NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

June 13, 2012

APPENDIX C:
HUMAN STUDIES OF CARDIOVASCULAR EFFECTS OF LEAD CONSIDERED IN DEVELOPING CONCLUSIONS

Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Blood Pressure and Hypertension							
Case-control Al-Saleh (2005) Saudi Arabia	185 Saudi women: 100 with and 85 without hypertension during or after menopausal period and not occupationally exposed to Pb; from the Polyclinic and Family Health Medicine Clinic; Year = 2001-2002; Male = 0%	45-92 years	4.66 (3.47) µg/dL Range= (1.19-28.3) µg/dL	Hypertension (based on medication use, controls had average of 3 readings ≤120/80mmHg with no reading ≥130/85 mmHg at any time in medical record)	Chi-squared test for categorical variables; binary logistic regression analysis for continuous variables; multiple regression In multiple regression only: Menopausal status, time since menopause, physical activity, history of breast feeding, family income, attended school, work status, family history of hypertension, heart diseases, rheumatologic diseases, other diseases, intake of supplements and minerals, age, creatinine and blood Pb levels as categorized by the median value	*Binary logistic regression* Hypertension status on blood Pb levels β (SE); OR (95% CI); p Q1 (≤ 2.82 µg/dL): Ref. Q2 (>2.82 to <3.86 µg/dL): β(SE)=0.17 (0.43) OR= 1.19 (0.52-2.69) *p*=0.68 Q3 (≥3.86 to 5.08 µg/dL): β(SE)= 0.77 (0.43) OR=2.16 (0.92-5.05) *p*=0.08 Q4 (≥5.08 µg/dL): β(SE)= -0.08 (0.42) OR= 0.92 (0.41-2.09) *p*=0.84 < 3.86 vs. ≥ 3.86 µg/dL: β(SE)= 0.24(0.30) OR=1.27 (0.71-2.26) p=0.42 *Multiple Regression (median blood Pb levels)* < 3.86 vs.≥ 3.86 µg/dL: β (SE)= 1.66 (0.885) OR=5.27 (0.93-29.86) p=0.06	Concurrent blood Pb was not significantly associated with hypertension in older women.
‡Cross-sectional Apostoli (1990) Verona, Italy	525 subjects (254 men and 271 women) sampled from a general medical practice near Verona, Italy; Year not stated Male = 48%	<10µg/dl: (mean men 30.6, women 34.6) 10-20µg/dl (mean men 38.4, women 39.3) >20µg/dl (mean men 39.2, women 38.7)	<10µg/dl (n=38 men, 151 women) 10-20µg/dl (n=152 men, 112 women) >20µg/dl (n=57 men, 12 women)	Systolic and diastolic blood pressure (SBP and DBP), average of 3 readings Hypertension (≥160/95 SBP/DBP) in 88 subjects (50 men, 38 women)	Variance analysis For hypertension, Student t test Multiple logistic regression Likelihood ratio test of significance for regression coefficients No adjustment for other factors	Males Blood Pb: mean SBP (SD)/ mean DBP (SD) < 10µg/dl (n=38): 134 (12)/83 (10) 10-20µg/dl (n=152): 133 (15)/ 85 (9) > 20µg/dl (n=57): 140 (18)/ 88 (10) ***P* value: SDP <0.05, DBP <0.005** Normotensive (n=204): 15.7 (6.0) Hypertensive (n=50): 17.8 (7.2) ***P* value: <0.05** Females Blood Pb: mean SBP (SD), mean DBP (SD) < 10µg/dl (n=151): 127 (15)/ 81 (8) 10-20µg/dl (n=112): 132 (16)/ 83 (10) > 20µg/dl (n=12): 137 (13)/ 89 (10) ***P* value: SDP <0.005, DBP <0.01** Normotensive (n=233): 10.1 (3.9) Hypertensive (n=38): 12.8 (5.2) ***P* value: <0.005**	Concurrent blood Pb was significantly associated with SBP, DBP, and hypertension in both men and women.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Case-Control Bakhtiarian (2006) Tehran, Iran	160 hospital patients without a history of kidney disease, diabetes, or occupational Pb exposure (80 with hypertension and 80 normotensives); Year =2003; % male not stated	Mean not reported Range: 40-70 years	3.8 µg/dl Range: 2.6-16.5 µg/dl	Hypertension (>190/140mmHg and anti-hypertensive medication) Systolic and diastolic blood pressure (SBP and DBP)	One-way ANOVA with Tukey test of significance ("Turkey" is likely a typo) No adjustment for other factors	Hypertensive, Normotensive mean blood Pb (S.D.), p-value: **All: 5.1 (0.4) µg/dl, 2.6 (0.3) µg/dl, p<0.0001** **Women: 4.8 (0.6) µg/dl, 3.0 (0.4) µg/dl, p<0.001** **Men: 5.6 (0.6) µg/dl, 2.3 (0.5) µg/dl, p<0.001** **40-49 years: 7.2 (2.4) µg/dl, 3.1 (0.05) µg/dl, p<0.01** **50-59 years: 4.3 (2.4) µg/dl, 1.9 (0.3) µg/dl, p<0.01** 60-69 years: 5.3 (2.3) µg/dl, 4.0 (1.9) µg/dl, NS In normotensives, mean SBP (S.D.) and DBP (S.D.): 0-1.18µg/dl: 112.4 (0.8), 70.7 (0.7) 1.19-2.22µg/dl: 124.55 (0.8), 73.1 (1.2) 2.23-3.5µg/dl: 130.0 (1.8), 80.2 (0.4) 3.51-5.76µg/dl: 132.1 (1.2), 82.0 (0.5) 5.77-16.48µg/dl: 123.1 (0.8), 80.3 (1.6)	Blood Pb was significantly higher in hypertension cases, but in normotensives blood Pb was not significantly associated with SBP or DBP.
‡Cross-sectional Bost (1999) England	5,326 adults over age 16 in the Health Survey for England; Year = 1995; Male = 48%	Calc mean: 47.6 Men: 47.5 (0.34) Women: 47.7 (0.33)	Calc mean: 3.13 Men: 3.7 Women: 2.6	Systolic and diastolic blood pressure (SBP and DBP)	Stepwise multiple regression analyses. Age, BMI, smoking, social class, region of residence, and alcohol	Standardized regression coefficients for blood Pb and $\log_{10}$(BP): Men, SBP: NS **Men, DBP: 0.061 *P* < 0.001** Women, SBP: NS Women, DBP: NS A halving of blood Pb is estimated to decrease DBP in men by 0.88 mm Hg (95%CI 0.13-1.63)	Concurrent blood Pb was significantly associated with increased DBP in men.
Prospective Chen (2006) USA	780 children with had blood Pb levels of 20-44 µg/dL at age 12-33 months who were enrolled in the Treatment of Lead Exposed Children (TLC) Study and followed every 3-4 months for 5 years.; Year = 1994-1997; Male = 56%;	12-33 months at baseline	Baseline: 25 (5) µg/dl Five-year follow-up: 8 (4) µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression models. Mixed models with repeated blood Pb and blood pressure measurements. Clinical center, race, sex, parent's education, single parent, age at measurement, height, BMI.	After initiation of treatment, children in the succimer group had lower blood levels than the placebo for 9-10 months; the two groups had similar blood Pb levels until the end of the study. Adjusted regression estimates [β (95% CI)] Baseline SBP = 1.36 (-0.58, 3.30) DBP = 1.47 (-0.16, 3.10) Day 42 (1st round of chelation) SBP = 0.07 (-1.33, 1.47) DBP = 1.19 (-0.07, 2.44) 12 months SBP = 0.24 (-0.97, 1.46) DBP = -0.28 (-1.26, 0.69) 24 months SBP = -0.68 (-1.76, 0.39) DBP = 0.32 (-0.52, 1.16) 60 months SBP = 0.01 (-1.71, 1.73) DBP = 0.15 (-1.25, 1.55)	Concurrent blood Pb was not significantly associated with BP when levels were over 20µg/dL at age 12-33 months or as Pb levels dropped below 10µg/dL over 60 months of follow up.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
†Prospective Cheng (2001) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	519 men in the Normative Aging Study who were not hypertensive when baseline Pb levels were measured and followed for 3 to 6 years (n=474); Year 1991-1997; Male = 100%	At baseline: Calc. mean = 66.5 Normotensive (n=337) 65.49 (7.17) Borderline hypertension (n=182) 68.30 (7.79)	**Blood at baseline:** Calc. mean = 5.9 Norm. (n=323) 5.87 (4.01) Borderline hypertension (n=174) 6.00 (3.69) **Bone at baseline:** Tibia calc. mean = 21.4 Patella calc. mean = 30.6 Norm. (n=337) Tibia 20.27 (11.55) Patella 28.95 (18.01) Borderline hypertension (n=182) Tibia 23.46 (15.02) Patella 33.73 (21.76)	Systolic and diastolic blood pressure (SBP and DBP) and hypertension in follow-up visit.	Multivariate regression of Pb with age, age^2, BMI, and family history of hypertension, alcohol intake, and calcium intake Proportional hazards model controlled for age, age^2, BMI, and family history of hypertension	Regression coefficient (95%CI) for systolic BP (n=519) based on 1 SD increase in Pb: Blood Pb (1 SD = 4.03µg/dl): -0.13 (-1.35 to 1.09) **Tibia Pb (1 SD = 13.65µg/g): 1.37 (0.02 to 2.73)** Patella Pb (1 SD = 19.55µg/g): 0.57 (-0.71 to 1.84) Cox proportional hazards model Rate Ratio (95%CI) for incident definite hypertension in those normotensive at baseline (n=474 with follow up) based on 1 SD increase: Blood Pb (1 SD = 4.03µg/dl): 1.00 (0.76 to 1.33) Tibia Pb (1 SD = 13.65µg/g): 1.22 (0.95 to 1.57) **Patella Pb (1 SD = 19.55µg/g): 1.29 (1.04 to 1.61)** Rate ratio of hypertension for an from the midpoint of the lowest to the highest quintile: **Tibia Pb: 1.49 (95% CI 0.89 to 1.49)** **Patella Pb: 1.71 (95% CI 1.08 to 2.70)** No association with blood Pb level.	Bone Pb was significantly associated with higher BP 3 to 6 years later, but blood Pb was not associated.
‡Cross-sectional Chu (1999) Taiwan	2,800 subjects who had lived in Taiwan for at least 6 months; Year= 1993-1994; Male = 53%	44.3 (15.4) years Range= 15 – 85 years	6.5 (4.7) Range: (0.1 – 69.1)	Systolic and diastolic blood pressure (SBP and DBP)	Pearson's correlation coefficients; multiple regression analyses; Univariate analyses – backward elimination Age, BMI, milk intake, alcohol intake, smoking	Regression analyses of blood Pb and BP: **SBP Male (p = 0.015)** β = 0.185 (0.076) R^2 = 0.241 SBP Female (p = 0.603) β = -0.057 (0.109) R^2 = 0.274 DBP Male (p = 0.159) β = 0.075 (0.053) R^2 = 0.117 DBP Female (p = 0.250) β = -0.083 (0.072) R^2 = 0.171	Concurrent blood Pb was significantly associated with higher DBP in men, but not with SBP or in women.
‡Cross-sectional Den Hond (2002) USA	13,781 adults age 20 or older (46.8% male) in NHANES III; Year= 1988-1994	White Males (n=4685): 44.3 (16.6) years	MEDIAN (interquartile range):	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression analysis by race and sex. Adjustments included	Change in SBP for a doubling of blood Pb: (95% CI), P White male = 0.3 (-0.2 to 0.7), P=0.29 White female = 0.1 (-0.4 to 0.5), P=0.8 **Black male = 0.9 (0.04 to 1.8), P=0.04**	Concurrent blood Pb was significantly associated with

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Population may overlap with Vupputuri (2003)		White Females (n=5138): 46.2 (17.8) years Black Males (n=1761): 40.5 (15.3) Black Females (n=2197): 41.5 (16.3)	White Males: 3.6 (2.3-5.3) White Females: 2.1 (1.3-3.4) Black Males: 4.2 (2.7-6.5) Black Females: 2.3 (1.4-3.9)		age, age^2, BMI, smoking, alcohol consumption, coffee consumption, dietary calcium, dietary sodium/potassium ratio, hematocrit, serum total calcium, serum total protein, anti-hypertensive drug use, and diabetes.	**Black female = 1.2 (0.4 to 2.0), *P*=0.004** Change in DBP for a doubling of blood Pb: (95% CI), *P* **White male = -0.6 (-0.9 to -0.3), *P*=0.0003** White female = -0.2 (-0.5 to 0.1), *P*=0.13 Black male = 0.3 (-0.3 to 1.0), *P*=0.28 **Black female = 0.5 (0.01 to 1.1), *P*=0.047**	higher SBP in black subjects and DBP in white males and black females.
Cross sectional Dolenc (1993) and Staessen (1995) Belguim *Population may overlap with Staessen (1991)*	1648 adults (827 men, 821 women; Cadmium in Belgium (Cadmibel) Study; Year: 1985-1989; Male = 50%	45 (15) years Range: 20-88 Men: 46 (15) years Women: 44 (15) years	OHAT calc. 8.3 µg/dl Range: (2.1-29.2) Men: 0.5 µmol/l (Range: 0.2-1.4) OHAT calc. 10.4 µg/dl (4.2-29.2) Women: 0.3µmol/l (Range: 0.1-0.8) OHAT calc. 6.25 µg/dl (2.1-16.7)	Systolic and diastolic blood pressure (SBP and DBP)	Free-running stepwise multiple regression Adjusted for: age, age^2, BMI, pulse rate, log γ-glutamyltranspeptidase, log serum creatinine, serum calcium, urinary potassium, smoking, alcohol intake, contraceptive pill intake*, and menopause* *in women only	Partial regression coefficients of BP and log blood Pb: **Men, SBP: -5.2 ± 2.4, partial r= -0.07, *P*=0.04** Men, DBP: -1.1 ± 1.6, NS Women, SBP: 0.5 ± 2.8, NS Women, DBP: -0.3 ± 1.7, NS 1.5mmHg decrease in SBP for a doubling of blood Pb Some indication of an interaction with serum calcium	Concurrent blood Pb was not associated with increased BP.
Cross sectional Elmarsafawy (2006) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	471 men from the Normative Aging Study (Low calcium ≤800 mg/d n=259, high calcium >800 mg/d n=212); Year=1991-1996; Male = 100%	351 <70 years, 140 ≥ 70 years (enrolled 1963-1968 with an average age of 42, range 21-80)	Blood: 6.6 ± 4.3 µg/dL Tibia: 21.6 ± 12.0 µg/g, Patella: 31.7 ± 18.3 µg/g	Hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg or a physician's diagnosis with use of antihypertensive medications), systolic and diastolic blood pressure (SBP and DBP)	Logistic regression models stratified by dietary calcium intake and linear regression with blood pressure. Age, family history of hypertension, history of smoking, and BMI	Odds Ratio of Hypertension (95% CI): Low calcium intake (≤800 mg/day) **Blood Pb (µg/dL): 1.07 (1.00-1.15)** **Tibia Pb (µg/g): 1.02 (1.00-1.04)** **Patella Pb (µg/g): 1.01 (1.00-1.03)** High calcium intake (>800 mg/day) Blood Pb (µg/dL): 1.03 (0.97-1.11) Tibia Pb (µg/g): 1.01 (0.97-1.04) Patella Pb (µg/g): 1.01 (0.99-1.03) OR for hypertension from a 1 SD increase in tibia Pb in the high calcium group = 1.3 (95% CI 0.97-1.74) Linear regression for hypertension with a 1µg/g increase in tibia Pb: **Low calcium = 0.19mmHg (95% CI 0.01-0.37)** **High calcium = 0.40mmHg (95% CI 0.11-0.70)** Blood and Patella Pb linear regressions N.S. (data not shown)	Blood Pb, tibia Pb, and patella Pb were significantly associated with hypertension which may be modified by dietary calcium intake.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
‡Cross sectional Elwood (1988a) and Elwood (1988b) Wales, England *Both papers included the Welsh Heart Programme as well.*	1,136 (1,137 in other paper) men from the Caerphilly Collaborative Heart Disease Studies, living in Caerphilly, South Wales; Year= 1985 Male = 100%	Range: 49-63 years	12.7 (6-26)	Systolic and diastolic blood pressure (SBP and DBP) Cold Pressor Test: the hand and wrist are immersed in water at 4°C for 1 min. The consequent rise in blood pressure has been shown to be predictive of ischemic heart disease.	Regression coefficients, partial regression coefficients, and correlation coefficients (*r*). The only covariant was age.	Regression coefficients of blood pressure on blood Pb (±SE) [NOT in the Cold Pressor Test]: SBP = 0.077 (±0.126) DBP = 0.049 (±0.068) Regression coefficients between resting blood pressure and the rise in log blood pressure in the Cold Pressor Test on log blood Pb (age adjusted): Resting blood pressure: SBP = 1.112 (±1.830) DBP = 0.879 (±0.984) Rise in cold pressor test: SBP = 0.0006 (±0.0006) DBP = 0.0002 (±0.0007) Correlation coefficients (*r*) between log blood Pb and log resting BP and the rise in log blood pressure in the Cold Pressor Test (age adjusted) [if r>0.06, p <0.05]: Resting blood pressure: SBP = 0.0183 DBP = 0.0230 Rise in Cold Pressor Test: SBP = 0.0342 DBP = 0.0078	Blood Pb was not significantly associated with blood pressure or blood pressure change after a cold pressor test.
‡Cross sectional Elwood (1988a) and Elwood (1988b) Wales, England *Both papers included the Caerphilly Collaborative Heart Disease Studies as well.*	1,721 adults from the Welsh Heart Programme (865 men and 856 women); Year= 1985 Male = 50%	18–64 years	Men (n=865): 11.6 (5.7- 23.3 Women (n=856): 9 (4.5-18.3) OHAT calc. mean: 10.3µg/dL	Systolic and diastolic blood pressure (SBP and DBP)	Regression coefficients, partial regression coefficients, and correlation coefficients (*r*). The only covariant was age.	Regression coefficients of blood pressure on blood Pb (±SE): Men: SBP = 0.050 (±0.108) DBP = 0.068 (±0.069) Women: SBP = 0.0 (± 0.135) DBP = 0.048 (±0.093) Partial regression coefficient between resting blood pressure and log blood Pb, adjusted for age: β(SE) Men: SBP = 0.82 (1.49) DBP = 1.29 (0.95) Women: SBP = 0.19 (1.46) DBP = 0.58 (1.00)	Blood Pb was not significantly associated with blood pressure.
