1.57)
Quartile 3 (3.56–6.23)	2,821	0.87 (−0.36 to 2.11)	1.85 (0.52 to 3.19)
Quartile 4 (> 6.23)	2,268	−0.24 (−1.40 to 0.89)	1.50 (−0.24 to 3.24)
p-Trend		0.775	0.116
90th–10th percentile		−0.15 (−1.18 to 0.88)	1.36 (−0.28 to 3.00)
Urine cadmium[a,b]			
Quartile 1 (≤ 1.51)	852	0.00 (reference)	0.00 (reference)
Quartile 2 (1.51–2.93)	895	−0.92 (−2.35 to 0.51)	−0.89 (−2.47 to 0.69)
Quartile 3 (2.93–5.51)	881	−1.01 (−3.25 to 1.23)	−0.55 (−3.03 to 1.93)
Quartile 4 (> 5.51)	868	−2.90 (−5.32 to −0.48)	−2.05 (−5.11 to 0.99)
p-Trend		0.031	0.251
90th–10th percentile		−2.92 (−5.47 to −0.37)	−1.78 (−4.76 to 1.19)

NS

Model 1 was adjusted for age (years modeled as restricted cubic spline with 5 knots), sex, race/ethnicity, education (< high school, high school, > high school). Model 2 was further adjusted for smoking status (never, former, current), cotinine (log10 nmol/L), alcohol intake (never, former, current), BMI (kg/m2), menopause status (yes, no), antihypertensive medication (yes, no), blood lead (log10 μ mol/L) **aAll models for urine cadmium are adjusted for urine creatinine levels. bSubsample (n = 3,496).**

Table 2. Change (95% CI) of <u>diastolic blood pressure</u> levels by blood cadmium and urine cadmium levels (nmol/L).

| | No. | Diastolic blood pressure (mmHg) | |
		Model 1	Model 2
Blood cadmium			
Quartile 1 (≤ 1.78)	2,508	0.00 (reference)	0.00 (reference)
Quartile 2 (1.78–3.56)	3,394	0.60 (−0.10 to 1.31)	1.00 (0.28 to 1.71)
Quartile 3 (3.56–6.23)	2,821	0.92 (−0.07 to 1.91)	2.01 (0.86 to 3.15)
Quartile 4 (> 6.23)	2,268	−1.06 (−1.80 to −0.32)	1.23 (0.10 to 2.35)
p-Trend		0.080	0.006
90th–10th percentile		−0.63 (−1.31 to 0.05)	1.68 (0.57 to 2.78)
Urine cadmium[a,b]			
Quartile 1 (≤ 1.51)	852	0.00 (reference)	0.00 (reference)
Quartile 2 (1.51–2.93)	895	−0.70 (−1.65 to 0.23)	−0.26 (−1.28 to 0.75)
Quartile 3 (2.93–5.51)	881	−0.63 (−1.78 to 0.51)	0.26 (−0.94 to 1.48)
Quartile 4 (> 5.51)	868	−2.01 (−3.68 to −0.33)	−0.45 (−2.34 to 1.44)
p-Trend		0.005	0.565
90th–10th percentile		−2.10 (−3.49 to −0.73)	−0.44 (−1.94 to 1.05)

** (Blood cadmium Model 2)

NS (Urine cadmium)

Model 1 was adjusted for age (years modeled as restricted cubic spline with 5 knots), sex, race/ethnicity, education (< high school, high school, > high school). Model 2 was further adjusted for smoking status (never, former, current), cotinine (log10 nmol/L), alcohol intake (never, former, current), BMI (kg/m2), menopause status (yes, no), antihypertensive medication (yes, no), blood lead (log10 μmol/L) **aAll models for urine cadmium are adjusted for urine creatinine levels. bSubsample (n = 3,496).**

Table 3. ORs (95% CIs) of <u>hypertension</u> by quartile of cadmium in U.S. adults (nmol/L).

