

Department of Epidemiology

Welch Center for Prevention, Epidemiology, and Clinical Research

Metals in blood and urine and risk of peripheral arterial disease

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Objectives

- **Use NHANES 1999 – 2000 data to:**
- **Evaluate the association between blood lead and cadmium with the prevalence of peripheral arterial disease (*Circulation* 2004;109:3196-201)**
- **Evaluate the association of urinary levels of 9 metals with the prevalence of peripheral arterial disease (*Env. Health Perspect.* 2005;113:164-9)**
- **Illustrate use of public data for Tracking purposes**

Peripheral Arterial Disease (PAD)

- **Atherosclerosis in arteries of the lower extremities**
- **Wide range of manifestations:**
 - **Subclinical:** ratio of blood pressure ankle vs. blood pressure in the arm
 - **Symptomatic:** cramping in the leg muscles when walking
- **Risk Factors:**
 - Hypertension, diabetes, hypercholesterolemia
 - Smoking



Lead and Cadmium – Cardiovascular Disease

- **Blood pressure**
- **Cardiovascular outcomes:**

Lead

- **NHANES II: cardiovascular mortality**
- **Denmark: cardiovascular incidence**
- **British men: cardiovascular incidence – no association**

Cadmium

- **Ecological studies: US (1966) The Netherlands (1993)**
- **Case-Control studies (1979 and 1982)**
- **Cross-sectional study in Belgium (1990s) – no association**

Lead and Cadmium – Atherogenic Mechanisms

- **Increase oxidative stress**
- **Affect endothelial function**
- **Promote inflammation**
- **Down regulate nitric oxide production**
- **Induce renal dysfunction**
- **Increase blood pressure levels**

Mechanistic studies have been conducted, in general, at higher doses than the general population is exposed to

National Health and Nutrition Examination Surveys (NHANES)

- **Probability samples of the US civilian non-institutionalized population**
 - NHANES I (1971 – 1974)
 - NHANES II (1976 – 1980)
 - NHANES III (1988 – 1994)
 - NHANES 1999 – 2002
- **Survey participants selected using a complex, stratified, multistage probability cluster sampling design**
- **<http://www.cdc.gov/nchs/nhanes.htm>**

Study Population



	N
NHANES 1999 – 2000	9,965
Subjects \geq 40 years	3,185
ABI measurements	2,381
Final sample size	2,125

Exclusion: 6 subjects with ABI $>$ 1.5

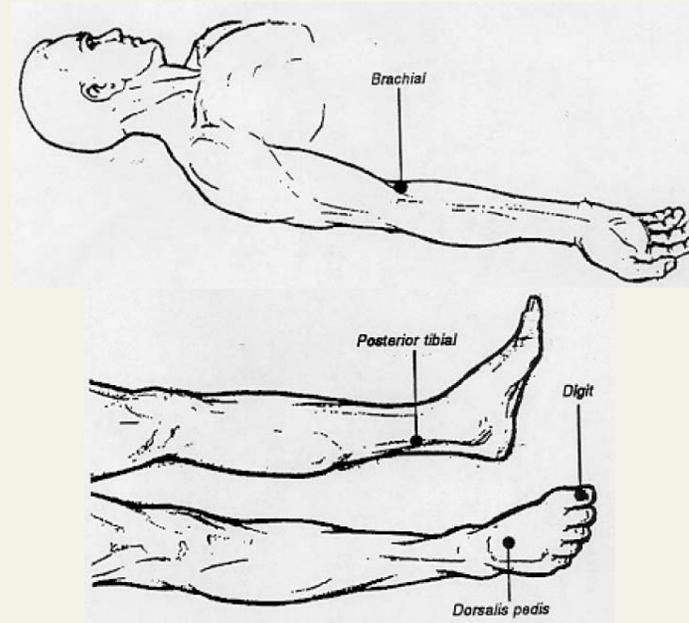
250 (11%) with missing values

PAD – Ankle Brachial Index (ABI)