Cross-sectional Factor-Litvak (1996) Kosovo, Yugoslavia	144 children residing in an unexposed town (Pristina), from a study of 281* children of women	5.5 years	Age 5.5: Unexposed 8.7 (2.8) [Exposed 37.3 (12.0)]	Systolic and diastolic blood pressure (SBP and DBP), mean of last two measures at the end of physical exam	Linear regression analysis SBP adjusted for: height, BMI, gender, ethnic group (Albanian, Serbian, other), and birth order	In the unexposed town with low blood Pb levels, estimated coefficient related to BPb: SBP: 0.17 (95% CI -0.47, 0.8) mmHg DBP: 0.052 (95% CI -0.37, 0.47) mmHg	Concurrent blood Pb was not significantly associated with BP in 5 year old children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Population may overlap with Factor-Litvak (1999)	recruited during pregnancy; here, we did not consider 137 children in the exposed town (Kosovska Mitrovica); Year=1985-1986 *abstract says 282		(12 measures of blood Pb from birth to age 5.5)		DBP adjusted for: waist circumference, ethnic group (Albanian, Serbian, other), and birth order		
Cross-sectional Factor-Litvak (1999) Kosovo, Yugoslavia *Population may overlap with Factor-Litvak (1996)*	577 children of women recruited during pregnancy from an exposed and an unexposed town. Year not stated % male not stated	Infants followed every 6 months until 7.5 years of age	mean not reported Range: 1 to 70 µg/dl	Systolic and diastolic blood pressure (SBP and DBP) K. Mitrovica: SBP: 100.5 ± 10.7 mm Hg DBP: 59.1 ± 7.5 mm Hg Pristina: SBP: 98.4 ± 10.0 mm Hg DBP: 58.4 ± 6.7 mm Hg	Least-squares regression (continuous variables) and unconditional maximum likelihood logistic regression (categorical variables) Covariates: SES (maternal education and intelligence), ethnicity, and quality of childrearing environment.	<u>At 5.5 years of age:</u> Association between BPb concentration and BP: SBP: β=0.054 (-0.024-0.13) DBP: β=0.042 (-0.010-0.090) 10µg/dl increase in BPb associated with adjusted increases in BP: SBP: 0.5 mm Hg (CI, -0.2-1.3) DBP: 0.4 mm Hg (CI, -0.1-0.9)	Blood Pb and BP were not significantly associated with BP in in 7 year old children.
‡Cross-sectional Gartside (1988) USA	20,325 subjects from the NHANES II; Year= 1976-1980; % male not stated	mean not reported Range: 21-65 years	mean not reported **limits utility*	Systolic and diastolic blood pressure (SBP and DBP)	Forward stepwise regression Demographic, socioeconomic dietary variables and other likely confounders details not provided	For all ages combined the increase in blood pressure for a doubling of blood Pb: White men: Systolic BP 2.777 mm Hg (SD = 0.972) Diastolic BP 1.323 mm Hg (SD = 0.476) White women: Systolic BP -0.335 mm Hg (SD = 0.374) Diastolic BP 0.700 mm Hg (SD = 0.276) Blacks: Systolic BP 0.915 mm Hg (SD = 3.730) Diastolic BP 2.88 mm Hg (SD = 3.088) Reports changes in SBP and DBP by gender and race showing how sensitive the significance is to age group categories.	Mean blood Pb was higher than 10µg/dl and was not significantly associated with increases in BP with a doubling of blood Pb levels.
†Cross-sectional Gerr (2002) WA, USA	508 participants with bone and BP Five-town cohort (exposed): 281 young adults (47% male) who had lived in one of 5 towns around a Pb smelter	24* 19-29 years in 1994 *from Navas-Acien (2008)	2.3 (1.9)* Bone Pb: <1 µg/g (n=210): 1.91 1-5 µg/g (n=126): 2.31	Systolic and diastolic blood pressure (SBP and DBP)	General linear regression models Age, sex, height, BMI, smoking, alcohol intake, use of birth control pills, hemoglobin, serum albumin, childhood residence group, recent	Mean BP by bone Pb content: Mean SBP (S.D.) by bone Pb (p=0.054): <1 µg Pb/g = 116.69 (12.23) 1 – 5 µg Pb/g = 116.63 (12.46) >5 – 10 µg Pb/g = 114.50 (10.80) >10 µg Pb/ = 119.72 (12.66) Mean DBP (S.D.) by bone Pb (p=0.080): <1 µg Pb/g = 73.10 (8.95)	Bone Pb was significantly associated with SBP and DBP in young adults some of which were exposure to environmental Pb as children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
	in Idaho as children in 1974/75 and a non-five-town cohort (unexposed): 287 young adults in Spokane WA; Year= 1994;		>5-10 µg/g (n=102): 2.43 >10µg/g (n=67): 3.15 *from Navas-Acien (2008)		Pb exposure, income category. Separate models with bone Pb as a four-ordinal variable (<1, 1 – 5, >5 – 10, >10 µgPb/g bone mineral) and as a continuous variable.	1 – 5 µg Pb/g = 72.75 (9.44) >5 – 10 µg Pb/g = 71.43 (8.12) >10 µg Pb/g = 75.00 (8.67) SBP by bone Pb estimate (S.E.) (<1 µg Pb/g = ref.): 1 – 5 µg Pb/g = 0.10 (1.11), p=0.93 >5 – 10 µg Pb/g = 0.98 (1.22), p=0.42 **>10 µg Pb/g = 4.26 (1.48), p=0.004** DBP by bone Pb estimate (S.E.) (<1 µg Pb/g = ref.): 1 – 5 µg Pb/g = -0.16 (0.94) p=0.868 >5 – 10 µg Pb/g = -0.01 (1.04), p=0.99 **> 10 µg Pb/g = 2.80 (1.25), p=0.03**	
†Prospective Glenn (2003) USA	496 men previously employed at a chemical-manufacturing facility on or after January 1, 1950 exposed to tetramethyl and tetraethyl Pb; Year= 1994 (baseline) followed until 1998; Male = 100%	55.8 (7.4) years at baseline Range 40-70 years	Baseline (1994) blood Pb = 4.6 (2.6) µg/dl Tibia Pb in 1997 = 14.7 (9.4) µg/g	Systolic and diastolic blood pressure (SBP and DBP)	Generalized estimating equation (GEE) SBP: baseline age, BMI, antihypertensive medications, smoking, education, technician, and years to each BP measurement DBP: baseline age; age^2; BMI; diabetes, arthritis or thyroid disease; race; education; technician; and years to each BP measurement	Average annual change in BP from 1994-1998 with one SD increase in Pb dose (blood Pb=2.6µg/dl, tibia Pb=9.4µg/g, peak tibia Pb=18.1µg/g): SBP: **Blood Pb (1994) β = 0.64 (0.14, 1.14)** **Tibia Pb (1997) β = 0.73 (0.23, 1.23)** **Peak Past Tibia Pb β = 0.61 (0.09, 1.13)** DBP: Blood Pb (1994) β = 0.09 (-0.24, 0.43) Tibia Pb (1997) β = 0.07 (-0.29, 0.42) Peak Past Tibia Pb β = 0.02 (-0.35, 0.39)	Blood and tibia Pb were significantly associated with increases in SBP but not DBP.
‡Prospective and cross-sectional Grandjean (1989) Denmark *Population may overlap with Møller (1992)*	861 adults with complete follow-up; born in 1936 and living in the 4 municipalities served by the Glostrup Hospital (Glostrup Population Study); Year = Baseline: 1976 (age 40); 5-year follow up: 1981 (age 45); Male = 42%	40 years old for first examination, 45 years old for second examination	Median (µg/dL) At 40 years: Men = 13 Women = 9 At 45 years: Men = 9 Women = 6	Systolic and diastolic blood pressure (SBP and DBP) Hypertension (SBP ≥160mmHg and/or DBP ≥95mmHg)	Multiple regression analysis. Adjusted for hemoglobin and alcohol	<u>Prospective</u> Increase in blood pressure at age 45 with a doubling in blood Pb at age 40, adjusted for age 45 confounders: SBP, age 40: Men: Unadj= 3.0*, Adj =1.4 Women: Unadj=2.3, Adj =p>0.5 DBP, age 40: Men: Unadj=1.1, Adj =p>0.5 Women: Unadj=0.7, Adj =p>0.5 <u>Cross-sectional</u> Increase in blood pressure with a doubling in blood Pb (multiplied regression coefficient by 0.3010): SBP, age 40: Men: Unadj= 2.6*, Adj =1.1 Women: Unadj=3.1*, Adj =p>0.5 DBP, age 40:	Blood Pb was not associated with BP or hypertension in prospective or cross-sectional analyses.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						Men: Unadj=p>0.5, Adj =-1.6 Women: Unadj=2.1*, Adj =1.2 SBP, age 45: Men: Unadj= 2.2, Adj =p>0.5 Women: no change (p>0.5 for all) DBP, age 45: Men: Adj hemo.=1.1, Adj =p>0.5 Women: Unadj=1.3, Adj =1.0 No difference in blood Pb levels between normotensive, increased (but not hypertensive) blood pressure, untreated, and treated hypertensives	
Prospective Gump (2005) NY, USA *Population may overlap with Gump (2007)* *Also listed for ECG Conduction Abnormalities*	122 children from Oswego Children's Study with established early childhood blood Pb levels; Year not stated Male = 45.9%	9.5	Cord = 2.97 (1.75) Childhood blood= 4.62 (2.51)* *Gump (2007) states this was abstracted from health records at average age of 2.6 years Correlation of cord and childhood Pb: *r* = 0.11, *p*>0.50	Systolic and diastolic blood pressure (SBP and DBP)	Linear regression Adjusted for: psychosocial variables, other toxicants, emotional response to tasks, *exact adjustment variables not reported*	<u>Cord blood Pb level µg/dL and BP:</u> **SBP: β=12.16 (4.96), p=0.016** DBP: β=8.45 (4.54), p=0.066 <u>Childhood blood Pb (µg/dL) and BP:</u> SBP and DBP had p-values >0.15 <u>Childhood blood Pb (µg/dL) and BP responses to acute stress tasks:</u> (β (95% CI), Standardized β, p-value) SBP: β= -0.009 (-.074 to .055), Std β=-0.026, p=0.773 **DBP: β= 0 .069 (-.001 to .138), Std β=0.182, p=0.052** (Cord blood and childhood blood Pb were not correlated (r=0.11, p>0.50)	Higher cord blood Pb levels were significantly associated with higher SBP while early childhood Pb levels were significantly associated with DBP response to acute stress.
Prospective Gump (2007) NY, USA *Population may overlap with Gump (2005)* *Also listed for ECG Conduction Abnormalities*	122 children from the Oswego Children's Study with established early childhood blood Pb levels; Year not stated Male = 45.9%	9.5	Cord = 2.97 (1.75) Childhood blood at age 2.6= 4.62 (2.51) *abstracted from health records	Includes family SES in evaluations of blood pressure	Sobel tests to evaluate mediation Linear regression Adjusted for: family SES, blood Pb levels, interaction of SES and blood Pb	<u>SES in relation to children's CV responses (β ; R^2; p-value of SES and Pb interaction)</u> SBP (mmHg): β=-1.192; R^2=0.102; p=0.007 DBP (mmHg): β=-0.701; R^2=0.037; p=0.013 <u>With SES X Pb interaction term</u>: SBP β=0.007, SE=0.003, *p*<0.01 DBP β=0.007, SE=0.003, *p*<0.05	Lower family SES was significantly associated with higher early childhood blood Pb levels and heightened BP responses to acute stress tasks at age 9-11 years.
Cross-sectional Gump (2011) NY, USA *Population may overlap with Gump (2005)*	140 children from the Oswego Children's Study Year not stated Male = 55%	10.21 (0.75) Range: 9-11	Median: 0.94 Range: 0-3.76	Systolic and diastolic blood pressure (SBP and DBP)	Generalized linear model with a linear contract test Adjusted for gender, age, race, BMI percentile standing, SES, family history of cardiovascular disease, and Hg level	<u>Adjusted associations of blood Pb and BP at baseline:</u> SBP (n=139): *p* linear trend = 0.51 Pb Q1 (0.14-0.68µg/dL): 106.10 Pb Q2 (0.69-0.93µg/dL): 102.60 Pb Q3 (0.94-1.20µg/dL): 107.34 Pb Q4 (1.21-3.76µg/dL): 102.47 DBP (n=139): *p* linear trend = 0.36 Pb Q1 (0.14-0.68µg/dL): 56.14	Concurrent blood Pb was not associated with statistically significant increases in SBP or DBP at baseline and in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Also listed for HRV and ECG Conduction Abnormalities						Pb Q2 (0.69-0.93µg/dL): 54.28 Pb Q3 (0.94-1.20µg/dL): 56.97 Pb Q4 (1.21-3.76µg/dL): 53.42 **BP significantly increased in response to acute stress tasks (SBP 106 to 113, *p*<0.0001 and DBP 57 to 61, *p*<0.0001).** Adjusted associations of blood Pb and BP reactivity to acute stress: SBP (n=139): *p* linear trend = 0.31 Pb Q1 (0.14-0.68µg/dL): 5.30 Pb Q2 (0.69-0.93µg/dL): 7.33 Pb Q3 (0.94-1.20µg/dL): 7.07 Pb Q4 (1.21-3.76µg/dL): 7.23 DBP (n=139): *p* linear trend = 0.29 Pb Q1 (0.14-0.68µg/dL): 4.02 Pb Q2 (0.69-0.93µg/dL): 5.64 Pb Q3 (0.94-1.20µg/dL): 5.09 Pb Q4 (1.21-3.76µg/dL): 5.53	response to acute stress tasks in children age 9-11.
‡ Cross-sectional Hense (1993) Germany *Population may overlap with Hense (1994)*	3,364 subjects participating in the WHO MONICA Project: Augsburg cohort first follow-up; Year= 1987-1988; Male = 50.6%	Range: 28 to 67 years	Median: Men = 8.3 µg/dL Women = 6.0 µg/dL	Systolic and diastolic blood pressure (SBP and DBP)	Linear regression with blood Pb as a continuous variable in univariate and multivariate models; Adjusted for: age, BMI, alcohol consumption, hematocrit Authors conclusion: Hematocrit and alcohol consumptions should always be considered confounders	Coefficients (95% CI) of the regressions of systolic and diastolic blood pressure on blood Pb concentrations: Men: **SBP: β (95% CI)=Unadj. 0.55 (0.34-0.76)** **Adj. 0.29 (0.08-0.49)** DBP: β (95% CI)= **Unadj. 0.27 (0.13-0.41)** Adj. 0.08 (-0.06-0.23) Women: SBP: β (95% CI)= **Unadj. 0.67 (0.34-1.00)** Adj. 0.17 (-0.14-0.48) **DBP: β (95% CI)= Unadj. 0.54 (0.35-0.73)** **Adj. 0.29 (0.09-0.49)**	Concurrent blood Pb was significantly associated with SBP and DBP in men and women, but adjustment for covariates including hematocrit and alcohol decreased the significance of the findings.
Cross-sectional Hense (1994) Germany *Population may overlap with Hense (1993)*	3,364 subjects participating in the WHO MONICA Project: Augsburg cohort first follow-up; Year= 1987-1988; Male = 50.6%	Range 28-67 years	Median: Men:8.3 µg/dL Women: 6.0 µg/dL	Systolic and diastolic blood pressure (SBP and DBP)	Linear regression with separate slopes model Stratified by drinking status: abstainers, moderate drinkers (0-40gm/day), and heavy drinkers (40+ gm/day) Adjusted for age, hematocrit, body mass index, place of residence,	Regressions of systolic and diastolic blood pressure on blood Pb concentrations: Women SBP: adjusted β (95% CI) Abstain (n=701): β=0.07 (-0.48-0.62) Moderate (n=877): β=0.12 (-0.28-0.52) **Heavy (n=83): β=1.30 (0.45-2.15)** Women DBP: adjusted β (95% CI) Abstain (n=701): β=0.21 (-0.14-0.56) **Moderate (n=877): β=0.27 (0.02-0.52)** **Heavy (n=83): β=0.86 (0.33-1.39)** Men, urban SBP: adjusted β (95% CI) Abstain (n=118): β=0.28 (-0.63-1.20)	Moderate and heavy drinkers had significant associations between concurrent blood Pb and BP in women and men residing in rural but not urban areas.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
					and smoking In men, further stratified by place of residence	Moderate (n=379): β=-0.2 (-0.46-0.42) Heavy (n=240): β=-0.16 (-0.65-0.33) Men, urban DBP: adjusted β (95% CI) Abstain (n=118): β=-0.23 (-0.85-0.39) Moderate (n=379): β=-0.08 (-0.38-0.22) Heavy (n=240): β=-0.22 (-0.55-0.11) Men, rural SBP: adjusted β (95% CI) Abstain (n=147): β=0.35 (-0.30-1.00) **Moderate (n=463): β=0.65 (0.21-1.09)** **Heavy (n=356): β=0.45 (0.05-0.99)** Men, rural DBP: adjusted β (95% CI) Abstain (n=147): β=0.03 (-0.41-0.47) **Moderate (n=463): β=0.39 (0.09-0.69)** **Heavy (n=356): β=0.30 (0.03-0.57)**	
†Cross-sectional Hu (1996) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	590 men in the Normative Aging Study; Year=1991-1994; Male = 100%	66.6 (7.2) years Range: 48-92	6.3 (4.1) Range <1-28 Tibia: 21.6 (12.1) µg/g Patella: 32.1 (18.7) µg/g	Hypertension (SBP >160mmHg or DBP ≥96mmHg at exam) or daily antihypertensive medication	*t* test Multiple logistic regression adjusted for age, race, BMI, family history of hypertension, pack-years of smoking, alcohol intake, dietary sodium, and dietary calcium	Mean Pb level for hypertensives (n=146)/normotensives (n=444) and *t* test *P*-value **Blood Pb: 6.9/6.1 µg/dl *P*<0.05** **Tibia Pb: 23.7/20.9 µg/g *P*<0.05** **Patella Pb: 35.1/31.1 µg/g *P*<0.05** Hypertension and Pb biomarkers: Adj. β (SE) *P* value Blood Pb: β=0.0344 (0.0237) *P*=0.15 Tibia Pb: β=0.136 (0.0085) *P*=0.11 Patella Pb: β=0.0087 (0.0055) *P*=0.11 Final backward elimination logistic regression model including BMI and family history of hypertension: **Tibia OR=1.019 (95% CI 1.004-1.035)** **χ^2 for covariates in final model=39.9 (3 *df*,) *P*<0.001** Odds Ratio of hypertension from an increase in tibia Pb from 8 to 37µg/g (middle of lowest to middle of highest quintile): **Tibia OR=1.5 (95%% CI: 1.1-1.8)**	Blood and bone Pb levels were significantly higher in hypertensives than nonhyper-tensives, and tibia Pb was associated with a significant increase in risk of hypertension.
Cross-sectional Kaewboonchoo (2007) Bangkok, Thailand *Population may overlap with Kaewboonchoo (2010) listed in Clinical Cardiovascular Disease*	438 male bus drivers in Bangkok Thailand; Year= 2002	41.5 (7.8) years Range = 23 – 59 years	6.3 (2.2) Range 2.5 – 16.2µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Student's *t*-test comparison of low and high Pb Pearson's correlation coefficient (*r*) Multiple regression analyses adjusting for age, BMI, alcohol intake, smoking, and physical exercise	**Mean SBP (SD), p=0.012** Low Pb (≤4.1µg/dL, n=62) = 128 (14) High Pb (≥ 8.5µg/dL, n=70) = 135 (19) **Mean DBP (SD), p=0.001** Low Pb (≤4.1µg/dL, n=62) = 78 (9) High Pb (≥ 8.5µg/dL, n=70) = 84 (11) Correlation with blood Pb: **SBP *r* = 0.176, p<0.01** **DBP *r* = 0.196, p<0.01** Univariate linear regression with blood Pb: **SBP *β*=0.902, p<0.01** **DBP *β*=0.648, p<0.01**	Concurrent blood Pb was significantly associated with increases in SBP and DBP.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Kim (2008) South Korea *Also listed for Clinical Cardiovascular Disease*	13,043 Pb workers in the Special Health Surveillance Program; Year = 2003 Male 69%	33.7 (10.0) years	Geometric mean 6.08 (2.53) Range: 0.002–123.22 70% of workers <10µg/dl women had lower levels than men	Blood pressure and Hypertension	*t*-test; ANOVA; Relative risk was calculated ala Lawes et al, 2003. No adjustment for other factors	Estimated increase in blood pressure (mmHg): 5 µg/dl ≤ PbB < 10 µg/dl = 0.458 (men) 0.266 (women) 10 µg/dl ≤ PbB < 15 µg/dl = 1.800 (men) 1.088 (women) 15 µg/dl ≤ PbB < 20 µg/dl = 3.050 (men) 1.952 (women) 20 µg/dl ≤ PbB = 3.750 (men) 2.400 (women) Relative Risk for Hypertension: PbB <5µg/dL (referent) 5 µg/dl ≤ PbB < 10 µg/dl = 1.055 (men) 1.045 (women) 10 µg/dl ≤ PbB < 15 µg/dl = 1.380 (men) 1.198 (women) 15 µg/dl ≤ PbB < 20 µg/dl = 1.683 (men) 1.358 (women) 20 µg/dl ≤ PbB = 1.853 (men) 1.441 (women) Significance tests or 95% CI not reported	Concurrent blood Pb was not statistically significantly associated with BP and risk of hypertension.