	Cases (n)	Noncases (n)	Model 1	Model 2
Blood cadmium				
Quartile 1 (≤ 1.78)	819	1,689	1.00 (reference)	1.00 (reference)
Quartile 2 (1.78–3.56)	1,419	1,975	0.89 (0.75 to 1.05)	0.98 (0.80 to 1.19)
Quartile 3 (3.56–6.23)	1,452	1,369	0.99 (0.85 to 1.16)	1.25 (0.98 to 1.59)
Quartile 4 (> 6.23)	979	1,289	0.77 (0.66 to 0.90)	1.03 (0.77 to 1.36)
p-Trend			0.005	0.303
90th–10th percentile			0.84 (0.75 to 0.94)	1.14 (0.89 to 1.45)
Urine cadmium[a,b]				NS
Quartile 1 (≤ 1.51)	301	551	1.00 (reference)	1.00 (reference)
Quartile 2 (1.51–2.93)	369	526	0.86 (0.64 to 1.17)	0.80 (0.54 to 1.21)
Quartile 3 (2.93–5.51)	430	451	0.93 (0.65 to 1.36)	1.02 (0.66 to 1.58)
Quartile 4 (> 5.51)	415	453	0.68 (0.48 to 0.97)	0.72 (0.43 to 1.21)
p-Trend			0.021	0.170
90th–10th percentile			0.63 (0.43 to 0.91)	0.66 (0.37 to 1.17)

Model 1 was adjusted for age (years modeled as restricted cubic splines with 5 knots), sex, race/ethnicity, education (< high school, high school, > high school). Model 2 was further adjusted for smoking (never, former, current), cotinine (log10 nmol/L), alcohol intake (never, former, current), BMI (kg/m2), menopause (yes, no), antihypertensive medication (yes, no), blood lead (log10 μ mol/ L).
aAll models for urine cadmium are adjusted for urine creatinine levels.
bSubsample (n = 3,496).

Table 4. Change (95% CI) of systolic blood pressure levels (mmHg) comparing the 90th to 10th percentile of blood and urine cadmium levels by sex and smoking status

	No.	Systolic blood pressure (mmHg)	p-Value for interaction
Blood cadmium	BP: Cd, smoking, current smoking × Cd, former smoking × Cd		
Sex			
Men	5,626	0.86 (−0.84 to 2.56)	Ref.
Women	5,365	1.40 (−0.82 to 3.62)	0.444
Smoking			
Never	5,486	2.35 (0.64 to 4.05)	Ref.
Former	2,999	1.69 (−1.55 to 4.92)	0.200
Current	2,506	0.02 (−1.97 to 2.01)	0.001
Urine cadmium[a,b]			
Sex			
Men	1,807	−3.27 (−5.48 to −1.05)	Ref.
Women	1,689	−4.68 (−6.94 to −2.43)	0.926
Smoking			
Never	1,731	−4.06 (−6.89 to −1.23)	Ref.
Former	975	−3.10 (−7.20 to 0.99)	0.996
Current	790	−4.72 (−8.27 to −1.18)	0.730

NS

Models were adjusted for age (years modeled as restricted cubic splines with 5 knots), race/ethnicity, education (< high school, high school, > high school), cotinine (log10 nmol/L), alcohol intake (never, former, current), BMI (kg/m2), menopause status (yes, no), antihypertensive medication (yes, no, only for systolic and diastolic blood pressure models), blood lead (log10 μmol/L), sex (models by smoking status), or smoking status (models by sex). **aAll models for urine cadmium are adjusted for urine creatinine levels. bSubsample (n = 3,496).**

Table 4. Change (95% CI) of diastolic blood pressure levels (mmHg) and ORs (95% CIs) of hypertension comparing the 90th to 10th percentile of blood and urine cadmium levels by sex and smoking status

	No.	Diastolic blood pressure (mmHg)	p-Value for interaction	OR of hypertension	p-Value for interaction
Blood cadmium		BP: Cd, smoking, current smoking × Cd, former smoking × Cd			
Sex					
Men	5,626	1.81 (0.40 to 3.22)	Ref.	1.00 (0.74 to 1.37)	Ref.
Women	5,365	1.78 (0.65 to 2.92)	0.495	1.31 (0.90 to 1.90)	0.487
Smoking					
Never	5,486	3.27 (1.69 to 4.84)	Ref.	1.25 (0.87 to 1.81)	Ref.
Former	2,999	1.55 (−0.39 to 3.49)	0.070	1.23 (0.72 to 2.07)	0.491
Current	2,506	0.69 (−0.69 to 2.06)	0.006	1.01 (0.72 to 1.44)	0.245
Urine cadmium[a,b]					
Sex					
Men	1,807	−1.74 (−3.38 to −0.09)	Ref.	0.60 (0.34 to 1.08)	Ref.
Women	1,689	−1.00 (−2.39 to 0.39)	0.595	0.51 (0.33 to 0.79)	0.762
Smoking					
Never	1,731	−1.08 (−2.69 to 0.53)	Ref.	NS (0.19 to 0.62)	Ref.
Former	975	−0.36 (−3.03 to 2.31)	0.948	0.89 (0.42 to 1.87)	0.123
Current	790	−2.67 (−5.22 to −0.11)	0.312	0.75 (0.41 to 1.38)	0.100