Specific protocol for ABI



Parks mini-lab vascular testing device



ABI = ankle SBP / brachial SBP for each leg

PAD = ABI < 0.90 in at least one leg

SBP: systolic blood pressure

Blood Lead and Cadmium

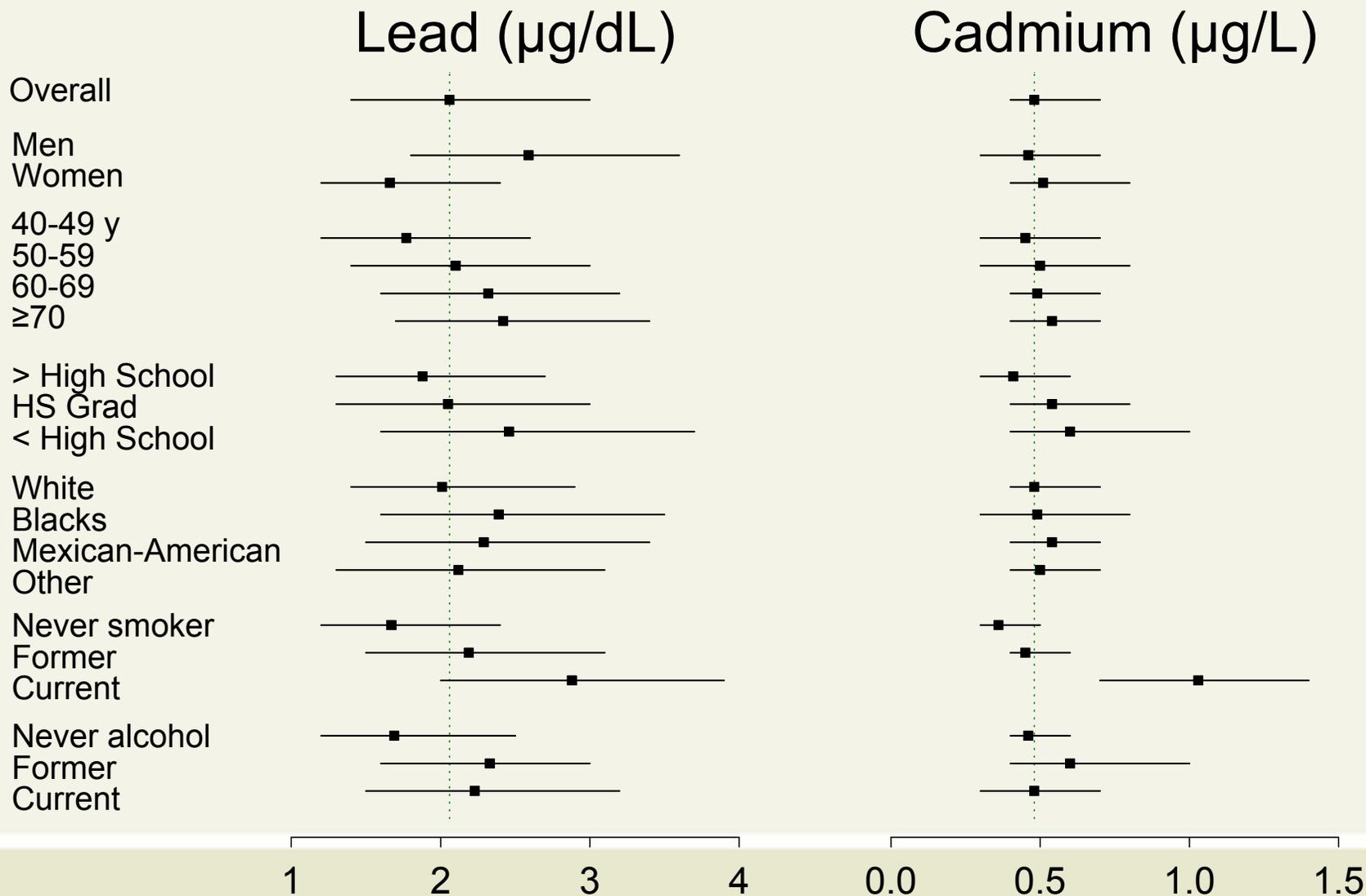
- **Blood collected in ordinary tubes (previous confirmation of no background contamination)**
- **Atomic absorption spectrometry (CDC/NCEH Laboratory)**
- **Limit of detection: lead 0.3 $\mu\text{g}/\text{dL}$, cadmium 0.3 $\mu\text{g}/\text{L}$**
- **No. of subjects < limit of detection: 2 for lead and 230 for cadmium**
- **Extensive quality control procedures**