Case-control Korrick (1999) Boston, MA, USA	284 women in the Nurses' Health Study (Hypertension cases, n=89; Normotensive controls, n= 195) Year = 1993-1995 Male = 0%	58.7 (7.2) years	Blood Pb: 3.125 µg/dl Tibia Pb: 13.3 (9.0) µg/g Patella Pb: 17.3 (11.1) µg/g	Hypertension: physician diagnosed between 1988 and 1994 or measured SBP ≥140 or DBP ≥90mmHg	Ordinal regression modeling Adjusted for: age, menopausal status, job status, alcohol intake, serum creatinine, hemoglobin, hematocrit, and caffeine intake.	Risk of hypertension and Pb: Blood (µmol/L): β (SE)= 0.972 (1.055); p-value=0.36 Tibia (µg/g): β (SE)= 0.003 (0.013); p-value=0.85 **Patella (µg/g): β (SE)= 0.025 (0.011); p-value=0.03** No significant interactions by alcohol, age, or postmenopausal status An increase from the 10th to the 90th % patella Pb (25µg/g) was associated with 2-fold increase in risk of hypertension **(95% CI: 1.1-3.2)**	Patella Pb was significantly associated with increased risk of hypertension, but blood and tibia Pb were not.
Cross-sectional Kuo (2006) Taiwan	2,565 adults, Hsin-yi County in rural Central Taiwan, annual health exams after age 40, 51.4% aboriginals (97.5% Bunnun tribe) Year not stated Male = 48%	≥ 40 years	Non-aboriginals Male (n=638) 5.3 (±1.2) Female (n=609) 5.3 (±1.1), Aboriginals: Male (n=588) 5.6 ±1.4 Female (n=730) 5.4 ±1.2;	Systolic and diastolic blood pressure (SBP and DBP)	Multiple linear regression models Adjusted for age, gender, BMI, alcohol, and ethnic group	Regression coefficient for Blood Pb and BP: **SBP: β = 0.85 mmHg/µg/dl (SE = 0.33) p<0.05** **DBP: β = 0.48 mmHg/µg/dl ((SE = 0.2) p<0.05** Odds Ratio of Hypertension with blood Pb: Non-aboriginals: <5ug/dL = ref. 5-7.5ug/dL= 1.09 **7.5ug/dL = 2.97 p<0.05** Aboriginals: <5ug/dL = ref. 5-7.5ug/dL = 0.94 7.5ug/dL = 0.9	Concurrent blood Pb was significantly associated with SBP and DBP; and with risk of hypertension in non-Aboriginal Taiwanese.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Magri (2003) Malta	143 primigravid women in their third trimester without a history of hypertension, a family history of gestational hypertension, gestational diabetes, renal disease, or on medication; Year not stated Male = 0%	Calc. mean = 29 Normotensive (n=110): 30 (6) years Gestational hypertension cases (n=33): 27 (6) years	Calc. mean = 6.7 Normotensive (n=93): 5.8 (3) Gestational hypertension cases (n=30): 9.6 (6)	Systolic and diastolic blood pressure (SBP and DBP)	Mann-Whitney *U*-test (hematocrit adjusted) Pearson correlation (Age, BMI, and hematocrit adjusted)	**Hematocrit adjusted mean blood Pb (p=0.009)** Normotensive (n=93) = 16.6 ± 7 Gestational hypertension (n=30) = 26.7 ± 17 Pearson correlation of blood Pb and BP (adjusted): **SBP = 0.210 (*p*=0.047)** **DBP = 0.208 (*p*=0.049)** Pearson correlation of blood Pb: ionized calcium ratio and BP (adjusted): **SBP = 0.355 (*p*=0.002)** **DBP = 0.297 (*p*=0.011)**	Third trimester blood Pb was significantly higher in gestational hypertension cases and significantly correlated with SBP and DBP.
† Cross-sectional Martin (2006) Baltimore, MD, USA	964 adults from the Baltimore Memory Study; Year=2001-2004; Male = 44.5%	59.4 (5.9) Range= 50-70 years	Blood Pb: 3.5 (2.3) µg/dL Tibia Pb (2002-2004): 18.8 (12.4) µg/g	Systolic and diastolic blood pressure (SBP and DBP) and hypertension (SBP > 140mmHg, DBP > 90 mmHg or antihypertensive medication)	Multiple linear regression (BP); Multiple logistic regression (hypertension) Adjusted for age, sex, BMI, antihypertensive medication use, dietary sodium intake, dietary potassium intake, time of day, testing technician, serum total cholesterol, race/ethnicity and socioeconomic status (model 4)	SBP adjusted coefficient from linear regression: **Blood Pb: β(95% CI)= 0.99 (0.47-1.51); p<0.01** Tibia Pb: β (95% CI)= 0.02 (-0.08-0.11); NS DBP adjusted coefficient from linear regression: **Blood Pb: β(95% CI)= 0.51 (0.24-0.79); p<0.01** Tibia Pb: β (95% CI)= 0.02 (-0.03-0.07); NS Hypertension adjusted odds ratio from logistic regression: Blood Pb: AdjOR (95% CI)= 1.01 (0.86-1.19); NS Tibia Pb: AdjOR (95% CI)= 1.16 (0.98-1.37); p=0.09	Blood Pb was significantly associated with increased SBP and DBP, while tibia Pb was higher (but not statistically significant) in hypertension cases.
‡ Cross-sectional; Menditto (1994) Rome, Italy	1,319 men in the New Risk Factors Project (participants in the 1979-1981 study). Year = 1989-1990; Male = 100%	63 (5) years Range: 55-75	Median = 11.3 Range: 4.0- 44.2	Systolic and diastolic blood pressure (SBP and DBP) and BP category: Normal (SBP≤140mmHg and DBP≤90), Borderline (SBP 140-160 or DBP 90-95), or High (SBP≥160mmHg or DBP≥95)	Kruskall-Wallis test of differences in BP category Linear correlation and multiple step-wise regression analyses. BMI, age, heart rate, skinfold thickness, smoking, serum lipids, and glucose levels	Median blood Pb values in BP categories: **(*p*=0.004)** Normal (n=668): 11.1 µg/dL Borderline (n=373): 11.35 µg/dL High (n=278): 12.0 µg/dL Log-normal blood Pb linear correlation: **SBP: r=0.1332, p<0.001** **DBP: r=0.0737, p=0.007** Adjusted linear regression coefficient with blood Pb: SBP: 5.6 mmHg/ln(ug/l) (6.8 unadjusted) DBP: 1.7 mmHg/ln(ug/l) (1.8 unadjusted) Alcohol Drinkers (n=1068)	Concurrent blood Pb was significantly associated with increased SBP and DBP in all the men and in the subset who drank alcohol.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
					DBP model did not adjust for skinfold thickness, non-HDL-cholesterol, or glucose levels	Log-normal blood Pb linear correlation: **SBP: r=0.1449, p<0.001** **DBP: r=0.1042, p<0.001** Adjusted linear regression coefficient with blood Pb: SBP: 5.6 mmHg/ln(ug/l) (7.5 unadjusted) DBP: 2.5 mmHg/ln(ug/l) (2.6 unadjusted) Non-drinkers (n=251) No significant relationships between blood Pb and BP Statistical significance of the regression coefficients was not included	
‡ Prospective and cross-sectional Møller (1992) Denmark *Population may overlap with Grandjean (1989)* *Also listed for Clinical Cardiovascular Disease and Cardiovascular Mortality*	1052 adults born in 1936 and living in the 4 municipalities served by the Glostrup Hospital (Glostrup Population Study); Year = Baseline: 1976; 5-year follow up: 1981 (both sexes); 11-year follow up: 1987 (men only) Male 48%	40 years at baseline	Baseline Calc. mean=11.5 Men (n=504): 13.6 (5.7) Range=5 – 60 Women (n=546): 9.6 (3.8) Range=4 – 39 1981 (age 45) Men (n=463): 9.6 (4.3) Range: 3 – 39 Women (n=430): 6.8 (3.5) Range: 2 – 41 1987 (age 51) Men (n=439): 8.3 (4.1) Range=2 – 62	Systolic and diastolic blood pressure (SBP and DBP)	Multiple linear regression Tobacco, BMI, physical activity, alcohol, hemoglobin† *1987 results are not adjusted for hemoglobin	Regression of BP on ln(blood Pb): SBP: Unadjusted; Multiply adjusted Men, 1976: β=3.88 (*p*=0.02); β=1.29 (*p*=0.45) Men, 1981: β=2.38 (*p*=0.11); β=0.88 (*p*=0.54) Men, 1987: β=2.35 (*p*=0.21); β=0.25 (*p*=0.89)* Women, 1976: β=4.21 (*p*=0.02); β=1.18 (*p*=0.51) Women, 1981: β=1.08 (*p*=0.45); β=1.62 (*p*=0.27) DBP: Unadjusted; Multiply adjusted Men, 1976: β=1.08 (*p*=0.44); β=-1.37 (*p*=0.33) Men, 1981: β=0.92 (*p*=0.44); β=0.59 (*p*=0.61) Men, 1987: β=-0.48 (*p*=0.68); β=-0.12 (*p*=0.32)* Women, 1976: β=3.49 (*p*=0.01); β=2.65 (*p*=0.07) Women, 1981: β=1.98 (*p*=0.07); β=2.78 (*p*=0.01) Regression of change in blood pressure on change in blood Pb in men from age 40 to age 51: SBP: Unadj. β=0.26 (*p*=0.03); Adj. β=0.16 (*p*=0.28) DBP: Unadj. β=0.03 (*p*=0.74); Adj. β =-0.06 (*p*=0.54)	Blood Pb was not significantly associated with SBP or DBP at baseline, or after 5 or 11 years of follow up; and change in blood Pb levels over time were not associated with SBP or DBP.
‡Cross-sectional Morris (1990) USA	251 adults without secondary hypertension, or antihypertensive mediations 1 month prior; Year = enrollment began in 1984 Male = 58%	23-79	Calc. mean: 7.5µg/dL Men: 8.0 (4.4) Women: 6.9 (3.6)	Systolic and diastolic blood pressure (SBP and DBP), after >5 minutes of supine rest and >2 minutes of standing, measured once a week for 4 weeks A 12 week calcium supplement intervention did not significantly change blood Pb levels.	Correlations Coefficients (*r*) Multiple linear regression (unadjusted reported here)	Correlation of blood Pb with BP (*p<0.05) Men (unadjusted): SBP: **Supine *r* = 0.16***, Standing *r* = 0.12 DBP: Supine *r* = 0.12**, Standing *r* = 0.15*** A 10µg/dL increase in blood Pb is related to a 5mmHg increase in supine SBP and a 2.9mmHg increase in standing DBP in men. Women (unadjusted): SBP: Supine *r* = 0.02, Standing *r* = -0.06 DBP: Supine *r* = -0.04, Standing *r* = -0.12 Multiple regression of Supine BP **SBP, Men (with age and Ca):** **Pb β=0.14; r=0.47, *P*<0.001**	Concurrent blood Pb levels were related to blood pressure in men, but not women.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						DBP, Men (with age smoking and hemoglobin): **Pb β=0.09; r=0.43, *P*<0.001** SBP, Women: blood Pb not in model DBP, Women: blood Pb not in model	
Cross-sectional Muntner (2005) USA *Also listed for Clinical Cardiovascular Disease*	9,961 adults in NHANES 1999-2002; Year = 199-2002; % male not stated	mean not reported all ≥18	1.64µg.dl (95% CI 1.59-1.68)	Hypertension: SBP/DBP ≥ 140/90mmHg and/or current antihypertensive medication	Multivariable logistic regression, χ^2 test for trend, Adjusted for age, sex, diabetes, BMI, current and former smoking, alcohol consumption, having a high school education, and having health insurance	Adjusted Odds Ratio (95% CI) of Hypertension by Quartile of Blood Pb: OR (95% CI); Disease % (SE) Non-Hispanic white Q1 (<1.06 µg/dl)=ref.; 18.7% (1.6) Q2 (1.06-1.63 µg/dl) OR=1.12 (0.83-1.50); 26.4% (1.6) Q3 (1.63-2.47 µg/dl) OR=1.03 (0.78-1.37); 32.0% (1.7) Q4 (≥2.47 µg/dl) OR=1.10 (0.87-1.41); 38.9% (1.9) *P* Value for Trend OR 0.61;**Prevalence <0.001** Non-Hispanic black Q1 (<1.06 µg/dl)=ref.; 20.9% (3.0) Q2 (1.06-1.63 µg/dl) OR=1.03 (0.63-1.67); 29.4% (2.4) Q3 (1.63-2.47 µg/dl) OR=1.12 (0.77-1.64); 37.5% (3.5) Q4 (≥2.47 µg/dl) OR=1.44 (0.89-2.32); 47.2% (2.0) *P* Value for Trend OR 0.06; **Prevalence <0.001** Mexican American Q1 (<1.06 µg/dl)=ref.; 10.3% (1.8) Q2 (1.06-1.63 µg/dl) OR=1.42 (0.75-2.71); 16.8% (1.7) Q3 (1.63-2.47 µg/dl) OR=1.48 (0.89-2.48); 17.8% (2.1) Q4 (≥2.47 µg/dl) OR=1.54 (0.99-2.39); 18.2% (1.7) ***P* Value for Trend OR 0.04; Prevalence <0.001**	Blood Pb and the prevalence of hypertension increased in all ethnicities and in non-Hispanic blacks and Mexican Americans there was a near statistically significant increase in the risk of hypertension.
Cross-sectional Nash (2003) USA *Population may overlap with Den Hond (2002) and others*	2,165 women aged 40-59 years from NHANES III; non-Hispanic black, non-Hispanic white, and Hispanic only; Year= 1988 – 1994 Male = 0%	48.2 (0.2) years	2.9 µg/dl Range = 0.50 – 31.1 µg/dl	Systolic and diastolic blood pressure (SBP and DBP) and Hypertension (SBP >140, DBP >90mmHg, or treatment with antihypertensive medication)	Multiple linear regression models; multiple logistic regression; Age, race and ethnicity, alcohol, smoking history, BMI, and serum creatinine family income, education,	Mean Blood pressure (SE) by blood Pb quartile: **SBP (χ^2 p=0.03, *p*<0.001 for trend)** **Q1 (0.5-1.6µg/dl) = 117.2 (0.95) mmHg** **Q2 (1.7-2.5µg/dl)= 117.7 (0.83) mmHg** **Q3 (2.6-3.9µg/dl)= 119.3 (1.10) mmHg** **Q4 (4.0-31.1µg/dl)= 121.2 (0.92) mmHg** DBP (χ^2 p=0.86, *p*= 0.79 for trend) Q1 (0.5-1.6µg/dl)= 73.7 (0.51) mmHg Q2 (1.7-2.5µg/dl)= 74.2 (0.53) mmHg Q3 (2.6-3.9µg/dl)= 74.2 (0.62) mmHg Q4 (4.0-31.1µg/dl)= 74.3 (0.62) mmHg Regression coefficient (SE), *P* value in women not treated for hypertension: All women (n=1786): **SBP: 0.32 (0.16), p=0.03** **DBP: 0.25 (0.09), p=0.009** Premenopausal women (n=1084): SBP: 0.14 (0.26), p=0.59 DBP: 0.38 (0.25), p=0.12	Blood Pb levels in middle aged women were significantly associated with increased BP and risk of hypertension. This association was strongest in postmenopausal women.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						Postmenopausal women (n=633): SBP: 0.42 (0.21), p=0.29 **DBP: 0.14 (0.13), p=0.04** <u>Adjusted odds ratio of general hypertension</u> (95% CI): All women (n=2165): Q1 = ref. Q2 (1.7-2.5µg/dl)= 1.0 (0.63-1.6) Q3 (2.6-3.9µg/dl)= 1.3 (0.87-2.0) Q4 (4.0-31.1µg/dl)= 1.4 (0.92-2.0) Premenopausal (n=1214): Q1 (0.5-1.4µg/dl)= ref. Q2 (1.5-2.1µg/dl)= 0.78 (0.38, 1.6) Q3 (2.2-3.3µg/dl)= 1.4 (0.82, 2.4) Q4 (3.4-28.7µg/dl)= 1.5 (0.78, 2.8) Postmenopausal (n=850): Q1 (0.5-1.9µg/dl)= ref. Q2 (2.0-3.1µg/dl)= = 0.73 (0.40, 1.3) Q3 (3.2-4.6µg/dl)= 1.3 (0.75, 2.2) Q4 (4.7-31.1µg/dl)= 1.3 (0.68, 2.3) <u>Premenopausal women untreated for hypertension, adjusted odds ratio of hypertension</u> (95% CI): Systolic hypertension (n=1084): Q1 (0.5-1.4µg/dl)= ref. Q2 (1.5-2.1µg/dl)= 0.88 (0.29-2.7) Q3 (2.2-3.3µg/dl)= 1.4 (0.49-3.7) Q4 (3.4-28.7µg/dl)= 1.6 (0.62-4.2) Diastolic hypertension (n=1084): Q1 (0.5-1.4µg/dl)= ref. Q2 (1.5-2.1µg/dl)= 1.1 (0.31-3.6) Q3 (2.2-3.3µg/dl)= 1.8 (0.76-4.2) Q4 (3.4-28.7µg/dl)= 3.5 (0.89-13.4) <u>Postmenopausal women untreated for hypertension, adjusted odds ratio of hypertension</u> (95% CI): Systolic hypertension (n=633): Q1 (0.5-2.0µg/dl)= ref. **Q2 (2.1-3.0µg/dl)= 3.0 (1.3-6.9)** **Q3 (3.1-4.6µg/dl)= 2.7 (1.2-6.2)** Q4 (4.7-31.1µg/dl)= 2.6 (0.89-7.5) Diastolic hypertension (n=633): Q1 (0.5-2.0µg/dl)= ref. **Q2 (2.1-3.0µg/dl)= 4.6 (1.1-19.2)** **Q3 (3.1-4.6µg/dl)= 5.9 (1.5-23.1)** **Q4 (4.7-31.1µg/dl)= 8.1 (2.6-24.7)**	

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Meta-analysis; Navas-Acien (2008) [†, below, denotes study included in this meta-analysis]	Meta-analysis of data from 3 prospective cohort studies and 7 cross-sectional studies with bone Pb measurements. One prospective and one cross-sectional study had mean blood Pb levels above 15µg/dl and were not included in this evaluation.	≥18 years	Range of Mean Blood Pb levels (µg/dL) 2.3 - 32.0 Range of Mean Tibia Bone Pb levels (µg/g): 4.2 - 38.4 Range of Mean Patella Bone Pb levels in 3 studies (µg/g): 17.3 - 32.1	Systolic and diastolic blood pressure (SBP and DBP); hypertension	Summary measures of association were calculated using inverse-variance weighted random-effects models. Not all seven studies were included in the cross-sectional analyses presented here.	Cross-sectional study summary: Associations with a 10 µg/g increase in tibia Pb: **SBP: 0.26 mm Hg (95% CI 0.02-0.50)** DBP: 0.02 mm Hg (95% CI -0.15-0.19) **Hypertension: OR (95% CI)= 1.04 (1.01-1.07)** Associations with a 10 µg/g increase patella Pb: Hypertension: OR (95% CI)= 1.04 (0.96-1.12) *Associations with 5 µg/dL increase of blood Pb:* SBP: 1.53 mmHg (-0.19-3.25) DBP: 1.19 mmHg (-0.69-3.08) Hypertension: OR (95% CI) = 1.02 (0.93-1.13) Prospective study summary: *Associations with a 10 µg/g increase in tibia Pb:* SBP: 0.33 mm Hg (-0.44-1.11) *Associations with 5 µg/dL increase of blood Pb:* **SBP: 0.71 mm Hg (0.01-1.43)**	A significant positive association was found between 10µg/g increase in tibia Pb and hypertension in a summary of cross-sectional studies. In tibia bone Pb levels the majority of the studies found a positive association with blood pressure and the risk of hypertension.