Models were adjusted for age (years modeled as restricted cubic splines with 5 knots), race/ethnicity, education (< high school, high school, > high school), cotinine (log10 nmol/L), alcohol intake (never, former, current), BMI (kg/m2), menopause status (yes, no), antihypertensive medication (yes, no, only for systolic and diastolic blood pressure models), blood lead (log10 μ mol/L), sex (models by smoking status), or smoking status (models by sex). **aAll models for urine cadmium are adjusted for urine creatinine levels. bSubsample (n = 3,496).**

Summary of the findings:

In NHANES samples,

1. Cd levels in blood, but not in urine, were associated with a modest elevation of BP levels.

2. There were no association between Cd levels and the prevalence of hypertention.

3. By smoking status, the association for blood Cd and BP was stronger among never smokers, intermediate among former smokers, and small/null among current smokers.

Blood Cd, but not urine Cd were associated with BP

-Recent cadmium exposure having a short-term effect on blood pressure levels?

- Blood cadmium could more readily reflect biologically active Cd?

Previous studies:

CadmiBel study in Belgium (N=2086: Staessen et al., 1991, 2000)

-Change in blood Cd between 1985-89 and 1991-95 were positively associated with changes in DBP but not in SBP
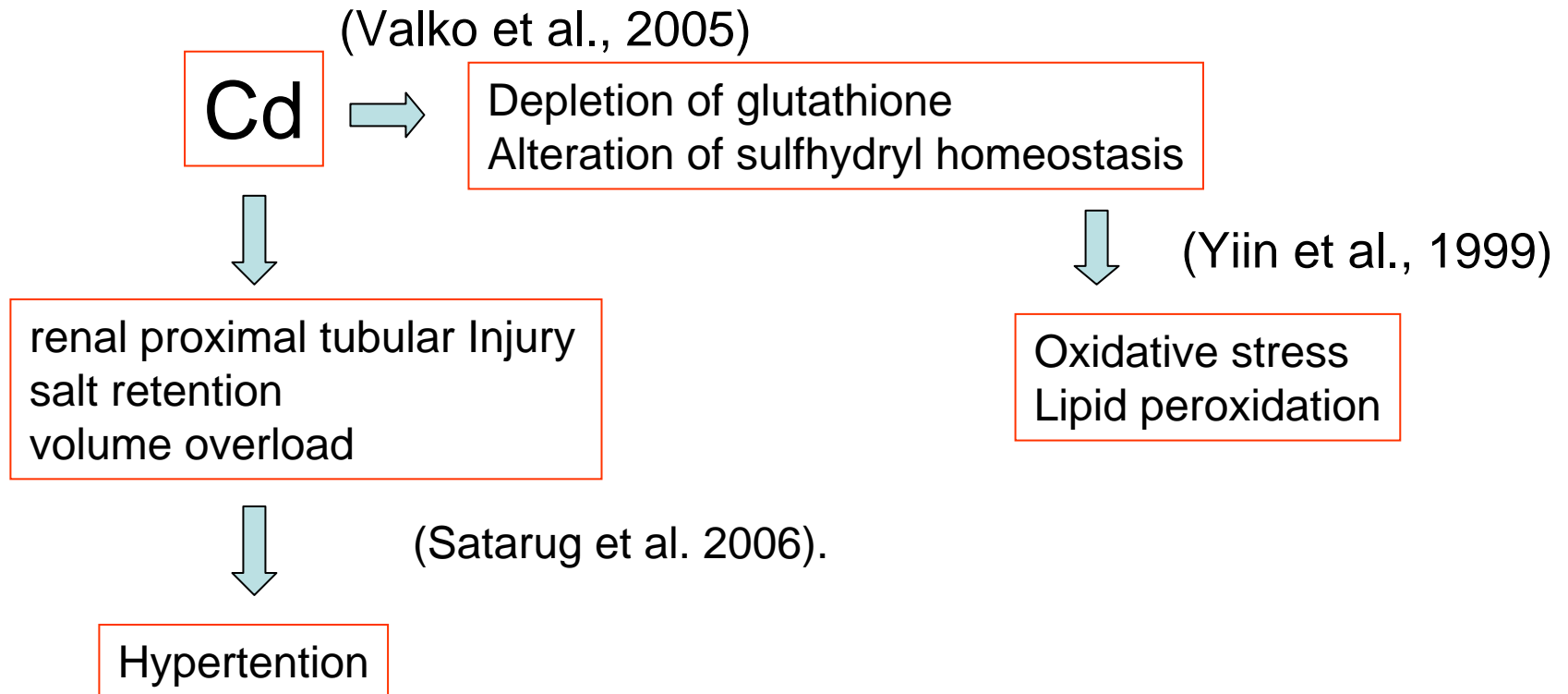- No association was found between urine Cd and BPs.