Other variables

- **Age, sex, race-ethnicity, education**
- **Smoking status and alcohol intake**
- **Body mass index**
- **Hypertension, hypercholesterolemia, diabetes**
- **C-reactive protein**
- **Glomerular filtration rate**
- **Serum cotinine**

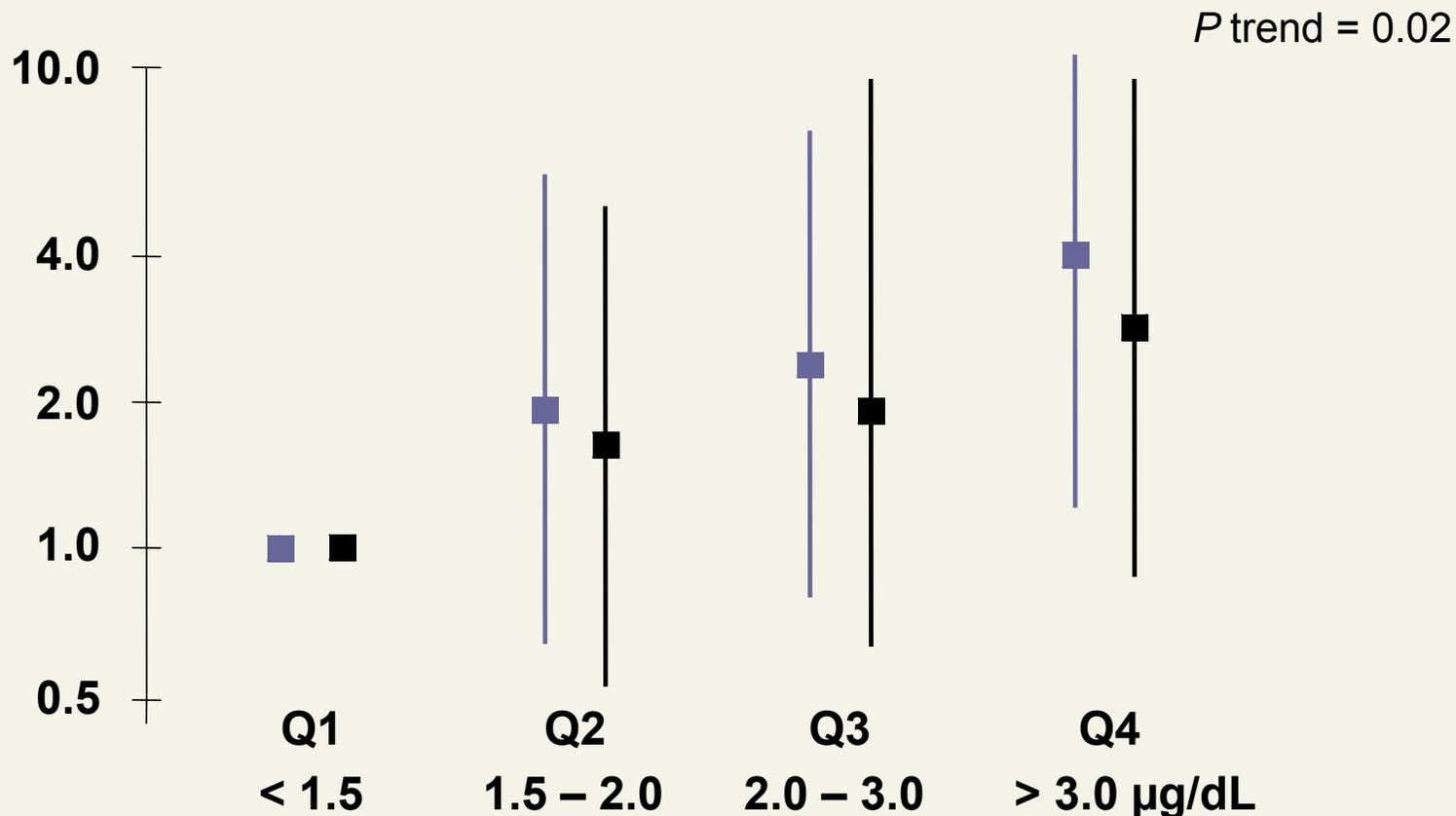
Information on income, urbanization, residence or occupation not available