Meta-analysis; Nawrot (2002) [‡, below, denotes study included in this meta-analysis]	Meta-analysis of 31 studies (19 general population surveys and 12 occupationally exposed surveys) including 58,518 total subjects. 8 studies had mean blood Pb levels above 15µg/dl and one was not in English and were not included	Not all studies included age, most in adults	Range of Mean Blood Pb levels 2.3-64 µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Estimation of association from a doubling of blood Pb at the mean of the study Combined *P*-values using Fisher's method with unweighted *P*-value between parentheses (χ^2) and Stouffer's method with one-sided *P*-value between parentheses (Z-score)	For a two-fold increase of the blood Pb concentration: Both sexes, all studies: **SBP (n=58518): 1.0 mmHg (0.5-1.4, *P*<0.001)** **DBP (n=58491): 0.6 (0.4-0.8, *P*<0.001)** Men, all studies: **SBP (n=32268): 1.2 mmHg (0.6-1.7, *P*<0.001)** **DBP (n=32263): 0.6 (0.4-0.8, *P*<0.001)** Women, all studies: **SBP (n=24057): 0.8 mmHg (0.2-1.4, *P*=0.003, 0.004)** **DBP (n=24035): 0.6 (0.3-0.9, *P*<0.001)**	This meta-analysis concludes a small but consistent association between BP and blood Pb, with no differences between genders.
Cross-sectional Nordberg (2000) Stockholm, Sweden	762 subjects in the Kungsholmen longitudinal study; Years (follow-up)= 1994-1996; Male=23%	87.3 (4.9) (all ≥75 years)	3.7 (2.3)µg/dl Men: 4.6µg/dl Women: 3.5µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression Specific adjustments to Pb and BP analyses are unclear.	Different multiple regression models with Pb as the dependent variable were tested and no relation to SBP or DBP was found (data not shown).	Blood Pb was not associated with SBP or DBP in these elderly subjects

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
‡Cross-sectional Orssaud (1985) Paris, France	431 men attached to a section of the Paris civil service living in the same urban area and not occupationally exposed to Pb; Year not stated Male = 100%	41.4 years Range: 24-55	Mean not reported <12.4: n=46 12.5-18.4: n=212 18.5-24.4: n=126 24.5-30.8: n=34 30.9-36.9: n=7 ≥37: n=6	Systolic and diastolic blood pressure (SBP and DBP)	Correlation coefficients using logarithms of blood Pb values. Adjusted for age, BMI, and alcohol consumption	Correlation coefficient between SBP and blood Pb: **All subjects: 0.23 ($p < 0.001$)** **Age 24-34 (n=145): 0.29 ($p < 0.001$)** **Age 35-44 (n=143): 0.20 ($p < 0.05$)** Age 45-55 (n=143): 0.14 (NS) DBP not included in the study. Adjusting for alcohol consumption and BMI did not modify the results.	Concurrent blood Pb was significant associated with SBP, particularly in younger men, but blood Pb levels >10µg/dL limit the utility to this evaluation.
Cross-sectional Perlstein (2007) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	593 men in the Normative Aging Study not treated with antihypertensive medication; Year = 1991-1997 Male = 100%	Calc. mean 66.6 By tibia Pb quintile: Q1 (n=111) 63.0±7.0 Q2 (n=119) 64.4±6.9 Q3 (n=122) 66.8±7.4 Q4 (n=119) 68±7.3 Q5 (n=122) 70.5±6.7	6.12 (4.03)	Systolic and diastolic blood pressure (SBP and DBP) and Pulse Pressure (the difference between systolic and diastolic blood pressure)	Spearman correlations, multiple linear regression, and test of linear trend Adjusting for age, age^2, height, race, heart rate, waist circumference, diabetes, family history of hypertension, education, smoking history, alcohol intake, fasting plasma glucose, and total cholesterol-to-HDL ratio	Spearman correlations (r) of Pb and BP: Tibia SBP: **unadj. r=0.13, p<0.01**, adj. r=0.06, p=0.15 Tibia DBP: **unadj. r=-0.14, p<0.01**, adj. r=-0.02, p=0.63 Blood SBP: **unadj. r=0.08, p=0.05**, adj. r=0.05, p=0.28 **Blood DBP: unadj. r=0.09, p=0.03, adj. r=0.12, p=0.01** Multivariate adjusted quintile mean differences in pulse pressure (Q1 ref): *P* for linear trend: Tibia Pb (*P*=0.02): Q5: 2.58 (95% CI -1.15 to 6.33) Q4: 2.64 (95% CI -0.93 to 6.21) Q3: -0.73 (95% CI -4.27 to 2.82) Q2: -3.02 (95% CI -6.48 to 0.44) Blood Pb (*P*=0.82): Q5: -1.49 (95% CI -4.93 to 1.94) Q4: -1.39 (95% CI -4.94 to 2.15) Q3: -2.56 (95% CI -5.78 to 0.67) Q2: -4.37 (95% CI -7.88 to -0.86) **Tibia Pb above the median had 4.2mmHg (95%CI 1.9-6.5) higher pulse pressure.**	Concurrent blood Pb was significantly correlated with DBP, and tibia Pb over the median was significantly associated with an increase in pulse pressure.
Cross-sectional Peters (2007) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	513 participants with baseline hypertension and 237 without hypertension from the Normative Aging Study Year = 1991-1996 Male = 100%	*Hypertensives:* 67.5 (6.8) years *Non-hypertensives:* 66.2 (7.4) years	Blood Pb: *Hypertensive* 6.3 (4) µg/dL *Non-hypertensive* 6.2 (4.2) µg/dL Patella Pb: *Hypertensive* 32.5 (20.1) µg/g *Non-Hypertensive* 30.3 (18.3) µg/g	Systolic and diastolic blood pressure (SBP and DBP)	Logistic regression Age, age^2, BMI, family history of hypertension, education, pack-years smoking; alcohol intake, physical activity, and sodium, calcium, and potassium intake	Tibia Pb OR (95% CI): Non-hypertensives: Referent Hypertensives: 1.17 (0.88-1.42) Patella Pb OR (95% CI) Non-hypertensives: Referent Hypertensives: 1.08 (0.85-1.38)	Bone Pb was not statistically significantly associated with hypertension.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Pizent (2001) Croatia	267 peasant women, residents of two rural areas in Croatia: Istra (low calcium intake, n=100) and Podravina (high calcium intake, n=167); Year not stated Male = 0%	Calc. mean: 60.5 Istra (Low Ca): 58 (40-86) Podravina (High Ca): 62 (41-85)	Calc. mean: 6.46µg/dl Istra (Low Ca): 7.4 (2.9-25.1) µg/dL Podravina (High Ca): 5.9 (2.1-26.3) µg/dL	Systolic and diastolic blood pressure (SBP and DBP), sitting after 10 min rest	Spearman's rank correlation Forward stepwise multiple regression Mann Whitney U-test (z, p) No adjustment for other factors	Correlation coefficient of blood Pb: *r*, *p*-value SBP: 0.070, NS DBP: 0.087, NS BP regression models did not include blood Pb Mean Blood Pb (µg/dl), Range Group 1 Low Ca, No alcohol (n=34): 6.4 (2.9-13.7) Group 2 Low Ca, Any alcohol (n=66): 7.8 (4.2-25.1) Group 3 High Ca, No alcohol (n=107): 5.1 (2.2-19.2) Group 4: High Ca, Any alcohol (n=60): 7.4 (2.1-26.3) **Group 2 vs. 1: p-value<0.01** **Group 3 vs. 2: p-value<10^{-8}** **Group 3 vs. 1: p-value<0.05** **Group 4 vs 3: p-value<10^{-5}**	Blood Pb was not statistically significantly associated with BP in this population, but low calcium and/or alcohol consumption was associated with higher Pb levels.
‡Cross-sectional Pocock (1984) England *Population may overlap with Pocock (1988)*	7,371 men randomly selected from general practices in 24 British towns (The Regional Heart Study); Year not stated Male = 100%	mean not reported 40-59 years	mean not reported <12.4 – 37.3 **limits utility*	Systolic and diastolic blood pressure (SBP and DBP)	Statistical methods not reported but statistics were presented as correlation coefficients (β); Alcohol consumption	Blood Pb was not associated with increased hypertension Correlation coefficients (r) of blood Pb: SBP = 0.03 DBP = 0.01 There was no significant trend in the proportion of men with hypertension across the blood Pb concentration groups.	Blood Pb was not associated with SBP, DBP or hypertension; but lack of mean blood Pb levels in this study limits the utility.
Cross-sectional Pocock (1988) England *Population may overlap with Pocock (1984)]*	7,371 randomly selected from general practices in 24 British towns (The Regional Heart Study); Year not stated Male = 100%	mean not reported 40-59 years	mean not reported **limits utility*	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression analyses Age, BMI, alcohol intake, smoking, social class, town of residence.	Regression coefficient of blood pressure on ln (blood Pb) [standard errors not given]: **SBP = 2.089 (*p*=0.003)** **DBP = 1.809 (*p*=0.001)** *Authors note that these significant results are due to the large sample size as the adjusted statistical associations are very weak, partial correlation coefficients being 0.04 and 0.05 for the SBP-blood Pb and DBP-blood Pb associations.*	Blood Pb was significantly associated with SBP and DBP; but lack of mean blood Pb levels in this study limits the utility.
‡Cross-sectional Proctor (1996) Boston, MA, USA *Population may overlap with Cheng (1998) and others*	798 men from the Normative Aging Study; Year= 1991-1993 Male = 100%	66.1 (7.4) Range: 43 – 93 years	6.5 (4) Median (range): 5.6 (0.5 – 35)	Systolic and diastolic blood pressure (SBP and DBP)	Multivariate linear regression analyses with systolic and diastolic pressure as continuous outcome variables. Age, BMI, dietary calcium (adjusted for total calorie intake), alcohol, sitting heart rate, weekly exercise, hematocrit, and smoking.	β (95% CI) for unit increase in ln blood Pb: Whole cohort: SBP: 0.85 (-1.1, 2.7); *P*>0.05 **DBP: 1.2 (0.1, 2.2) mmHg; *P*=0.03** ≤74 years (n=681): SBP: 1.2 (-0.86, 3.2); *P*>0.05 **DBP: 1.6 (0.42, 2.7) mmHg; *P*=0.007** *When men on anti-hypertensive medication were removed from the analysis the associations with DBP became non-significant.*	Blood Pb was significantly associated with DBP with a large effect in men under 74, but when men taking anti-hyper-tensives were excluded it was no longer statistically significant.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
‡Cross-sectional Rabinowitz (1987) Boston, MA, USA	3,851 women whose babies were delivered consecutively at the Boston Hospital for Women; Year= 1979-1981 Male = 0%	28 (5) years	Umbilical cord blood: 6.9 ± 3.3 (range: 0-35)	Systolic and diastolic blood pressure (SBP and DBP) during labor (last recorded), pregnancy hypertension, and preeclampsia	Multiple linear regression analyses; Maternal age, parity, hematocrit, BMI, race, and diabetes.	High (mean 11.24µg/dl) vs. Low (mean = 3.50µg/dl) quartile of cord blood Pb: **SBP: F = 9.39, df = 3, p<0.001** **DBP: F = 4.75, df = 3, p<0.003** **Pregnancy hypertension: χ^2 (3 df) = 12.38, P<0.01** Pearson correlation coefficient for blood Pb and BP during labor: **SBP: r = 0.081 (p=0.0001)** **DBP: r = 0.051 (p=0.002)** Relative risk of hypertension during pregnancy at selected blood Pb levels (% with greater Pb levels) β = 0.34, SE = 0.12: **0.7 µg/dL (98.7%) = ref.** **6.3 µg/dL (50.0%) RR = 1.7 (1.3-2.1)** **15 µg/dL (1.7%) RR = 2.2 (1.5-2.9)** **25 µg/dL (0.2%) RR = 2.5 (1.5-3.5)**	Umbilical cord blood Pb was significantly associated with SBP, DBP, and pregnancy hypertension, but not preeclampsia.
‡Cross-sectional Rothenberg (1999) Los Angeles, CA, USA *Population may overlap with Rothenberg (2002)*	1,627 women in their 3rd trimester of pregnancy recruited at the King-Drew Medical Center prenatal care clinics; Year= 1995-1998 Male = 0%	Immigrants (n=1,188, 98% Latin counties): 27.7 (0.2) years Non-immigrants (n=439): 24.7 (0.3) years	Immigrants: 2.3 (0.04) µg/dL Non-immigrants: 1.9 (0.06) µg/dL	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression models Age, BMI, coffee intake, iron supplement, and job stress.	Multiple Regression Model of blood Pb and BP: Robust HC3 coefficients Immigrants: **SBP = 1.708 (SE=.536, p=0.001) 95%CI 0.656-2.758** **DBP = 1.476 (SE=.399, p<0.001) 95%CI 0.531-1.939** Non-Immigrants: SBP = 0.367 (SE=.968, p=0.705) 95%CI -1.535-2.269 DBP = 0.086 (SE=.985, p=0.93) 95%CI -1.849-2.021 In the immigrant group between the 5th and 95th percentiles (0.9-6.2µg/dl), each natural-log increase in blood Pb was associated with an increase of 2.8 mmHg in SBP and 2.4 mmHg in DBP	A statistically significant association between blood Pb and blood pressure during late pregnancy was only found in the immigrant, predominantly Hispanic, group.
†Cross-sectional Rothenberg (2002) Los Angeles, CA, USA *Population may overlap with Rothenberg (1999)*	667 third trimester and postpartum women recruited at the King-Drew Medical Center prenatal care clinics; Year= 1995-2001 Male = 0%	31.0 (7.7)	Prenatal Blood (geometric mean) = 1.9 (+3.6/-1.0) Postnatal Blood (geometric mean) = 2.3 (+4.3/-1.2) Tibia (µg/g) = 8.0 (11.4) Calcaneus (µg/g)	Systolic and diastolic blood pressure (SBP and DBP) and third trimester hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg)	*t*-tests; Fishers exact tests, logistic regression analyses; multiple regression models. Postpartum hypertension, education, immigrant status, current smoking, parity, age, BMI	Adjusted odds ratio for third trimester hypertension from a 1µg/dl blood or 10µg/g bone increase: Third trimester: Concurrent lnBlood Pb: OR = 0.75 (0.21, 2.65) Tibia Pb: OR = 0.98 (0.92, 1.04) **Calcaneus Pb OR = 1.86 (1.04, 3.32)** Postpartum: Concurrent lnBlood Pb: OR = 1.24 (0.64, 2.42) Tibia Pb: OR = 1.00 (0.96, 1.04) Calcaneus Pb: OR = 1.22 (0.86, 1.73) Multiple regression analysis in normotensive women for a 1µg/dl blood or 10µg/g bone increase: Third trimester: Concurrent lnBlood Pb:	Calcaneus Pb was significantly associated with risk of gestational hypertension and with third trimester SBP and DBP in normotensive women. Significant associations between

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
			= 10.7 (11.9)			SBP β = -0.04 (-1.26, 1.18) DBP β = 0.20 (-0.78, 1.18) Tibia Pb: SBP β = 0.07 (-0.62, 0.77) DBP β = 0.18 (-0.38, 0.74) **Calcaneus Pb:** **SBP β = 0.70 (0.04, 1.36)** **DBP β = 0.54 (0.01, 1.08)** Postpartum: **Concurrent lnBlood Pb:** **SBP β = -1.52 (-2.83, -0.20)** **DBP β = -1.67 (-2.85, -0.50)** Tibia Pb: SBP β = 0.10 (-0.64, 0.84) DBP β = 0.14 (-0.43, 0.70) Calcaneus Pb: SBP β = 0.36 (-0.32, 1.03) DBP β = 0.23 (-0.29, 0.75)	postpartum blood Pb and lower SBP and DBP are not in the expected direction.
Cross-sectional Schuhmacher (1994) Barcelona, Spain	36 workers occupationally exposed to Pb (welders and PCV-workers) and 40 workers not occupationally exposed to Pb or cadmium; Year not stated Male = 100%	Exposed: 43.7 (6.7) Unexposed: 46.3 (3.2)	Exposed: 39.5 µg/dL Range 18.3-119.3 Unexposed: 9.8 µg/dL Range: 2.4-17.9	Systolic and diastolic blood pressure (SBP and DBP)	Kruskal-Wallis test No adjustment for other factors	In the controls: Blood Pb by BP: geometric mean (SD) SBP <140 (n=31): 9.5 (1.5) µg/dl SBP >140 (n=9): 10.9 (1.7) µg/dl *p*, not significant DBP <90 (n=36): 9.7 (1.6) µg/dl DBP >90 (n=4): 10.6 (1.7) µg/dl *p*, not significant	In unexposed workers, blood Pb was not significantly higher in subjects with higher SBP and DBP.
Cross-sectional Schwartz (1991) USA *Also listed for Clinical Cardiovascular Disease*	9,932 participants from NHANES II; Year= 1976 - 1980; % male not stated	mean not reported Range = 20 – 74 years	mean not reported **limits utility*	Diastolic blood pressure (DBP)	Step-wise regression; SURREGR; RTILOGIT Age, BMI, race, family history, cholesterol, height, smoking, serum zinc, triceps skin fold thickness	Regression results for DBP: **Men = β (SE): 2.928 (1.002); *p*= 0.0063** **Women = β(SE): 1.640 (0.6963); *p*= 0.0247**	Blood Pb was significantly associated with DBP, but lack of mean blood Pb levels in this study limits the utility to the evaluation.