NHANES II in US, 1976-88 (n=951: Whittemore et al., 1991)

-positive but moderate association between urine Cd and BPs

Other studies: smaller samples=random variability (5 refs cited)

Itai-Itai diseases in Japan, n=52 women with the disease had lower BPs than the matched controls (Kagamimori et al., 1986)

Possible mechanisms:

(Valko et al., 2005)

Cd ⟹ Depletion of glutathione
Alteration of sulfhydryl homeostasis

(Yiin et al., 1999)

renal proximal tubular Injury
salt retention
volume overload

Oxidative stress
Lipid peroxidation

(Satarug et al. 2006).

Hypertention

partial agonism for calcium channels (Varoni et al. 2003)
direct vasoconstrictor action
activation of the sympathetic nervous system
inhibition of vasodilator substances such as nitric oxide (Bilgen et al. 2003;
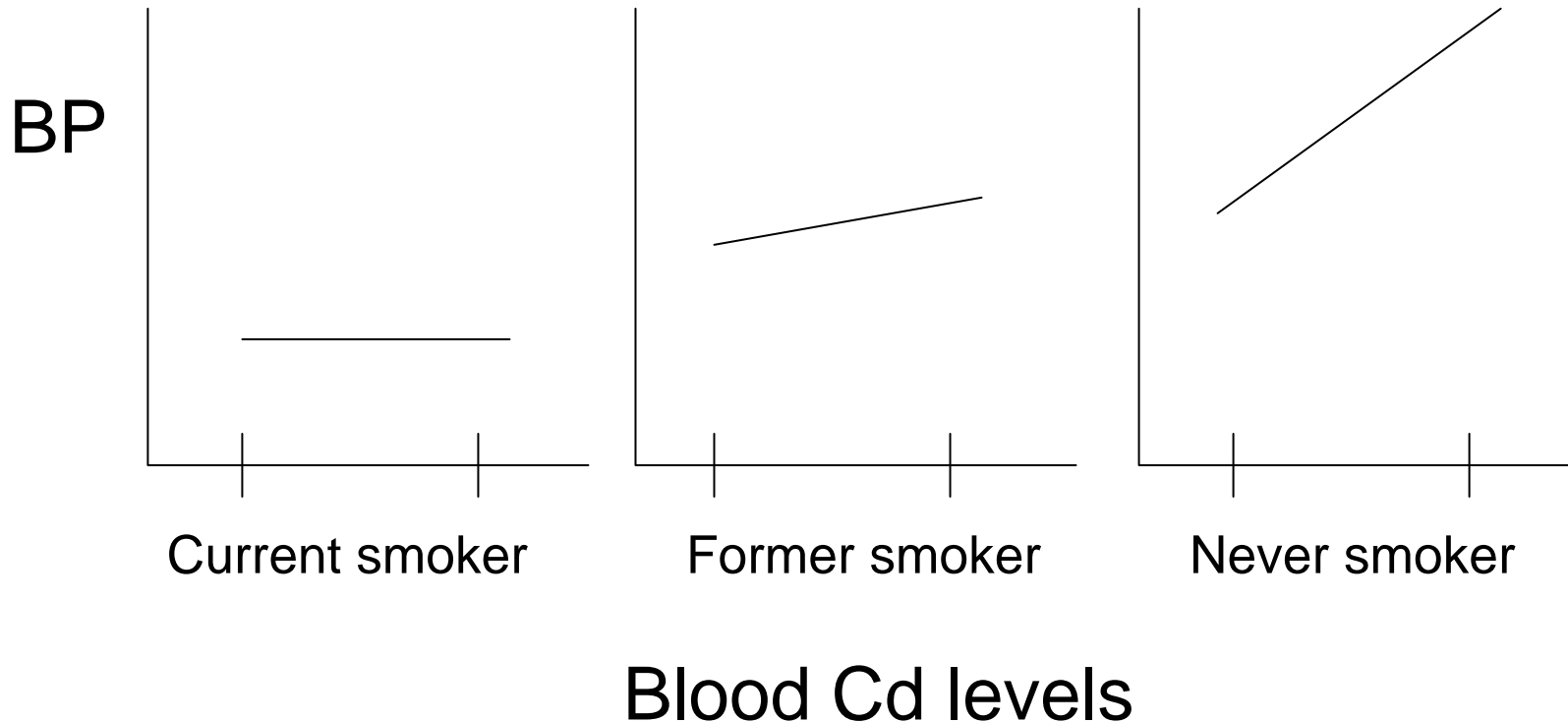Varoni et al. 2003).