Geometric Mean and IQR by Participant Characteristics



Blood Lead and PAD

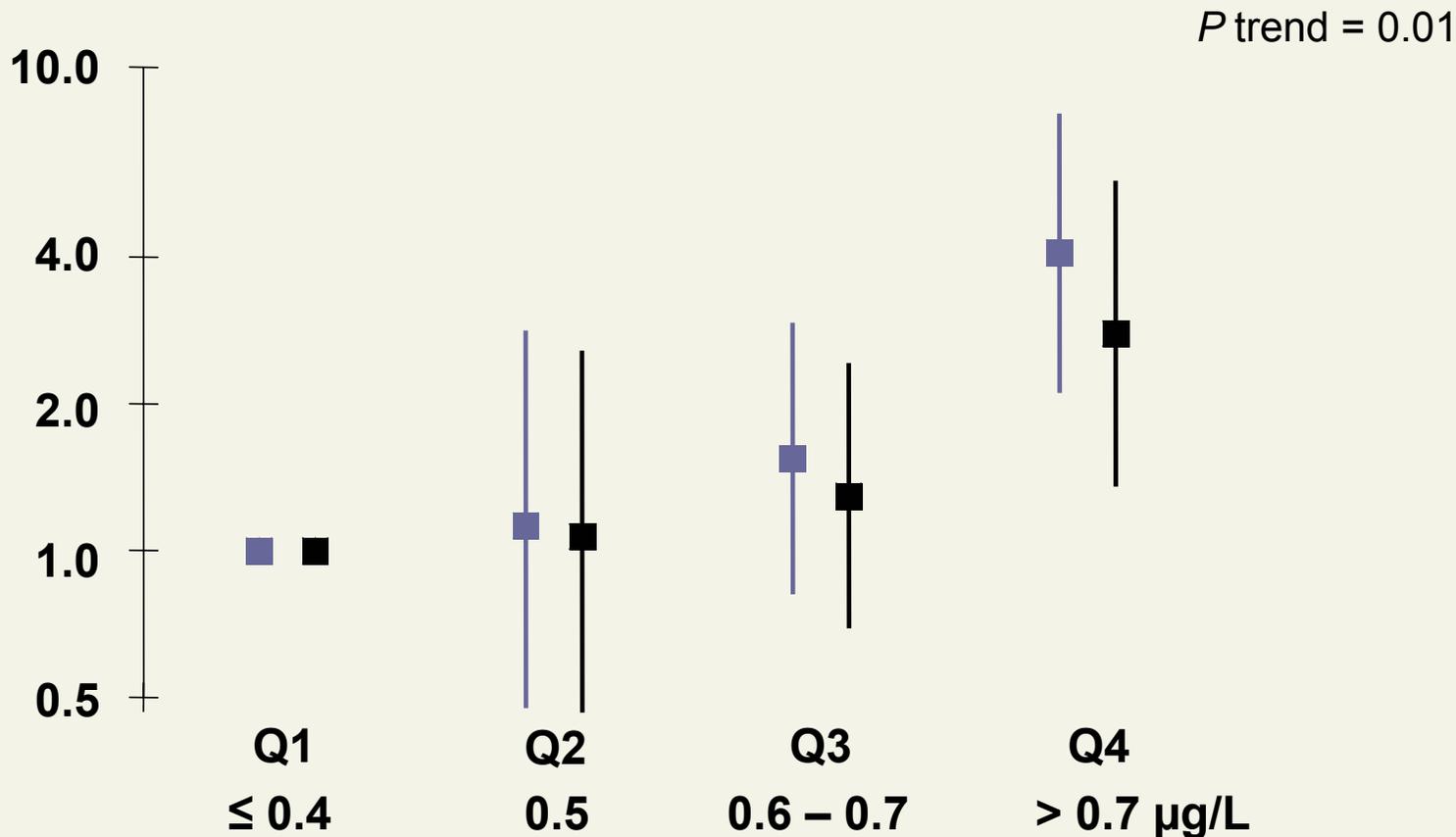
OR and 95% CI



- Adjusted for age, sex, race, education, body mass index, alcohol intake, hypertension, diabetes, hypercholesterolemia, glomerular filtration rate and C-reactive protein
- Further adjusted for smoking status (never/former/current) and serum cotinine

Blood Cadmium and PAD

OR and 95%CI



■ Adjusted for age, sex, race, education, body mass index, alcohol intake, hypertension, diabetes, hypercholesterolemia, glomerular filtration rate and C-reactive protein

■ Further adjusted for smoking status (never/former/current) and serum cotinine

Smoking and PAD

OR and 95%CI

	Cases, n	Noncases, n	Not Adjusted for Lead or Cadmium	Adjusted for Lead	Adjusted for Cadmium	Adjusted for Lead and Cadmium
Smoking status						
Never	43	942	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Former	56	667	1.31 (0.82–2.10)	1.22 (0.75–1.99)	1.04 (0.65–1.68)	1.02 (0.63–1.65)