Cross-sectional Scinicariello (2010) USA *Population may overlap with Den*	6,016 participants in NHANES III with available DNA; Year=1988-1994; Male = 47.9%	44 years	All: 2.99 (0.09) Non-Hispanic Whites (n=2,387): 2.87 (0.09)	Systolic and diastolic blood pressure (SBP and DBP) in subjects not on antihypertensive medication and hypertension (SBP ≥140mmHg, DBP ≥	Multivariable logistic and linear regression stratified by race/ethnicity. OR adjusted for age, sex, BMI, alcohol, smoking,	Adjusted Prevalence OR for hypertension: (95%CI) Blood Pb Quartile (ref=0.7-1.4 µg/dL) Non-Hispanic Whites: 1.5-2.3 µg/dL=1.21 (0.66-2.24) 2.4-3.7 µg/dL=1.57 (0.88-2.80) 3.8-52.9 µg/dL=1.52 (0.80-2.88) **Non-Hispanic Blacks:**	Blood Pb was significantly associated with increased SBP and DBP and risk of hypertension, particularly in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Hond (2002) and others			Non-Hispanic Blacks (n=1,670): 3.59 (0.20) Mexican Americans (n=1,746): 3.33 (0.11)	90mmHg, or antihypertensive medication). *ALAD* polymorphism was also genotyped.	education, serum creatinine, serum total calcium, glycosylated hemoglobin, and hematocrit β-coefficient adjusted for age, sex, BMI, alcohol, smoking, education, serum creatinine, serum total calcium, glycosylated hemoglobin, and hematocrit	**1.5-2.3 µg/dL=1.83 (1.08-3.09)** **2.4-3.7 µg/dL=2.38 (1.40-4.06)** **3.8-52.9 µg/dL=2.92 (1.58-5.41)** Mexican Americans: 1.5-2.3 µg/dL=0.74 (0.24-2.23) 2.4-3.7 µg/dL=1.43 (0.61-3.38) 3.8-52.9 µg/dL=1.27 (0.59-2.75) *ALAD* genotype was not significantly associated with hypertension. Linear regression models of Ln blood Pb and BP: β-coefficient ± SE: **Non-Hispanic Whites, SBP: 1.05 ± 0.37, *P*=0.01** Non-Hispanic Whites, DBP: -0.14 ± 0.49, *P*=0.77 **Non-Hispanic Blacks, SBP: 2.55 ± 0.49, *P*=0.001** **Non-Hispanic Blacks, DBP: 1.99 ± 0.44, *P*=0.0002** Mexican Americans, SBP: 0.84 ± 0.46, *P*=0.08 Mexican Americans, DBP: 0.74 ± 0.38, *P*=0.06 Including interaction of *ALAD* 2 allele in the model reduced the statistical significance of the β estimates all $p > 0.05$.	non-Hispanic blacks. Genetic variation in *ALAD* may modify this association.
Cross-sectional Scinicariello (2011) USA *Population may overlap with Den Hond (2002) and others*	16,222 participants in NHANES ≥20 years old (pregnant and nursing mothers excluded) and blood Pb ≤10µg/dL; Year=1999-2006; Male = 50.7%	44 years	All race/ethnicity and gender geom. mean (SE) 99-00: 1.75(0.03) 01-02: 1.56(0.03) 03-04: 1.52(0.04) 05-06: 1.41(0.03) White men (n=4538) 99-00: 2.16(0.05) 01-02: 1.95(0.05) 03-04: 1.79(0.05) 05-06: 1.69(0.07) White women (n=4319) 99-00: 1.38(0.03) 01-02: 1.24(0.03) 03-04: 1.23(0.04) 05-06: 1.18(0.04) Black men (n=1767) 99-00: 2.29(0.09) 01-02: 2.22(0.13)	Systolic and diastolic blood pressure (SBP and DBP) in subjects not on antihypertensive medication, pulse pressure, and hypertension (SBP ≥140mmHg, DBP ≥ 90mmHg, or antihypertensive medication). Serum creatinine and blood Cd were also measured.	Multivariable linear and logistic regression stratified by race/ethnicity. Adjusted for age, education, smoking status, alcohol intake, BMI, self-reported diabetes, serum creatinine levels (as a marker of kidney function), serum Ca, serum Na, hematocrit, and blood Cd	Multivariable linear regression coefficient and SE for lnBlood Pb (≤10µg/dL) and BP outcomes: Systolic BP **All Subjects: 1.07 (0.35), *p* <0.05** White Men: 0.87 (0.53) White Women: 0.89 (0.55) **Black men:2.30 (0.71), *p* <0.05** **Black Women: 2.40 (1.14), *p* <0.05** Mex-Amer. Men: 0.10 (0.70) Mex-Amer. Women: -0.03 (0.64) Diastolic BP **All Subjects: 0.71 (0.27), *p* <0.05** **White Men: 0.90 (0.45) *p* <0.05** **White Women: 0.95 (0.38), *p* <0.05** **Black Men: 2.75 (0.82), *p* <0.05** Black Women: 0.30 (0.81) **Mex-Amer. Men: -1.34 (0.66), *p* <0.05** Mex-Amer. Women: -0.74 (0.44) Pulse Pressure All Subjects: 0.37 (0.34) White Men: -0.02 (0.55) White Women: -0.03 (0.62) Black Men: -0.42 (0.93) Black Women: 2.21 (1.17) **Mex-Amer. Men: 1.42 (0.70), *p* <0.05**	Only including subjects ≤10µg/dL, blood Pb was significantly associated with increased SBP and DBP in white and black subjects, but not in Mexican-Americans. Blood Pb was significantly associated with an increased prevalence odds ratio of hypertension in black men.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
			03-04: 2.07(0.10) 05-06: 1.80(0.08) Black women (n=1854) 99-00: 1.61(0.07) 01-02: 1.35(0.07) 03-04: 1.48(0.12) 05-06: 1.24(0.06) Mex-Amer. men (n=1925) 99-00: 2.56(0.07) 01-02: 2.17(0.11) 03-04: 2.07(0.11) 05-06: 1.87(0.09) Mex-Amer. women (n=1819) 99-00: 1.53(0.06) 01-02: 1.18(0.06) 03-04: 1.32(0.06) 05-06: 1.09(0.04)			Mex-Amer. Women: 0.70 (0.63) Adjusted prevalence odds ratios for hypertension with blood Pb: POR (95% CI) Q2 (1.01-1.59µg/dL) vs. Q1 (≤ 1.00µg/dL) All Subjects: 1.00 (0.82 - 1.21) White Men: 1.05 (0.76 – 1.47) White Women: 0.85 (0.65 – 1.12) Black Men: 1.36 (0.73 – 2.52) **Black Women: 0.58 (0.40 – 0.84)** Mex-Amer. Men: Mex-Amer. Women: Q3 (1.60-2.39µg/dL) vs. Q1 (≤ 1.00µg/dL) All Subjects: 1.01 (0.81 – 1.27) White Men: 0.93 (0.67 – 1.34) White Women: 0.93 (0.67 – 1.29) Black Men: 1.38 (0.81 – 2.36) Black Women: 0.85 (0.53 – 1.37) Mex-Amer. Men: 1.26 (0.67 – 2.37) Mex-Amer. Women: 0.87 (0.57 – 1.32) Q4 (2.40-10µg/dL) vs. Q1 (≤ 1.00µg/dL) All Subjects: 0.97 (0.77 – 1.22) White Men: 0.97 (0.69 – 1.36) White Women: 0.82 (0.58 – 1.15) Black Men: 1.71 (0.94 – 3.10) Black Women: 1.02 (0.60 – 1.74) Mex-Amer. Men: 0.86 (0.46 – 1.60) Mex-Amer. Women: 0.87 (0.51 – 1.47) 90^{th} (≥3.50 µg/dL) vs 10^{th} (≤0.70 µg/dL) percentile All Subjects: 1.26 (0.98 – 1.61) White Men: 1.20 (0.74 – 1.96) White Women: 1.07 (0.69 – 1.66) **Black Men: 2.69 (1.08 – 6.72)** Black Women: 1.04 (0.50 – 2.16) Mex-Amer. Men: 1.03 (0.23 – 4.59) Mex-Amer. Women: 0.67 (0.37 – 1.20) LN blood Pb All Subjects: 0.99 (0.89 – 1.11) White Men: 0.97 (0.84 – 1.13) White Women: 0.94 (0.77 – 1.14) **Black Men: 1.41 (1.05 – 1.88)** Black Women: 1.04 (0.76 – 1.42) Mex-Amer. Men: 0.91 (0.67 – 1.24) Mex-Amer. Women: 0.89 (0.69 – 1.16) Blood Pb All Subjects: 0.99 (0.95 – 1.03)	

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						White Men: 0.99 (0.94 – 1.05) White Women: 0.98 (0.89 – 1.08) **Black Men: 1.11 (1.00 – 1.22)** Black Women: 1.02 (0.90 – 1.16) Mex-Amer. Men: 0.97 (0.87 – 1.07) Mex-Amer. Women: 0.98 (0.86 – 1.11)	
‡Cross-sectional Sharp (1988) San Francisco, CA, USA *Population may overlap with Sharp (1990)*	288 bus drivers not being treated for hypertension; Year = 1986 (from Sharp (1990)) Male = 91%	Men 42.7 (7.13) Range: 30.6-64.7 Women 40.3 (6.89) Range: 27.9-54.5	Median: 6.4µg/dl Range: 2-15µg/dl	Systolic and diastolic blood pressure (SBP and DBP); Average of 3 measures (AVESYS, AVEDIA in paper)	Multiple regression models Adjusted for age, BMI, sex, caffeine use, and race	Regression coefficient of BP and lnBlood Pb (adjusted model with outlier removed): SBP: β =0.79 mm Hg/ln (µg/dL) [95% CI: -2.68, 4.27] **DBP: β = 2.45 mm Hg/ln (µg/dL) [90% CI: 0.10, 4.80]**	Concurrent blood Pb was significantly associated with DBP in these bus drivers.
‡Cross-sectional; San Francisco, CA, USA; Sharp (1990) *Population may overlap with Sharp (1988)*	249 bus drivers not being treated for hypertension; drivers; Year= 1986; Male = 100%	Blacks (n=132): 42.6 (7.05) Range 30.8 - 64.7 years Nonblacks (n=117): 42.7 (7.22) Range 30.6 - 58.9 years	Blacks (n=132): 6.9 (2.63) Range 3-21 µg/dl Nonblacks (n=117): 6.6 (2.32) Range 2-15 µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression models Age, age2, BMI, caffeine use, tobacco use, and race (in nonblacks).	Adjusted regression coefficient of BP and lnBlood Pb (outliers removed): Blacks (n=130): **SBP β = 6.92 (95% CI 0.67 to 13.2)** **DBP β = 5.08 (95% CI 0.88 to 9.27)** Black infrequent caffeine users (n=52): **SBP β = 12.14 (95% CI 1.34 to 22.9)** DBP β = 7.34 (95% CI -0.51 to 15.2) Black habitual caffeine users (n=78): SBP β = 3.22 (95% CI -4.7 to 11.1) DBP β = 2.55 (95% CI -2.5 to 7.6) Nonblacks (n=117): SBP β = -5.71 (95% CI -12.0 to 0.6) DBP β = 0.76 (95% CI -3.4 to 4.9) Nonblack infrequent caffeine users (n=33): SBP β = -1.98 (95% CI -17.1 to 13.1) DBP β = 1.39 (95% CI -7.87 to 10.6) Nonblack habitual caffeine users (n=84): SBP β = -4.55 (95% CI -12.2 to 3.0) DBP β = 2.55 (95% CI -2.54 to 7.63)	Concurrent blood Pb was significantly associated with SBP and DBP in blacks, but not in non-blacks. The effect in blacks was stronger in infrequent caffeine users than in habitual caffeine users.
Cross-sectional Sirivarasai (2004) Bangkok, Thailand	212 men without known exposures to Cd and Pb; Year not stated Male = 100%	41.1 (4.81) Range: 34-53	Calc mean: 7.48µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Pearson's correlation coefficient Stepwise multiple regression Adjusted for age, weight, BMI, blood cadmium, serum uric acid, current smoking, and current alcohol consumption	Correlation between Blood Pb and BP: **SBP: 0.342, p < 0.001** DBP: 0.209, NS β-coefficient ± S.D. (square partial corr. coefficient) **SBP: 15.67 ± 3.00 µmol/L (r^2 = 2.6), p<0.001** DBP: (data not shown), NS	Concurrent blood Pb was significantly associated SBP but not DBP.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
‡Cross-sectional Sokas (1997) MD, USA	264 unionized Maryland construction workers not known to currently be performing Pb work; Year= 1989-1990 Male = 99%	43 years Range = 18 – 79 years	Mean= 8.0 Median: 7 Range: 2 – 30	Systolic and diastolic blood pressure (SBP and DBP)	Multiple linear regression; t test; simple Pearson correlations. Age, BMI, hematocrit, race, smoking, alcohol consumption, years of education.	<u>Regression coefficients of blood Pb and BP:</u> SBP = -0.49 [SE not reported] (p=0.13) DBP = -0.18 [SE not reported] (p=0.38)	Blood Pb levels were not significantly associated with SBP or DBP.
Prospective Sowers (2002) Camden, NJ, USA	705 pregnant women followed through pregnancy without serious nonobstetric conditions including chronic hypertension; Year not stated Male = 0%	20.5 (SE=0.2) Range 12-34 years	1.2 (SE = ±0.03)	Hypertension in pregnancy (HIP), preeclampsia, or toxemia based on >140/90mmHg Data and blood collections in each trimester, at delivery, and first postpartum visit.	Longitudinal regression with mixed models Age, race/ethnicity, and in-pregnancy dietary calcium	<u>Association of change in Pb concentration across pregnancy and HIP/toxemia</u>: HIP/toxemia (n=71): β=1.02 (SE=0.02) No HIP/toxemia (n=631): β=0.98 (SE=0.01) **Adjusted p=0.03** Maternal blood Pb levels were not associated with other reproductive outcomes: preterm delivery, small for gestational age, low birth weight, or Apgar scores.	Increases in blood Pb across pregnancy was significantly associated with hypertension in pregnancy/toxemia.
‡Cross-sectional Staessen (1990) London, England	531 London civil servants without industrial exposure to heavy metals; Year= 1982; Male = 75%	Calc. mean: 47.7 years <u>Men</u>: 47.8 (5.8) years Range: 37 – 58 <u>Women</u>: 47.5 (5.7) years Range: 38 – 57	Calc. mean: 11.8 µg/dl <u>Men</u>: 12.5 (4.37) Range: 6.25-35.4 <u>Women</u>: 10.2(3.96) Range: 4.17-31.25	Systolic and diastolic blood pressure (SBP and DBP)	Linear regression; t tests; step wise multiple regression. Age, sex, body weight, BMI, pulse rate, employment grade, smoking, alcohol consumption, serum creatine, serum calcium, γ-glutamyltranspep-tidase.	<u>Correlation between BP and log blood Pb:</u> Men: SBP r=0.05 (N.S.), DBP r=0.08 (N.S.) Women: SBP r=0.12 (N.S.), DBP r=-0.01 (N.S.) **All: SBP r=0.11 (p<0.02) DBP r=0.11 (p<0.02)** In the step wise multiple regression, the correlation between blood Pb and SBP or DBP did not approach statistical significance (data shown in figure only).	Correlations between blood Pb and SBP and DBP were not significant after adjustment for covariates.
Cross-sectional Staessen (1991) Belgium *Population may overlap with Dolenc (1993) and Staessen (1995)*	1,982 Belgians selected from a stratified random sample of the population of 4 Belgian districts; Cadmium in Belgium (Cadmibel) Study; Year: 1985-1989 (from Staessen (1995)) Male = 49%	48 Range: 20-80	Calc. mean: 9.5 Men: 11.6 Women: 7.5	Systolic and diastolic blood pressure (SBP and DBP)	Univariate analysis, stepwise regression Adjusted for age, age^2, BMI, pulse rate, log γ-glutamyltranspeptidase, smoking habits, and contraceptive pill use in women	<u>Univariate analysis, adjusted partial correlation coefficient:</u> Men (n=963): **SBP: 0.07, p-value=0.03** DBP: 0.01, p-value=0.80 Women (n=1019) SBP: 0.01, p-value=0.87 DBP: 0.04, p-value=0.18 <u>Multiple regression analysis</u> (348 subjects on hypotensive medication, such as diuretics, removed): Men (n=824) **SBP: β= -5.904 (sig. level for inclus. not reported)** DBP: NS Women (n=810) SBP: NS DBP: NS	Blood Pb was not significantly associated with increases in SBP or DBP.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
‡Prospective Staessen (1996) Belgium	728 adults from 2 regions, 1 of which was polluted by the emissions of non-ferrous smelters; Year= Baseline 1985-1989 and follow up 1991-1995 (mean 5.2 years between) Male = 49%	Men (n=359) Baseline: 46.3 (14.6) years Follow-up: 51.5 (14.6) years Women (n=369) Baseline: 45.7 (14.3) years Follow-up: 50.9 (14.3) years	Baseline: 8.7µg/dl Men Baseline: 11.4 Follow-up: 7.7 Women Baseline: 6.6 Follow-up: 4.8	Systolic and diastolic blood pressure (SBP and DBP) – 15 readings at home per subject Normotension: ≤140 mm Hg SBP and ≤90 mm Hg DBP Borderline Hypertension: 141-159 SBP OR 91-94 DBP Hypertension: ≥160 SBP OR ≥95 DBP, or medication	Multivariate analyses of time-integrated estimates of BP and Pb Adjusted for age, BMI, hematocrit or hemoglobin, γ-glutamyltransferase activity, and menopausal status (if applicable)	Correlation with stepwise adjustments: DBP in women (all others NS) **Unadjusted: β=5.37 mmHg, SE=2.05, p=0.009** Adj. hematocrit: β=4.14 mmHg, SE=2.25, p=0.06 Adj. hemoglobin: β=3.69 mmHg SE=2.05, p=0.07 Risk ratio of becoming hypertensive with a doubling of baseline blood Pb (adjusting for sex, age and BMI): All: RR=1.01 (95% CI 0.69-1.46) Excluding borderline hypertension: RR=1.21(0.72-2.03)	Blood Pb was not significantly associated with SBP, DBP, or with increased risk of hypertension after adjusting for relevant covariates.
Cross-sectional Telisman (2001) Croatia	154 Croatian men without occupational Pb exposure; Year = 1998-1999 Male = 100%	Median = 31.2 Range: 19.3-52.8	Median = 5.7 Range: 2.5-25.4	Systolic and diastolic blood pressure (SBP and DBP) Also measured erythrocyte protoporphyrin, blood Cd and serum Cu, Zn, and Se	Spearman's rank correlation and stepwise multiple regression Covariates included in the model: BMI, alcohol, smoking, serum Cu,	Spearman's rank correlation coefficient with blood Pb: **SBP: *r* = 0.229, *P*<0.005** **DBP: *r* = 0.207, *P*<0.01** BMI and erythrocyte protoporphyrin were also significantly correlated. Multiple regression coefficient of log blood Pb and BP (including a Pb x serum Se interaction term): SBP model (plus BMI): **logPb (*B*=12.9, *P*<0.02),** **logPb*SSe (*β*=-1.16, *P*<0.007)** DBP model (plus BMI and alcohol): **logPb (*B*=7.02, *P*<0.04),** **logPb*SSe (*β*= -0.95, *P*<0.0007)**	Concurrent blood Pb was significantly associated with SBP and DBP.
Case-control Vigeh (2004) Tehran, Iran	110 pregnant women not occupationally exposed to Pb (55 cases with pregnancy-induced hypertension and 55 age-and gravidity-matched normotensive controls) Year = 2001 Male = 0%	27 (5.6) years Range: 17-40 years	Cases: 5.7(2) Range 2.2-12.6 Controls: 4.8(1.9) Range 1.9-10.6 (blood collected 24 hours after delivery)	Systolic and diastolic blood pressure (SBP and DBP)	Wilcoxon signed-rank test or McNemar test; Spearman's correlation coefficient; logistic regression analysis	LnBlood Pb and hypertension during pregnancy (case vs. control): **β=1.37; p<0.05** **Odds Ratio (95% CI): 3.9 (1.3-11.7)** Correlations of lnblood Pb and BP in hypertensive cases: **SBP: r_s = 0.01, p>0.05** **DBP: r_s = 0.18, p>0.05** No significant differences in blood Pb concentrations among hypertensive subjects with proteinuria and those without proteinuria.	Blood Pb was significantly associated with hypertension during pregnancy and SBP and DBP in cases.