Metallothionine:

A low-molecular-weight metal-binding protein induced by Cd exposure

Induction of metallothionine: dose and frequency of Cd exposure

| Smokers | → | Induction of metallothionine |

↓

Protection of kidney and
other organs from toxic effects of Cd
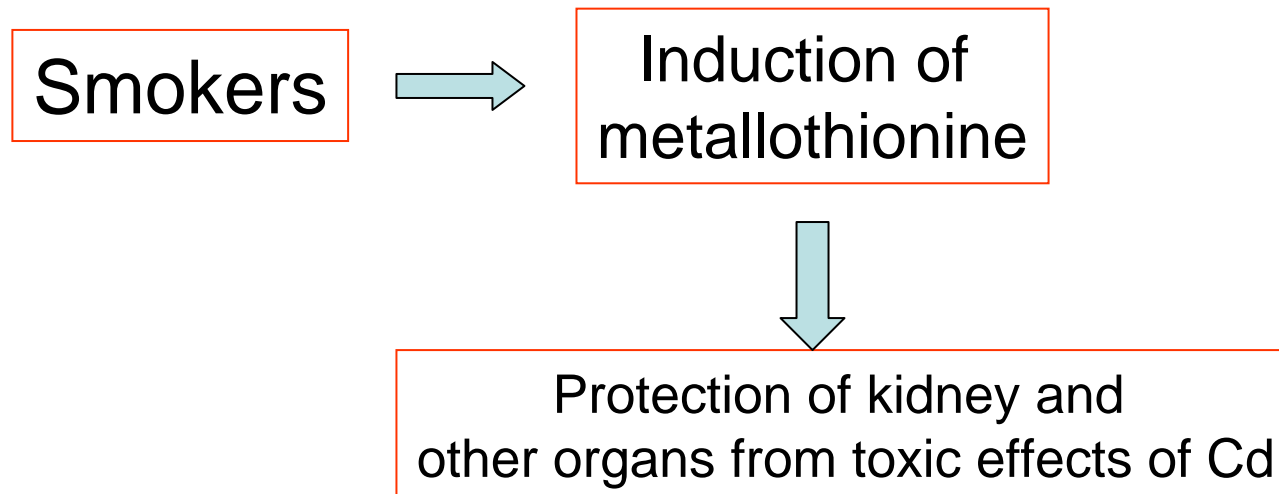
Inclusion of metallothionine in the study design

Smoking, Cd exposure and BP

BP (y-axis), Blood Cd levels (x-axis)

Current smoker | Former smoker | Never smoker

Potential explanations include markedly different sources, routes, and patterns of cadmium exposure for smokers versus nonsmokers, unknown differences in participant characteristics or co-exposures by smoking status.

Conclusion:

Cadmium levels in blood, but not in urine, were associated with a modest elevation in blood pressure levels. The association was stronger among never smokers, intermediate among former smokers, and small or null among current smokers. Our findings add to the concern of renal and cardiovascular cadmium toxicity at chronic low levels of exposure in the general population.