Current	40	377	4.13 (1.87–9.12)	3.38 (1.56–7.35)	1.84 (0.78–4.39)	1.75 (0.74–4.10)
Cotinine levels, nmol/L						
<0.7 (0.1 ng/mL)	68	1096	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
0.7–57 (0.1–10 ng/mL)	23	439	0.83 (0.43–1.63)	0.78 (0.39–1.55)	0.80 (0.42–1.53)	0.76 (0.39–1.48)
57–852 (10–150 ng/mL)	11	170	1.50 (0.48–4.70)	1.35 (0.45–4.01)	0.87 (0.31–2.46)	0.86 (0.31–2.40)
852–1704 (150–300 ng/mL)	25	190	3.87 (1.83–8.20)	3.22 (1.53–6.75)	1.95 (0.87–4.37)	1.83 (0.80–4.17)
≥1704 (300 ng/mL)	12	91	4.33 (1.67–11.23)	3.44 (1.33–8.89)	2.30 (0.81–6.57)	2.10 (0.74–5.97)

All models were adjusted for sex, age, race, education, body mass index, alcohol intake, hypertension, diabetes, hypercholesterolemia, and glomerular filtration rate.

Study Population



	N
NHANES 1999 – 2000	9,965
Urinary metals	2,465
ABI measurements	796
Final sample size	790