Cross-sectional Vupputuri (2003) USA *Population may*	14,952 subjects in NHANES III (including whites and blacks ≥18 years old and excluding	White men = 43.9 (0.5) years Black men = 39.9 (0.5) years	White men = 4.4 (0.1) µg/dl Black men = 5.4 (0.2) µg/dl	Systolic and diastolic blood pressure (SBP and DBP) and hypertension	Multivariate-adjusted linear regression models; linear and logistic regression models.	Differences in BP associated with one SD (3.3µg/dl) increase in blood Pb: SBP: White men = 0.29 (-0.24, 0.83) **Black men = 0.82 (0.19, 1.44) (*p*< 0.05)**	Concurrent blood Pb was significantly associated with SBP and DBP in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
overlap with Den Hond (2002) and others	non-black, non-white, and those taking anti-hypertension medication); Year= 1988 – 1994 Male = 50%	White women = 47.4 (0.6) years Black women = 42.0 (0.4)	White women = 3.0 (0.1) µg/dl Black women = 3.4 (0.1) µg/dl		Age, high school education, BMI, alcohol intake, leisure-time physical activity, dietary intake of sodium, potassium, and total energy.	White women = 0.34 (-0.49, 1.17) **Black women = 1.55 (0.47, 2.64) (*p*< 0.01)** DBP: White men = 0.01 (-0.38, 0.40) **Black men = 0.64 (0.08, 1.20) (*p*< 0.05)** White women = -0.04 (-0.56, 0.47) **Black women = 1.07 (0.37, 1.77) (*p*< 0.01)** Odds Ratio and 95% CI of Hypertension associated with a 1-SD increase in blood Pb: White men = 1.04 (0.93, 1.16) Black men = 1.08 (0.99, 1.19) (*p*= 0.08) **White women = 1.32 (1.14, 1.52) (p<0.001)** **Black women = 1.39 (1.21, 1.61) (p<0.001)**	blacks, but not whites; and with risk of hypertension in women, but not men.
Cross-sectional Wells (2011) Baltimore, MD, USA	285 pregnant women who gave birth at Johns Hopkins Hospital in the Baltimore THREE Study; Year = 2004-2005 Male = 0%	Age at delivery: 26 years Range:14-43	Cord blood Pb: 0.66 µg/dL (95% CI: 0.61-0.70)	Systolic and diastolic blood pressure (SBP and DBP) during pregnancy, gestational hypertension (GH), preeclampsia, and any hypertension	Multivariate regression Age, race, median household income, parity, smoking during pregnancy, prepregnancy BMI, and anemia	Change in SBP at Admission by cord blood Pb quartile: Q1 (≤0.46 µg/dL): referent Q2 (0.47-0.65 µg/dL): 2.89 (-2.16, 7.94) Q3 (0.66-0.95 µg/dL): 1.05 (-4.04, 6.14) **Q4 (≥0.96 µg/dL): 6.87 (1.51, 12.21)** **p-trend= 0.033** Change in DBP at Admission by cord blood Pb quartile: Q1 (≤0.46 µg/dL): referent Q2 (0.47-0.65 µg/dL): 0.00 (-3.95, 3.96) Q3 (0.66-0.95 µg/dL): 0.81 (-3.17, 4.80) **Q4 (≥0.96 µg/dL): 4.40 (0.21, 8.59)** **p-trend= 0.036** Change in maximum SBP by cord blood Pb quartile: Q1 (≤0.46 µg/dL): referent Q2 (0.47-0.65 µg/dL): 2.47 (-3.08, 8.02) Q3 (0.66-0.95 µg/dL): -1.76 (-7.36, 3.85) **Q4 (≥0.96 µg/dL): 7.72 (1.83, 12.60)** p-trend= 0.055 Change in maximum DBP by cord blood Pb quartile: Q1 (≤0.46 µg/dL): referent Q2 (0.47-0.65 µg/dL): 3.93 (-2.86, 10.72) Q3 (0.66-0.95 µg/dL): -0.42 (-7.27, 6.43) **Q4 (≥0.96 µg/dL): 8.33 (1.14, 15.53)** p-trend= 0.086 There were no significant associations between Pb and GH, preeclampsia, or hypertension (data not shown).	Umbilical cord blood Pb was significantly associated with elevations in maternal BP during labor and delivery, but not other BP related conditions.
Cross-sectional Wolf (1995) Austria	507 law enforcement agents without occupational exposure to Pb; Year not stated	44.9 (8.2)	8.0 (3.5)	Systolic and diastolic blood pressure (SBP and DBP); after sitting for at least 3 minutes	Stepwise linear regression Age, height, weight, nicotine consumption, alcohol intake, blood Pb,	Standardized estimates (STE) and p-value for logPb in regression model (with BMI, age and alcohol): SBP: STE=0.02, p=0.6418, R^2=0.1978 **DBP: STE=0.09, p=0.0355, R^2=0.1798** Standardized estimates (STE) and p-value for logPb in	Concurrent blood Pb was significantly associated with DBP, but not SBP.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
	Male = 100%				SBP, DBP, erythrocyte count	regression model (excluding alcohol intake): SBP: STE= 0.05, p=0.2096, R^2=0.1887 **DBP: STE= 0.12, p=0.0049, R^2=0.1742** Standardized estimates (STE) and p-value for logPb in regression model (including erythrocyte count): SBP: STE= 0.02, p=0.6170, R^2=0.1986 **DBP: STE= 0.09, p=0.0323, R^2=0.1827**	
Cross-sectional Yazbeck (2009) France	971 pregnant women enrolled at two French maternity wards before 24 weeks of gestation with no history of chronic hypertension; The EDEN study; Year= 2003, 2005; Male = 0%	29.3 (4.9)	At 24-28 wks Calc. mean: 1.9µg/dl PIH cases (n=106): 2.2 (1.4) No PIH (n=865): 1.9 (1.2) Measured 24-28 weeks gestation	Pregnancy induced hypertension (PIH): SBP ≥140 mmHg and/or DBP ≥90 mmHg averaged over visits before 24wks (P1); 24-36 wks (P2), and after 36 weeks (P3)	Multivariable logistic regression Maternal age, cadmium, manganese and selenium blood levels, hematocrit, parity, BMI, gestational diabetes, education level, socioeconomic status, geographic residence, and smoking status during pregnancy Additionally alcohol consumption for PIH according to parity analysis	Difference in mean blood Pb between PIH and no PIH: PIH cases 2.2 (1.4); No PIH (n=865): 1.9 (1.2) **Adj. p-value=0.02** Adj. Odds ratios (95% CI) for PIH by maternal blood Pb distribution: **Log Pb (continuous): 3.29 (1.11-9.74), *p*=0.03** Q1 (<1.20 µg/dl): referent Q2 (1.20-1.70 µg/dl): 1.84 (0.77-4.41), *p*=0.84 Q3 (1.71-2.30 µg/dl): 2.07 (0.83-5.13), *p*=0.50 Q4 (>2.30 µg/dl): **2.56 (1.05-6.22)**, *p*=0.09 Adj.ORs (95% CI) for PHI according to parity (per unit increase in blood Pb level): Nulliparous (10.7% with PIH): 2.9 (0.6-15.7) **Multiparous (11.4% with PIH): 4.6 (1.0-21.6)** Correlation of BP and log blood Pb: **24-36 wks, SBP: *r*=0.08, *p*=0.03** **24-36 wks, DBP: *r*=0.07, *p*=0.03** After 36 weeks also significantly associated (data not shown) Each decimal-log increase in blood Pb was associated with a 3.5 mmHg SBP and 2.5 mmHg DBP increase.	Blood Pb levels at mid-pregnancy were significantly associated with risk of pregnancy induced hypertension, particularly in multiparous women.
Cross-sectional Zhang (2010) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	619 men from the Normative Aging Study; Year = 1991-1995 Male = 100%	Calc. mean: 66.6 Wild type (n=409): 66.4 (7.0) *C282Y* (n=72): 66.9 (7.1) *H63D* (n=138): 66.9 (6.8)	Median (interquartile range) Tibia: 19 (13-27) µg/g Patella: 26 (18-37) µg/g	Pulse Pressure (PP, the difference between systolic and diastolic blood pressure) *HFE H63D* and *C282Y* polymorphisms also genotyped.	Mixed model Adjusted for age; education; alcohol intake; smoking; daily intakes of calcium, sodium, and potassium; total calories; family history of hypertension; diabetes; height; heart rate; high-density lipoprotein (HDL); total cholesterol:HDL ratio; and waist circumference	Adjusted estimators in the difference in PP for an IQR increase in bone Pb by *HFE* genotype: β (95% CI) Tibia Pb (IQR= 13 µg/g): **Wild type: 0.38 (0-1.96)** ***H63D*: 3.30 (0.16-6.46)** ***C282Y*: 0.89 (0-5.24)** **Any *HFE* variant: 2.90 (0.31-5.51)** Patella Pb (IQR= 19 µg/g): **Wild type: 0.26 (0-1.78)** ***H63D*: 2.95 (0-5.92)** ***C282Y*: 0.55 (0-1.66)** **Any *HFE* variant: 2.83 (0.32-5.37)** *HFE* variants were not independently associated with pulse pressure or bone Pb levels.	Bone Pb was significantly associated with pulse pressure and this association was modified by genetic variation in the *HFE* gene.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Heart Rate Variability (HRV)							
Cross-sectional Gump (2011) NY, USA *Population may overlap with Gump (2005)* *Also listed for ECG Conduction Abnormalities*	140 children from Oswego Children's Study (n=95 for high frequency HRV measurement) Year not stated Male = 55%	10.21 (0.75) Range: 9-11	Median: 0.94 Range: 0-3.76	Heart Rate Variability (HRV) in response to acute stress tasks: Pre-ejection period (PEP, decreases = ↑ sympathetic), high frequency (HF-HRV, ↑ with parasympathetic), cardiac autonomic regulation (CAR) and cardiac autonomic balance (CAB)	Generalized linear model with a linear contract test For Pb as a continuous measure: partial correlation of log transformed blood Pb Adjusted for gender, age, race, BMI percentile standing, SES, family history of cardiovascular disease, and Hg level	<u>Adjusted associations of blood Pb and HRV at baseline:</u> PEP (n=140): *p* linear trend = 0.11 Pb Q1 (0.14-0.68µg/dL): 107.75 Pb Q2 (0.69-0.93µg/dL): 108.39 Pb Q3 (0.94-1.20µg/dL): 105.17 Pb Q4 (1.21-3.76µg/dL): 104.45 HF-HRV (n=95): *p* linear trend = 0.12 Pb Q1 (0.14-0.68µg/dL): 5775.77 Pb Q2 (0.69-0.93µg/dL): 5237.09 Pb Q3 (0.94-1.20µg/dL): 5014.43 Pb Q4 (1.21-3.76µg/dL): 8798.16 CAR (↑HF↓PEP, n=95): *p* linear trend = 0.07 Pb Q1 (0.14-0.68µg/dL): 0.00 Pb Q2 (0.69-0.93µg/dL): -0.09 Pb Q3 (0.94-1.20µg/dL): 0.07 Pb Q4 (1.21-3.76µg/dL): 0.85 CAB (↓HF↓PEP, n=95): *p* linear trend = 0.80 Pb Q1 (0.14-0.68µg/dL): 0.27 Pb Q2 (0.69-0.93µg/dL): 0.17 Pb Q3 (0.94-1.20µg/dL): -0.06 Pb Q4 (1.21-3.76µg/dL): 0.47 **PEP and HF-HRV significantly decreased in response to acute stress tasks (PEP 105.6 to 104, *p*<0.0001 and HF-HRV 5002 to 2267, *p*<0.0001).** <u>Blood Pb in quartiles and cardiac responses to acute stress</u>: *F* (degress of freedom), *p*-value **Smaller ↓ in PEP: 4.11 (1,130), *p* < 0.05** **Greater ↓ in HF-HRV: 4.59 (1,85), *p* < 0.05** **↓ CAR (↑HF-HRV↓PEP): 6.33 (1,85), *p* < 0.05** ↔ CAB (↓HF-HRV↓PEP): 2.31 (1,84), p>0.10 <u>Continuous blood Pb and cardiac responses to acute stress</u>: *r*, *p*-value **PEP: *r*=0.17, *p* = 0.05** **HF-HRV: *r*=-0.22, *p* < 0.05** **CAR (↑HF-HRV↓PEP): *r*=-0.24, *p* < 0.05** CAB (↓HF-HRV↓PEP): data not shown	Concurrent blood Pb was significantly associated with impaired autonomic response to acute stress in children aged 9-11 years as assessed by heart rate variability measures.
Cross-sectional Jhun (2005) Seoul, Korea	331 public officials and their family members in Seoul with no history of occupational exposure to Pb; Year not stated	37.9 (17.3) years Range <10 (n=27) to ≥60 (n=29)	2.34 (0.86) µg/dl Median: 2.16µg/dl	Heart Rate Variability (HRV) at low frequency (0.04-0.15 Hz), high frequency (0.15-0.30 Hz), and total power spectrum (0.04-0.30)	ANOVA; Univariate association followed by step-wise multiple regression analyses Models included age, heart rate, alcohol	<u>Univariate analysis of blood Pb related to heart rate variability measures</u>: **ln Low Frequency = -0.53 (*p*<0.01)** **ln High Frequency = -0.98 (*p*<0.01)** **ln Total Power Spectrum = -0.57 (*p*<0.01)** Other metals were also examined: As and Cd were	Blood Pb was significantly associated with decreased low and high frequency heart rate variability,

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
	Male = 55%			Low: sympathetic/ parasympathetic mediation; High: only parasympathetic mediation	drinking, blood As or Cd, and serum Co or Zn.	significantly associated, but Al, Co, Cu, and Zn were not. Pb was not included in multiple regression analyses of HRV, while As, Cd, Co, and/or Zn were retained in the models.	but it may confounded by correlation with other metals.
Cross-sectional Park (2006) Boston, MA, USA *Population may overlap with Park (2008) and others*	413 participants in the Normative Aging Study; Year 2000-2004; Male = 100%	72.9 (6.5)	Patella bone Pb: 23 (15-34) µg/g Tibia bone Pb: 19 (11-28) µg/g	Heart rate variability (HRV) High-frequency (HF) Low-frequency (LF)	Linear regression Age, BMI, fasting blood glucose, HDL, triglyceride, cigarette smoking, alcohol consumption, use of beta-blockers, use of calcium channel blockers, use of angiotensin converting enzyme (ACE) inhibitors, room temperature, and season	Estimated change (95% CI) in HRV parameters associated with one IQR increase in bone Pb markers: Tibia (µg/g) High-frequency: -0.9 (-3.8 to 2.1) Low-frequency: 0.9 (-2.0 to 3.9) Log_{10} LF/HF (%): 3.3 (-10.7 to 19.5) Patella (µg/g) High-frequency: -0.6 (-3.1 to 1.9) Low-frequency: 0.6 (-1.9 to 3.1) Log_{10} LF/HF (%): 3.0 (-8.7-16.2)	Bone Pb was not significantly associated with changes in heart rate variability.
Cross-sectional Park (2008) Boston, MA, USA *Population may overlap with Park (2006) and others*	384 participants in the Normative Aging Study; Year= 2000 – 2004 Male = 100%	73 (6.5) years	Median bone Pb (µg/g) Tibia Pb: 19 Patella Pb: 23	Heart Rate Variability (HRV) Air pollutants also measured	Linear regression analyses; cubic spline; linear trend. Age, BMI, fasting blood glucose, antihypertensive medication, smoking, alcohol intake, season, apparent temperature, mean arterial pressure, temperature of the room where the heart rate was measured, education, cumulative traffic.	Tibia: Estimated changes in Heart Rate Variability (high and low frequency) associated with air pollution, by quartiles of Pb: **High Frequency, Sulfate (p<0.01 for trend)** **1st quartile = 50.7 (5.4, 115.5)** 2nd quartile = 1.4 (-30.1, 47.1) 3rd quartile = -8.4 (-35.9, 30.9) 4th quartile = -22.2 (-40.4, 1.6) **High Frequency, Ozone (p<0.01 for trend)** 1st quartile = 16.1 (-18.9, 66.2) 2nd quartile = -3.2 (-29.7, 33.2) 3rd quartile = -22.4 (-45.4, 10.3) 4th quartile = -37.9 (-54.6, -14.9) **Low Frequency, Sulfate (p=0.04 for trend)** 1st quartile = 28.3 (-3.6, 70.6) 2nd quartile = -2.6 (-27.6, 31.1) 3rd quartile = -10.6 (-32.8, 18.8) 4th quartile = -11.7 (-28.6, 9.3) **Low Frequency, Ozone (p<0.01 for trend)** 1st quartile = 4.2 (-21.8, 38.8) 2nd quartile = -14.5 (-33.8, 10.4) 3rd quartile = -24.3 (-42.9, 0.2) 4th quartile = -38.1 (-51.9, -20.4) Patella: Estimated changes in Heart Rate Variability (high and low frequency) associated with air pollution, by quartiles of Pb: **High Frequency, Ozone (p=0.01 for trend)**	Bone Pb significantly modified associations between cardiac autonomic function and short-term exposure to air pollutants.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						1st quartile =6.8 (-21.8, 45.8) 2nd quartile = -14.1 (-39.9, 22.9) 3rd quartile = -19.3 (-44.0, 16.4) 4th quartile = -41.4 (-59.9, -15.0) **Low Frequency, Ozone (*p*<0.01 for trend)** 1st quartile = 2.1 (-20.4, 31.1) 2nd quartile = -12.2 (-34.1, 16.9) 3rd quartile = -28.2 (-46.4, -3.6) 4th quartile = -36.4 (-52.8, -14.3)	
Electrocardiographic (ECG) Conduction Abnormalities							
Cross-sectional Cheng (1998) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	775 men from the Bone Pb Substudy of the Normative Aging Study; Excluded those with a history of heart disease, hypertension, diabetes, cancer, peptic ulcer, gout, recurrent asthma, bronchitis, sinusitis Year= 1991 – 1995 Male = 100%	67.8 (7.3) years Range = 48 – 93 years	Blood = 5.8 (3.44) µg/dl Tibia = 22.2 (13.4) µg/g Patella = 30.8 (19.2) µg/g	QT and QRS intervals, intraventricular conduction defect (IVCD), atrioventricular conductive defect (AVCD), other arrhythmias	Multivariate linear and logistic regression models Age, alcohol intake, BMI, diastolic pressure, fasting glucose, serum HDL	<u>Multivariate-adjusted parameter estimates of heart rate-corrected QT and QRS intervals associated with a 10-unit increase in Pb</u>: QT (ms) (< 65 years old, n=277) Blood Pb: β = -0.65 (-10.40, 9.10) (p= 0.90) **Tibia Pb: β = 5.03 (0.83, 9.22) (p= 0.02)** **Patella Pb: β = 3.00 (0.16, 5.84) (p= 0.04)** QRS (ms) (< 65 years old) Blood Pb: β = -3.49 (-10.72, 3.75) (p= 0.35) **Tibia Pb: β = 4.83 (1.83, 7.83) (p < 0.01)** **Patella Pb: β = 2.23 (0.10, 4.36) (p= 0.04)** Not sig. in ≥65 population (n=498) <u>Multivariate-adjusted parameter estimates of IVCD and AVCD associated with a 10-unit increase in Pb:</u> IVCD (< 65 years old, not sig in ≥65) Blood Pb: OR = 0.63 (0.12, 3.31) (p= 0.59) **Tibia Pb: OR = 2.33 (1.28, 3.90) (p < 0.01)** Patella Pb: OR = 1.32 (0.90, 1.95) (p= 0.16) AVCD (≥ 65 years old, not sig in < 65) Blood Pb: OR = 1.19 (0.41, 3.47) (p= 0.75) **Tibia Pb: OR = 1.22 (1.02, 1.47) (p= 0.03)** Patella Pb: OR = 1.14 (1.00, 1.29) (p= 0.06) Not sig. for Arrhythmia	Tibia and patella Pb were significantly associated with longer QT and QRS intervals in subjects under age 65 and tibia Pb was significantly associated with increased risk of conduction defects, but not arrhythmias, at any age. Blood Pb was not significantly associated with any outcome.