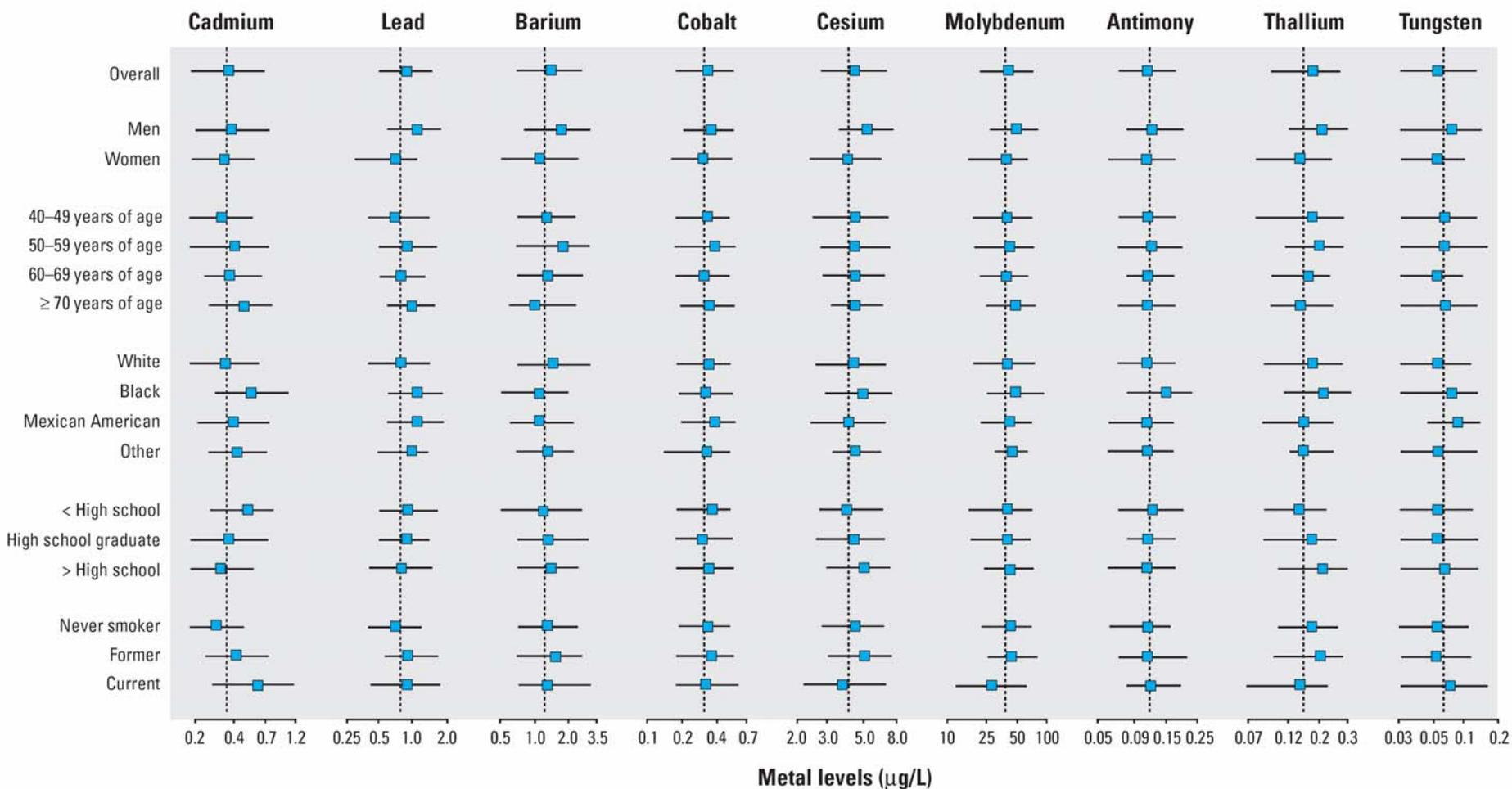
Exclusion: 1 subjects with $ABI > 1.5$
5 with missing values

Some people had missing data for some metals

Urinary Metals

- **Spot urine specimen**
- **Inductively coupled plasma-mass spectrometry (CDC/NCEH Laboratory)**
- **Available levels of cadmium, lead, barium, cobalt, cesium, molybdenum, antimony, thallium, tungsten**
- **Range of limits of detection: thallium 0.01 µg/L – molybdenum 0.85 µg/L**
- **Range of subjects < LOD: 0.5% for cesium – 30% for tungsten**
- **Extensive quality control methods**

Metal Levels in Urine ($\mu\text{g/L}$)



lines (—) represent interquartile ranges and squares (■) represent medians. The dotted vertical line is plotted at the geometric mean for the overall study sample.

Ratio of the Geometric Mean of Metal Levels in PAD cases vs. non-cases

	Cases	Noncases	Model 1 ^a	Model 2 ^b	Model 3 ^c
Cadmium	49	679	1.81 (1.24–2.62)	1.62 (1.19–2.21)	1.36 (1.01–1.83)
Lead	54	736	1.09 (0.86–1.37)	1.08 (0.85–1.38)	0.92 (0.74–1.15)
Barium	45	659	0.99 (0.67–1.47)	0.99 (0.68–1.45)	0.82 (0.60–1.11)
Cobalt	54	736	1.13 (0.80–1.59)	1.13 (0.82–1.57)	0.98 (0.69–1.40)
Cesium	54	736	1.05 (0.83–1.32)	1.12 (0.89–1.42)	0.96 (0.79–1.16)
Molybdenum	49	679	0.97 (0.66–1.42)	1.08 (0.74–1.57)	0.91 (0.72–1.15)
Antimony	49	676	1.18 (0.92–1.51)	1.17 (0.92–1.50)	1.03 (0.87–1.22)
Thallium	54	722	0.97 (0.71–1.34)	1.08 (0.78–1.48)	0.94 (0.74–1.19)
Tungsten	51	700	1.75 (0.98–3.10)	1.67 (0.96–2.89)	1.49 (0.90–2.49)

^aAdjusted by age, sex, race, and education. ^bFurther adjusted by smoking status (never/former/current). ^cFurther adjusted by urinary creatinine.

Odds Ratio of PAD – 75th vs. 25th Percentile of Metal Level

	Cases	Noncases	Model 1 ^a	Model 2 ^b	Model 3 ^c
Cadmium	49	676	2.67 (1.40–5.07)	2.14 (1.11–4.13)	3.05 (0.97–9.58)
Lead	54	736	1.17 (0.81–1.69)	1.17 (0.78–1.76)	0.89 (0.45–1.78)
Barium	45	659	1.02 (0.67–1.56)	1.07 (0.72–1.58)	0.88 (0.57–1.36)
Cobalt	54	736	1.21 (0.65–2.23)	1.22 (0.67–2.20)	1.01 (0.33–3.14)
Cesium	54	736	1.08 (0.73–1.60)	1.19 (0.78–1.80)	0.91 (0.33–2.48)
Molybdenum	49	679	0.98 (0.60–1.60)	1.10 (0.69–1.77)	0.83 (0.49–1.41)
Antimony	49	676	1.25 (0.93–1.68)	1.30 (0.95–1.77)	1.15 (0.81–1.63)
Thallium	54	722	0.96 (0.53–1.73)	1.18 (0.60–2.32)	0.87 (0.30–2.52)
Tungsten	51	700	2.45 (1.12–5.37)	2.23 (1.03–4.82)	2.25 (0.97–5.24)

^aAdjusted by age, sex, race, and education. ^bFurther adjusted by smoking status (never/former/current). ^cFurther adjusted by urinary creatinine.