Prospective Eum (2011) USA *Population may overlap with Proctor (1996) and others*	496 men in the Normative Aging Study free of ECG abnormalities at baseline Year = Pb was measured (1991-1995) with a follow up ECG 8 years later, on average Male = 100%	Baseline: 66.7 (7.0) years	5.8 (3.6) <u>Patella</u>: 30.3µg/g (17.7) <u>Tibia</u>: 21.6µg/g (12.0)	Intraventricular conduction defect (IVCD), atrioventricular conduction defect (AVCD), other arrhythmia, heart rate corrected QTc interval (≥440 ms), QRSc durations, JTc interval (>360 ms); classified by the Minnesota code, on	Multiple regression Adjusted for age, age^2, education, BMI, smoking, diabetes, albumin-adjusted serum calcium (mg/dL) at baseline, years between ECG tests, and QT-prolongation medications at the time of ECG	<u>Adjusted 8 year change (95% CI) in ECG by baseline Pb:</u> QTc Interval Tibia Pb (µg/g) ***P* for trend = 0.03** <16 (n=191) ref. **16.0-23 (n=208) 7.49 (1.42-13.75)** **23+ (n=195) 7.94 (1.42-14.45)** Patella Pb (µg/g) *P* for trend = 0.45 <22 (n=207) ref. 22-33 (n=190) 4.14 (-2.19-10.46) 33+ (n=202) 2.69 (-3.68-9.06) QRSc Duration	Tibia Pb was significantly associated with increases over 8 years of follow up in QT interval, QRS duration, and increased risk of QT and JT prolongation. Results were

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
				average 8.1 (SD=3.1) years after Pb measurement		Tibia Pb (µg/g) ***P* for trend = 0.005** <16 (n=191) ref. 16.0-23 (n=208) 0.52 (-3.60-4.65) **23+ (n=195) 5.94 (1.66-10.22)** Patella Pb (µg/g) *P* for trend = 0.20 <22 (n=207) ref. 22-33 (n=190) 2.87 (-1.02-7.33) 33+ (n=202) 3.16 (-1.34-7.07) None sig. for JTc interval None sig. with Blood Pb <u>Adjusted Odds Ratio (95% CI) for incident cardiac abnormality at follow-up by Pb at baseline:</u> QT prolongation (≥ 440ms) Tibia Pb (µg/g), 67 case/387 cont., ***P*-trend = 0.003** 16.0-23 vs. <16 OR=0.86 (0.39-1.88) **23+ vs. <16 OR= 2.53 (1.22-5.25)** Patella Pb (µg/g), 68 case/391 cont., *P*-trend = 0.14 **22-33 vs. <22 OR=2.67 (1.28-5.56)** 33+ vs. <22 OR=2.10 (0.96-4.60) JT Prolongation (≥360 ms) Tibia Pb (µg/g), 32 case/425 cont., ***P*-trend = 0.04** 16.0-23 vs. <16 OR=0.93 (0.32-2.72) 23+ vs. <16 OR=2.53 (0.93-6.91) Patella Pb (µg/g), 32 case/429 cont., *P*-trend = 0.21 22-33 vs. <22 OR=2.24 (0.81-6.20) 33+ vs. <22 OR=2.18 (0.75-6.35) IVCD (MN codes 7-1-1, 7-2-1, 7-4) Tibia Pb (µg/g), 33 case/458 cont., *P*-trend = 0.55 16.0-23 vs. <16 OR=1.46 (0.56-3.85) 23+ vs. <16 OR=1.45 (0.52-4.08) Patella Pb (µg/g), 33 case/463 cont., *P*-trend = 0.75 **22-33 vs. <22 OR=3.77 (1.37-10.33)** 33+ vs. <22 OR=1.57 (0.49-5.00) No increased risk of AVCD No increased risk of Arrhythmia No increased risk with Blood Pb	similar, but weaker, for patella Pb and there was no association with blood Pb. There were no associations between Pb and JT interval, IVCD, AVCD or other arrhythmias.
Prospective and Cross-sectional Gump (2005) NY, USA *Population may overlap with Gump (2007)*	122 children from Oswego Children's Study (n=202) with established early childhood blood Pb levels. Year not stated Male= 45.9%	9.5	Cord = 2.97 (1.75) Age 2.6 blood= 4.62 (2.51)* *Gump (2007) states this was abstracted from	ECG measured stroke volume (SV), heart rate, cardiac output (CO: meanSV*meanHR for a time period), total peripheral resistance (TPR: [(SBP-DBP)/3+DBP]/CO*80), and mean successive	Linear regression Adjusted for: psychosocial variables, other toxicants, emotional response to tasks, *exact adjustment variables not reported*	<u>Childhood blood Pb (µg/dL) and cardiovascular functioning:</u> Heart Rate: β=-0.62 (0.35), p<0.10 Stroke Volume, CO, and TPR had p-values >0.15 <u>Childhood blood Pb (µg/dL) and cardiovascular responses to acute stress tasks:</u> β (95% CI), Standardized β, p-value **Stroke Volume (mL): β=-0.069 (-.124 to -.015), Std β=-**	Blood Pb in early childhood was significantly associated with decreased SV and increased TPR in response to acute stress at age 9-11 years,

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Also listed for Blood Pressure and Hypertension			health records Correlation of cord and childhood Pb: r = 0.11, p>0.50	difference for each data series/time period (MSD)		**0.219, p=0.013** Heart rate (beats/min): β=0.013 (-.046 to .072), Std β=0.038, p=0.659 CO (L/min): β=-0.0056 (-.113 to .001), Std β=-0.170, p=0.054 **TPR (dyn-s/cm5): β=0.088 (.024 to .152), Std β=0.241, p=0.007** MSD (ms): β=-0.028 (-.098 to .042), Std β=-0.078, p=0.424 Cord blood was not associated with responses to acute stress tasks	but cord blood Pb was not.
Cross-sectional Gump (2007) NY, USA *Population may overlap with Gump (2005)* *Also listed for Blood Pressure and Hypertension*	122 children from Oswego Children's Study (N=202) with established early childhood blood Pb levels; Year not stated Male= 45.9%	9.5	Cord = 2.97 (1.75) Age 2.6 blood = 4.62 (2.51) abstracted from health records	ECG measured stroke volume (SV), heart rate, cardiac output (CO: meanSV*meanHR for a time period), total peripheral resistance (TPR: ([(SBP-DBP)/3+DBP]/CO*80), and mean successive difference for each data series/time period (MSD)	Sobel tests to evaluate mediation Linear regression Adjusted for: family socioeconomic status (SES), blood Pb levels, interactor for SES and blood Pb	<u>SES in relation to children's CV responses (β ; R^2; p-value of SES and Pb interaction)</u> Heart rate (beats/min): β=0.048; R^2=0.001; p=0.232 SV (mL): β=-0.176; R^2=0.003; p=0.663 CO (L/min): β=-0.319; R^2=0.019; p=0.279 TPR (dyne-s/cm^5): β=-0.398; R^2=0.017; p=0.070 MSD (seconds): β=-0.269; R^2=0.016; p=0.191 Responses to acute stress tasks With SES X Pb interaction term: TPR β=0.005, SE=0.003, p<0.10	Lower family SES was associated with higher blood Pb levels in early childhood and heightened TPR responses to acute stress tasks, but the interaction was not statistically significant.
Cross-sectional Gump (2011) NY, USA *Population may overlap with Gump (2005)* *Also listed for Blood Pressure and Hypertension and Heart Rate Variability*	140 children from the Oswego Children's Study; Year not stated Male= 55%	10.21 (0.75) Range: 9-11	Median: 0.94 Range: 0-3.76	ECG measured heart rate , stroke volume (SV), cardiac output (CO: meanSV*meanHR for a time period), total peripheral resistance (TPR: [(SBP-DBP)/3+DBP]/CO*80)	Generalized linear model with a linear contract test Adjusted for gender, age, race, BMI percentile standing, SES, family history of cardiovascular disease, and Hg level	<u>Adjusted associations of blood Pb and HR at baseline:</u> Heart Rate (n=140): p linear trend = 0.16 Pb Q1 (0.14-0.68µg/dL): 82.47 Pb Q2 (0.69-0.93µg/dL): 83.24 Pb Q3 (0.94-1.20µg/dL): 83.69 Pb Q4 (1.21-3.76µg/dL): 78.55 **Heart rate significantly increased in response to acute stress tasks (85.3 to 86.1, p<0.05).** <u>Adjusted associations of blood Pb and reactivity to acute stress:</u> Heart Rate (n=140): p linear trend = 0.85 Pb Q1 (0.14-0.68µg/dL): 0.91 Pb Q2 (0.69-0.93µg/dL): 0.19 Pb Q3 (0.94-1.20µg/dL): 0.86 Pb Q4 (1.21-3.76µg/dL): 0.58 **Stroke Volume (n=140): p linear trend = 0.04** **Pb Q1 (0.14-0.68µg/dL): 2.23** **Pb Q2 (0.69-0.93µg/dL): 0.91**	Concurrent blood Pb was significantly associated with decreased stroke volume, decreased cardiac output, and increased total peripheral resistance in response to acute stress tasks in children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						Pb Q3 (0.94-1.20µg/dL): -3.47 **Pb Q4 (1.21-3.76µg/dL): -0.89** **Cardiac Output (n=140): *p* linear trend = 0.05** **Pb Q1 (0.14-0.68µg/dL): 3.26** **Pb Q2 (0.69-0.93µg/dL): 1.19** **Pb Q3 (0.94-1.20µg/dL): -2.31** **Pb Q4 (1.21-3.76µg/dL): -0.20** **Total Peripheral Resist. (n=140): *p* linear trend = 0.03** **Pb Q1 (0.14-0.68µg/dL): 2.91** **Pb Q2 (0.69-0.93µg/dL): 8.18** **Pb Q3 (0.94-1.20µg/dL): 9.55** **Pb Q4 (1.21-3.76µg/dL): 9.51**	
Cross-sectional Park (2009) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	613 older men in the Normative Aging Study with bone Pb and gene polymorphisms measured; Year 1991-1995; Male = 100%	67.3 (7.2) years	Blood median: 5µg/dl (IQR 4-7) Tibia median: 19µg/g (IQR 14-27) Patella median: 26µg/g (IQR 18-37)	QTc interval (time from start of the Q wave to end of the T wave) Genotyped polymorphisms in iron metabolism genes: hemochromatosis (*HFE*), transferrin C2 (*TFC2*), and heme oxygenase-1 (*HMOX-1*)	Linear regression Adjusted for age, BMI, albumin-adjusted serum calcium, smoking status, and diabetes status	Difference in QTc interval per IQR increase in Pb, stratified by number of gene variants: β (95% CI) Blood Pb (IQR=3µg/dl) All (n=613): β=1.30 (-0.76-3.36) 0 variants (n=237): β=-0.82 (-4.35-2.71) 1 variant (n=276): β=2.65 (-0.66-5.96) 2 or 3 variants (n=100): β=6.71 (-0.70-14.13) ***p* for trend=0.04** Tibia Pb (IQR=13µg/g) **All (n=613): β=2.85 (0.29-5.40)** 0 variants (n=237): β=-2.43 (-7.05-2.37) **1 variant (n=276): β=5.17 (2.02-8.32)** 2 or 3 variants (n=100): β=7.26 (-0.72-15.25) ***p* for trend=0.01** Patella Pb (IQR=19µg/g) **All (n=613): β=2.64 (0.13-5.15)** 0 variants (n=237): β=-0.53 (-5.23-4.18) **1 variant (n=276): β=3.77 (0.57-6.98)** 2 or 3 variants (n=100): β=5.38 (-1.74-12.49) *p* for trend=0.10	BonePb was significantly associated with increases in QT interval, which was stronger in carriers of iron metabolism gene polymorphisms. Concurrent blood was only significantly associated in with QT interval carriers of one iron metabolism gene variant.
Clinical Cardiovascular Disease							
Case-control Afridi (2010a) Hyderabad, Pakistan	130 patients admitted with myocardial infarction and 61 healthy controls in the same city, matched by age group and SES with no history of CVD or family history of MI or cardiac death	Range: 45-60	No blood Pb Hair Pb: Range of group means 6.4-18.6µg/g Estimated range: 2-6 µg/dl based on children with blood and hair Pb available	Number of myocardial infarction (MI) attack and survival (32 patients were admitted for their 3rd MI attack and 25 of them died.) Excluded renal or hepatic disease,	Linear regression, pearson correlation coefficient, unpaired student *t* test of mean differences	Hair Pb levels: mean (SD); Regression, Correlation **Men, *p* <0.001** Controls: 7.5 (0.4) µg/g; (ref.) 1st MI: 9.7 (1.2) µg/g; β=0.214, r=0.065 2nd MI: 13.6 (6.7)µg/g; β=8.59, r=0.33 3rd MI: 18.6 (5.4) µg/g; β=10.4, r=0.53 **Women, *p* <0.001** Controls: 6.4 (1.6) µg/g; (ref.) 1st MI: 7.9 (0.7) µg/g; β=0.028, r=0.06 2nd MI: 11.2 (5.3) µg/g; β=1.12, r=0.33 3rd MI: 14.5 (3.9) µg/g; β=0.912, r=0.50	Hair Pb levels increased with number of heart attacks and patients who died after a third MI had higher Pb levels.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
	before age 55 Year = 2007-2008; Male = 59% cases, 54% controls		(Afridi *et al.* 2010b)	vascular disease, and antioxidant or aspirin treatment			
Cross-sectional Guallar (2006) USA	4,447 participants over age 40 from NHANES without missing data, including cadmium; Year= 1999-2002; Male = 48.3%	OHAT calc mean: 56.4 Cases: 68.5 (0.6) Noncases: 55.5 (0.2)	OHAT calc mean: 1.95µg/dl Cases: 2.56 (95% CI 2.41-2.72) Noncases: 1.91 (95% CI 1.86-1.97)	Peripheral arterial disease (PAD, n=310 cases): ankle-brachial index lower than 0.9 in at least one leg	Multivariable logistic regression, χ^2 test for trend, Adjusted for age, sex, race/ethnicity, education, smoking status, alcohol intake, BMI, C-reactive protein, serum folate and/or vitamin B12 and blood cadmium level PAD models further adjusted for diabetes, hypertension, hypercholesterolemia, estimated glomerular filtration rate, and homocysteine	Ratio (95% CI) of geometric mean plasma homocysteine levels by quintile of Blood Pb (fully adjusted model): Q1 (<1.1 µg/dl): ref. **Q2 (1.1-1.6 µg/dl): 1.03 (1.00-1.06)** **Q3 (1.6-2.2 µg/dl): 1.06 (1.03-1.19)** **Q4 (2.2-3.2 µg/dl): 1.10 (1.07-1.13)** **Q5 (≥3.2 µg/dl): 1.12 (1.09-1.17)** **P_{trend} <0.001** Adjusted Odds Ratio (95% CI) for PAD by quintile of blood Pb (n=cases/noncases); Q1 (<1.1 µg/dl, n=43/939): ref. Q2 (1.1-1.6 µg/dl, n=41/821): 0.99 (0.53-1.85) Q3 (1.6-2.2 µg/dl, n=53/811): 1.19 (0.74-1.92) **Q4 (2.2-3.2 µg/dl, n=73/809): 1.64 (1.02-2.61)** **Q5 (≥3.2 µg/dl, n=100/757): 1.65 (1.07-2.56)** **P_{trend} = 0.045**	Concurrent blood Pb was significantly associated with risk of PAD, independent of plasma homocysteine.
Cross-sectional Ishida (1996) Japan	128 ceramic painters not on medications; 26.6% of the area's ceramic painters; Year not stated Male = 45%	53.3 years Range: 29-75 Men: 55 yrs Women: 52 yrs	13.3µg/dl Range: 2.1-69.5 Men 16.5 (2.1) Range: 3.5-69.5 Women 11.1 (1.7) Range: 2.1-31.5	Median nerve maximal conduction velocity (MCV, measure of motor nerve function), coefficient of variation of R-R interval on electrocardiography (supine= CVRR, while breathing deeply=D-CVRR; measures of parasympathetic function), postural changes in finger blood flow volume (ΔFBF), and changes in finger blood flow drop velocity (FDV) from the supine to standing position (sympathetic function)	Analysis of variance and correlation Stepwise multiple regression analysis: ΔFBF model included age, BMI, smoking, and alchol	ΔFBF mean (SD) by Pb concentration: All subjects: **ANOVA p=0.002** **r=-0.313, p<0.001** **β=0.213; p=0.010** Men: ≤9.9 µg/dl (n=15): 0.42 (0.27) 10.0-19.9 µg/dl (n=19): 0.39 (0.25) 20.0-29.9 µg/dl (n=10): 0.21 (0.25) ≥30 µg/dl (n=11): 0.31 (0.20) r=-0.296, **p=0.032** Women: ≤9.9µg/dl (n=28): 0.47 (0.19) 10.0-19.9 µg/dl (n=32): 0.47 (0.17) 20.0-29.9 µg/dl (n=4): 0.35 (0.11) ≥30 µg/dl (n=1): 0.65 r=-0.208, p=0.097 No significant differences with blood Pb in the other physiological tests: MCV, CVRR, D-CVRR, and FDV	Concurrent blood Pb was significantly associated with decreases in postural changes in finger blood flow volume is consistent with an atherosclerotic effect.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Prospective Jain (2007) Boston, MA, USA; *Population may overlap with Proctor (1996) and others*	837 men in the Normative Aging Study without a history of ischemic heart disease at time of Pb measurement. Year = 1991-2001; Male = 100%	Noncases (n=754): <60=162, 60-69=378, ≥70=214 Cases (n=83): <60=10, 60-69=48, ≥70=25	Calc. mean = 6.3 Noncases (n=738): 6.2 (4.3) Cases (n=80): 7.0 (3.8) Patella Pb Noncases (n=487): 30.6 (19.7) µg/g Cases (n=63): 36.8 (20.8) µg/g TIbia Pb Noncases (n=486): 21.4 (13.6) µg/g Cases (n=63): 24.2 (15.9) µg/g	Coronary Artery Disease (described as ischemic heart disease by diagnosis of myocardial infarction or angina pectoris)	Cox proportional hazards model including age, race, and serum high density lipids	Age, blood and patella Pb were significantly higher in cases than noncases (p<0.05 for all 3). Unadjusted Cox proportional HR (95%CI): **Blood Pb ≥ 5 µg/dl: 1.64 (1.00-2.68)** Log Blood Pb: 1.40 (0.99-1.98) **Log Patella Pb: 3.27 (1.41-7.58)** Log Tibia Pb: 2.76 (0.94-8.12) Adjusted Cox proportional HR (95%CI): **Blood Pb ≥ 5 µg/dl: 1.73 (1.05-2.87), p=0.05** **Log Blood Pb: 1.45 (1.01-2.06), p=0.05** **Log Patella Pb: 2.64 (1.09-6.37), p=0.05** Log Tibia Pb: 1.84 (0.57-5.90), p=0.31	Blood and patella Pb were significantly associated with increased risk of coronary artery disease in this prospective study.