Odds Ratios of PAD by Metal Levels in Urine

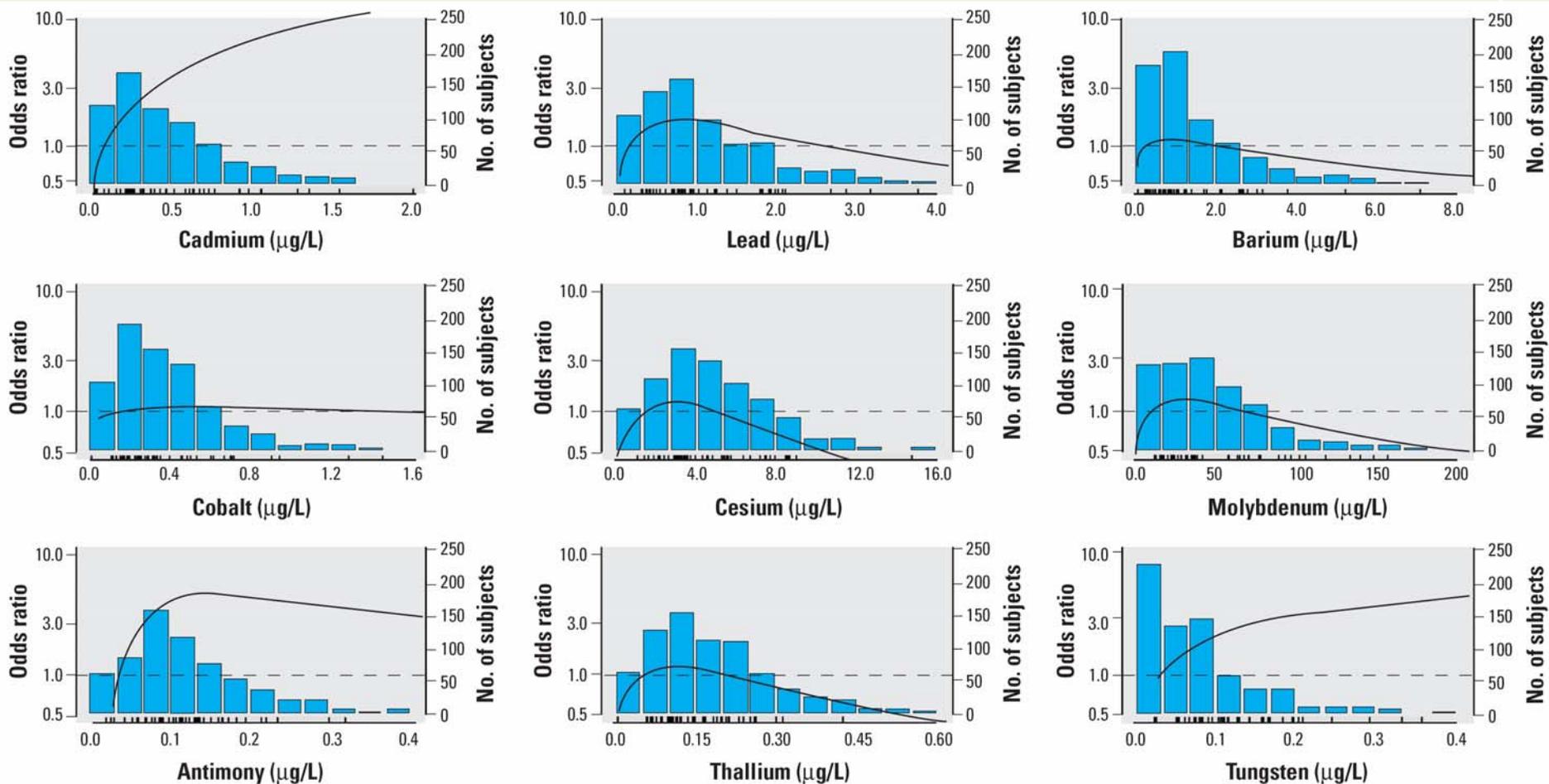


Figure 2. Odds ratios of PAD by metal levels in urine. The curves are odds ratios adjusted for age, sex, race, education, smoking, and urinary creatinine based on restricted cubic spline transformations. The reference value (odds ratio = 1) was set at the 10th percentile of the distribution for each metal. The bar histograms represent the frequency distribution of each metal in the study sample. The tick marks at the bottom of the histogram represent the metal level of the cases of PAD.

Tungsten

- **Little is known on its toxicity and carcinogenicity**
- **Insufficient human or animal data on cardiovascular effects**
- **Tungsten is thrombogenic and pro-inflammatory (tungsten coils used in abnormal vascular connections)**
- **CDC nominated tungsten to the National Toxicology Program (NTP) as a priority candidate for toxicological assessment**

Antimony

- **Inconclusive cardiovascular data**
- **Similar chemical and toxicological properties with arsenic and frequent co-exposure**
- **Association between arsenic and PAD well-known**
- **No arsenic levels in NHANES 1999-2000**
- **Further studies on antimony and cardiovascular endpoints are needed**

Limitations

- **Cross-sectional design and prevalent PAD**
- **Confounding by socioeconomic status, urbanization, other pollutants**
- **One single blood or urine sample**
- **Small number of cases for analyses of urinary metals**
- **Exploratory hypothesis for analyses of most urinary metals**

Strengths

- **Sampling design – representative of US population**
- **Quality of measurements in NHANES**
- **ABI – non invasive and subclinical measure of atherosclerosis**
- **Biomarkers that integrate all routes of exposure**
- **Large sample size for analysis of blood lead and cadmium levels**

Conclusions

- **Blood lead and cadmium were associated with the prevalence of PAD**
- **Cadmium may mediate the atherogenic effects of smoking**
- **Urinary cadmium was strongly associated with PAD**
- **Tungsten and maybe antimony were also associated with PAD, although the results need to be interpreted cautiously**
- **No association between PAD and other metals in urine**
- **Usefulness of public data for Tracking**