Cross-sectional Kaewboonchoo (2010) Bangkok, Thailand *Population may overlap with Kaewboonchoo (2007) listed in Blood Pressure and Hypertension*	420 bus drivers without a history of hypertension, heart disease, or tachycardia at the time of SDPTG measurement; Year not stated Male = 100%	41.6 (7.7) Range: 20 - 60 years	6.3 (2.2) Range: 2.5-16.2µg/dl	Second derivative finger photoplethysmogram waveform (SDPTG) and a mean aging index of SDPTG (SDPTG-AI) Higher values of SDPTG-AI indicate lower central and peripheral arterial functions	Mean comparison by Student's *t* test Pearson's correlation coeffieicient (*r*) Multiple regression analysis adjusted for age, BMI, smoking, alcohol, physical exercise	Mean SDPTG-AI (SD): **p=0.015** Low Pb (<4.1µg/dl, n=54) = -0.56 (0.30) High Pb (>8.5µg/dl, n=83) = -0.42 (0.30) Correlation of SDPTG-AI and Log blood Pb: ***r* = 0.185, p<0.01** Blood Pb regression with SDPTG-AI: ***β* = 0.017 (p=0.003)** Age, BMI, and smoking also included in model	Concurrent blood Pb was significantly associated with higher mean aging index of SDPTG – a marker of poor arterial function.
Cross-sectional Kim (2008) South Korea *Also listed for Blood Pressure and Hypertension*	13,043 Pb workers in the Special Health Surveillance Program; Year = 2003; Male = 69%	33.7 (10.0) years	Geometric mean 6.08 (2.53) Range; 0.002 - 123.22 70% of workers <10µg/dl	Coronary Artery Disease (described as ischemic heart disease) and Cerebral Vascular Disease,	Relative risk was calculated as in Lawes (2003). No adjustment for other factors	Relative Risk [95% CI not reported] for Ischemic Heart Disease: PbB <5µg/dL (referent) 5 µg/dl ≤ PbB < 10 µg/dl = 1.026 (men) 1.017 (women) 10 µg/dl ≤ PbB < 15 µg/dl = 1.122 (men) 1.070 (women) 15 µg/dl ≤ PbB < 20 µg/dl = 1.210 (men) 1.125 (women) 20 µg/dl ≤ PbB = 1.260 (men) 1.154 (women) Relative Risk [95% CI not reported] for Cerebral Vascular Disease: PbB <5µg/dL (referent) 5 µg/dl ≤ PbB < 10 µg/dl = 1.034 (men) 1.022 (women) 10 µg/dl ≤ PbB < 15 µg/dl = 1.168 (men) 1.095 (women) 15 µg/dl ≤ PbB < 20 µg/dl = 1.292 (men) 1.172 (women) 20 µg/dl ≤ PbB = 1.362 (men) 1.212 (women) The impact fractions for cardiac diseases among Pb workers from increases in blood pressure were estimated 4.9 to 12.8 times the general population.	Blood Pb was not significantly associated with increased risk of coronary artery disease or cerebral vascular disease in these Pb exposed workers.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Prospective Møller (1992) Denmark *Population may overlap with Grandjean (1989)* *Also listed for Blood Pressure and Hypertension and Cardiovascular Mortality*	1, 050 adults born in 1936 and living in the 4 municipalities served by the Glostrup Hospital (Glostrup Population Study); Year = Baseline 1976, Follow up through 1990; Male = 48%	40 years at baseline	Baseline Calc. mean=11.5 Men (n=504): 13.6 (5.7) Range=5 – 60 Women (n=546): 9.6 (3.8) Range=4 – 39	Coronary heart disease and cardiovascular disease (fatal and non-fatal cases)	Multiple regression analyses and Cox proportional hazards model. Tobacco, cholesterol, physical activity, sex, SBP, and alcohol	<u>Regression of cardiovascular endpoints on ln(blood Pb) from 1976 – 1990</u>: β, Relative Hazard (RH), *p* value Coronary heart disease for a 1 ln blood Pb unit change: **Unadjusted β=1.10, RH=2.14, *p*=0.003** Fully adjusted β=0.66, RH=1.58, *p*=0.15 Cardiovascular disease for a 1 ln blood Pb unit change: **Unadjusted β=0.66, RH=1.58, *p*=0.05** Fully adjusted β=0.14, RH=1.10, *p*=0.74	After adjustment there was no significant association between blood Pb and coronary heart disease or cardiovascular disease.
Cross-sectional Muntner (2005) USA *Population may overlap with Den Hond (2002) and others* *Also listed for Blood Pressure and Hypertension*	9,961 participants from NHANES; Year= 1999-2002 Male = 50.3%	mean not reported all ≥ 18	1.64µg/dl 95% CI: 1.59-1.68	Peripheral artery disease (PAD): ankle-brachial index lower than 0.9	Multivariable logistic regression, χ^2 test for trend, Adjusted for age, sex, diabetes, BMI, current and former smoking, alcohol consumption, having a high school education, and having health insurance	<u>Adjusted Odds Ratio (95% CI) of Peripheral Artery Disease by Quartile of Blood Pb</u>: Disease % (SE) Q1 (<1.06 µg/dl)=ref.; 2.6% (0.6) Q2 (1.06-1.63 µg/dl) OR=1.00 (0.45-2.22); 3.0% (0.5) Q3 (1.63-2.47 µg/dl) OR=1.21 (0.66-2.23); 4.8% (0.6) **Q4 (≥2.47 µg/dl) OR=1.92 (1.02-3.61); 7.7% (0.6)** ***P* Value for Trend <0.001;**	Concurrent blood Pb was significantly associated with increased risk of PAD.
Cross-sectional Navas-Acien (2004) USA *Population may overlap with Den Hond (2002) and others*	2,125 participants from NHANES 40 years and older; Year= 1999-2000 Male = 50.3%	40-49 (n=556), 50-59 (n=447), 60-69 (n=583), ≥70 (n=539)	Geometric mean: 2.1 µg/dL	Peripheral artery disease (PAD)	Adjusted odds ratios; regression models. Sex, age, BMI, education, race, smoking, serum cotinine, alcohol intake, hypertension, diabetes, hypercholesterolemia, glomerular filtration rate, C-reactive protein, blood cadmium levels	Subjects with Peripheral Artery Disease (PAD) had **13.8% (95% CI 5.9, 12.9)** higher mean levels of blood Pb. <u>Odds ratios (95% CI) of PAD by quartile of blood Pb:</u> 1st quartile (<1.4µg/dL) = ref. 2nd quartile (1.4-2.1µg/dL) = 1.63 (0.51, 5.15) 3rd quartile (2.1-2.9µg/dL) = 1.92 (0.62, 9.47) 4th quartile (>2.9µg/dL) = 2.88 (0.87, 9.47) ***p*= 0.02 for trend, but 0.05 after adjusting for cadmium**	Blood Pb was significantly associated with increased prevalence of PAD, but adjustment for blood cadmium reduced statistical significance.
Prospective Pocock (1988) England	7,371 men randomly selected from general practices in 24 British towns (The Regional Heart Study); Year not stated Male =100%	[mean not provided] Range = 40 – 59 years.	mean not reported **limits utility*	Coronary Artery Disease (described as ischemic heart disease)	Multiple regression analyses Age, BMI, alcohol intake, smoking, social class, town of residence.	Mean blood Pb for men with Ischemic heart disease: 16.3 µg/dL Others: 15.22µg/dL Mean blood Pb for men with Stroke: 16.7µg/dL Others: 15.3 µg/dL	Lack of information on blood Pb levels in this study limits the utility in this evaluation.
Cross-sectional Schwartz (1991) USA	9,932 participants from NHANES II; Year= 1976 – 1980; % male not stated	mean not reported Range = 20 – 74	mean not reported **limits utility*	Left ventricular hypertrophy	Step-wise regression; SURREGR; RTILOGIT Age, BMI, race, family	Regression of blood Pb and left ventricular hypertrophy: **β(SE): 0.0283 (0.0100); *p*= 0.0087**	Blood Pb was significantly associated with left ventricular

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Also listed for Blood Pressure and Hypertension		years			history, cholesterol, height, smoking, serum zinc, tricep skin fold thickness		hypertrophy, but the mean levels are above 10µg/dl.
Cross-sectional Zeller (2010) Innsbruck, Austria	197 women, Atherosclerosis Risk Factors in Female Youngsters study Year = 2005; Male = 0%	mean not reported 18-22 years	mean not reported Tertiles: <0.72µg/dl, 0.72-0.82µg/dl, and >0.82µg/dl	Intima-media thickness of the common and carotid arteries *most of this paper focused on in vivo and in vitro studies of mechanism	Multivariate logistic regression Systolic blood pressure, smoking, fasting glucose, insulin resistance, cholesterol, waist circumference, social status family history for hypertension, GOT, lipoprotein(a), C-reactive protein, homocysteine, T-cell reactivity against human Hsp60, soluble Hsp60 in serum, asthma and oral contraceptives	<u>Increased serum Pb levels and intima-media thickness for 1 SD increase</u>: **OR = 1.6 (1.1, 2.4) p=0.01** The risk increased over tertile groups (**p<0.05 for linear trend**) 8 other metals tested were not significantly associated	Concurrent serum Pb levels in healthy young women were significantly associated with an increased risk for high intima-media thickness.
Cardiovascular Mortality							
Prospective Lin (2011) Taiwan	927 patients on maintenance hemodialysis for 6 months without previous Pb exposure, malignancies, infections, or hospitalization or surgery in the last 3 months; 803 completed follow-up for 18 months; Year not stated Male = 51%	55.7 (13.4) Range: 18-93 years	Median: 10.4µg/dl Range: 1.1-41.8) Tertile 1 (<8.51) median = 6.3µg/dl Tertile 2 (8.51-12.64) median = 10.4µg/dl Tertile 3 (>12.64) median = 16.4µg/dl	Mortality and cause of death (59 patients died after 18 months of follow up) *Figure says 36-month infection cause, but text says 18-month, and there is no other mention of 36 months of follow up	Kaplan Meier survival analysis Cox multivariable analysis adjusted for age, diabetes, education, hemodialysis vintage, using biocompatible membrane of dialyzers, normalized protein catabolic rate, daily residual urine<100 mL, hemoglobin, serum albumin, HDL, creatinine, phosphate, cardiothoracic ratio, logarithmic transformation of ferritin, intact parathyroid hormone, and high-sensitivity C-reactive protein	<u>All-cause mortality</u>: Kaplan Meyer survival **Tertile 3 (10.0%) vs 1 (2.6%): χ^2 =14.51, p<0.001** Tertile 2 not formally tested (mortality est. 6.5% Fig 2) <u>All-cause mortality</u> Hazard Ratio (95% CI): Blood Pb (Tertile 1=ref.): Tertile 2 vs. 1: HR=2.69 (0.47-3.44) **Tertile 3 vs. 1: HR=4.70 (1.92-11.49)** Hemoglobin Corrected Blood Pb: (Tertile 1=ref.): Tertile 2 vs. 1: HR=3.52 (0.41-5.01) **Tertile 3 vs. 1: HR=4.98 (1.86-13.33)** <u>Cardiovascular-cause mortality</u> HR (95% CI): Blood Pb (Tertile 1=ref.): **Tertile 2 vs. 1: HR=3.70 (2.06-6.48)** **Tertile 3 vs. 1: HR=9.71 (2.11-23.26)** Hemoglobin Corrected Blood Pb: (Tertile 1=ref.): Tertile 2 vs. 1: HR=3.52 (0.51-6.33) **Tertile 3 vs. 1: HR=7.35 (1.64-33.33)** <u>Infection-cause mortality*</u> HR (95% CI): Blood Pb (Tertile 1=ref.): Tertile 2 vs. 1: HR=4.33 (0.35-6.54) **Tertile 3 vs. 1: HR=5.35 (1.38-20.83)** Hemoglobin Corrected Blood Pb: (Tertile 1=ref.): Tertile 2 vs. 1: HR=3.02 (0.23-2.07) **Tertile 3 vs. 1: HR=4.72 (1.27-17.54)**	Blood Pb was significantly associated with increase risk of death due to cardiovascular or infection causes in dialysis patients.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Prospective Møller (1992) Denmark *Population may overlap with Grandjean (1989) Also listed for, Blood Pressure and Hypertension and Clinical Cardiovascular Disease.*	11, 050 adults born in 1936 and living in the 4 municipalities served by the Glostrup Hospital (Glostrup Population Study); Baseline: 1976 Follow up through 1990; Male = 48%	40 years at baseline	Baseline Calc. mean=11.5 Men (n=504): 13.6 (5.7) Range=5 – 60 Women (n=546): 9.6 (3.8) Range=4 – 39	Total Mortality	Multiple regression analyses and Cox proportional hazards model. Tobacco, cholesterol, physical activity, sex, SBP, and alcohol	Regression of total mortality on ln(blood Pb) from 1976 – 1990: β, Relative Hazard (RH), *p* value (n=1050): Total mortality **Unadjusted β=1.11, RH=2.16, *p*=0.001** Fully adjusted β=0.66, RH=1.58, *p*=0.12 Analyses of coronary heart disease and cardiovascular disease included fatal and non-fatal cases	After adjustment there was no significant association between blood Pb and total mortality
Prospective Menke (2006) USA *Population may overlap with Den Hond (2002) and others*	13,946 adult participants of NHANES III (≥17 years of age at baseline and matched to the National Death Index records for up to 12 years for all-cause and cause-specific mortality); Year= Baseline was 1988 – 1994; follow-up through 2000; Male= 47%	44.4 (0.5) years	Geometric mean at baseline: 2.58 µg/dl	Mortality by all cause, cardiovascular disease, myocardial infarction, stroke, and cancer	Cox regression analyses with Schoenfeld residuals; restricted quadratic splines. Age, race-ethnicity, sex, urban residence, smoking, alcohol intake, education, physical activity, household income, menopausal status, BMI, CRP, total cholesterol, diabetes mellitus.	Hazards ratio by tertile of blood Pb at baseline Tertile 1: ≤1.03 µg/dL (reference) Tertile 2: 1.94-3.62 µg/dL Tertile 3 ≥3.63 µg/dL **All-cause mortality (p=0.002 for trend)** Tertile 2 vs. 1: HR (95% CI) = 0.91 (0.72, 1.15) **Tertile 3 vs. 1: HR (95% CI) = 1.25 (1.04, 1.51)** **Cardiovascular Disease (*p*=0.003 for tend)** Tertile 2 vs. 1: HR (95% CI) = 1.03 (0.69, 1.55) **Tertile 3 vs. 1: HR (95% CI) = 1.55 (1.08, 2.24)** **Myocardial infarction (*p*=0.007 for tend)** Tertile 2 vs. 1: HR (95% CI) = 1.02 (0.55, 1.89) **Tertile 3 vs. 1: HR (95% CI) = 1.89 (1.04, 3.43)** **Stroke (*p*=0.017 for tend)** Tertile 2 vs. 1: HR (95% CI) = 2.19 (0.87, 5.53) **Tertile 3 vs. 1: HR (95% CI) = 2.51 (1.20, 5.26)** Cancer (*p*=0.101 for tend) Tertile 2 vs. 1: HR (95% CI) = 0.72 (0.46, 1.12) Tertile 3 vs. 1: HR (95% CI) = 1.10 (0.82, 1.47)	Blood Pb was significantly associated with all cause mortality and mortality from cardiovascular disease, myocardial infarction, and stroke, but not cancer over 12 years of follow-up in adults.
Cross-sectional Schober (2006) USA *Population may overlap with Den Hond (2002) and others*	9,757 participants ≥40 years at baseline from the NHANES III matched to the 2000 National Death Index records; Year= Baseline was 1988 – 1994; follow-up through 2000; Male = 48%	Calc. overall mean: 58.6 <5µg/dL (n=6608): 57.0 5-9µg/dL (n=2532): 60.6 >10µg/dL (n=617): 62.0	mean not reported <5µg/dL n=6608 5-9µg/dL n=2532 >10µg/dL n=617	Mortality from all causes, cancer, and cardiovascular disease	Cox proportional hazard regression analysis; multivariate proportional hazard models Sex, race/ethnicity, education, and smoking status	Relative risk (95% CI): <5 µg/dL = ref. All causes **5-9 µg/dL: 1.24 (1.05-1.48)** **≥10 µg/dL: 1.59 (1.28-1.98)** **P-value for trend <0.001** Cardiovascular disease 5-9 µg/dL: 1.20 (0.93-1.55) **≥10 µg/dL: 1.55 (1.16-2.07)** **P-value for trend <0.01** Cancer **<5 µg/dL: 1.44 (1.12-1.86)** **≥10 µg/dL: 1.69 (1.14-2.52)** **P-value for trend <0.01**	Blood Pb was significantly association with increased risk of death from all causes, cardiovascular disease, and cancer over 12 years of follow-up of adults over age 40.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Prospective Weisskopf (2009) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	860 men with valid patella bone Pb from the Normative Aging Study; Year = bone Pb began in 1994 and follow up continued through 2007; Male = 100%	67.3 (7.3) years in 1994	Patella Pb = 31.2 (19.4) µg/g bone mineral Blood Pb = 5.6 (3.4) µg/dl	All-cause mortality, cardiovascular disease mortality, and cancer mortality	Cox proportional hazards regression with multivariable models Results presented adjusted for age, smoking, and education. Those with disease at baseline excluded.	Hazards ratio and 95% CI by tertile of patella Pb (<22 µg/g served as reference) All-cause (***p*=0.02 for trend**) 22 – 35 µg/g, HR = 1.75 (0.82, 3.75) **>35 µg/g, HR = 2.52 (1.17, 5.41)** All-cardiovascular (***p*=0.003 for trend**) 22 – 35 µg/g, HR = 1.63 (0.51, 5.18) **>5 µg/g, HR = 5.63 (1.73, 18.3)** Cancer (*p*=0.14 for trend) 22 – 35 µg/g, HR = 0.82 (0.26, 2.59) >35 µg/g, HR = 0.32 (0.08, 1.35) Hazards ratio and 95% CI by tertile of blood Pb (<4 µg/dl served as reference) All-cause (*p*=0.67 for trend) 4 – 6 µg/dl, HR = 0.69 (0.41, 1.19) >6 µg/dl, HR = 0.84 (0.50, 1.42) All-cardiovascular (*p*=0.44 for trend) 4 – 6 µg/dl, HR = 0.63 (0.29, 1.38) >6 µg/dl, HR = 0.69 (0.33, 1.47) Cancer (*p*=0.15 for trend) 4 – 6 µg/dl, HR = 1.03 (0.42, 2.55) >6 µg/dl, HR = 0.53 (0.20, 1.39)	Bone Pb, but not blood Pb, was significantly associated with all-cause and cardiovascular mortality, but not cancer mortality in men.

Abbreviations: ΔFBF - changes in finger blood flow volume; Adj – adjusted; Al - aluminum; ANOVA - analysis of variance; As - arsenic; AVCD - atrioventricular conduction defect; BMI - body mass index; BP - blood pressure; CAB - cardiac autonomic balance; CAR - cardiac autonomic regulation; Cd – cadmium; CI - confidence interval; Co – cobalt; CO - cardiac output; Cu- copper; CVRR - coefficient of variation of R-R interval on electrocardiography; DBP - diastolic blood pressure; ECG - electrocardiographic; FDV - flow drop velocity; GH – gestational hypertension; GOT - glutamic oxalic transaminase; HDL – high-density lipoprotein; HF-HRV – high frequency heart rate variability; HF - high-frequency; *HFE* – hemochromatosis; Hg – mercury; *HMOX-1* - heme oxygenase-1; HR - hazards ratio; HRV - heart rate variability; Hz - hertz; IVCD - intraventricular conduction defect; LF - low-frequency; MCV - maximal conduction velocity; MI - myocardial infarction; MSD - mean successive difference; NS – not significant; OR - odds ratio; PAD – peripheral artery disease; PP - pulse pressure; RR - relative risk; PEP - pre-ejection period; SBP - systolic blood pressure; SD – standard deviation; SDPTG - second derivative finger photoplethysmogram waveform; SDPTG-AI - mean aging index of SDPTG Se – selenium; SE – standard error; SES – socioeconomic status; SV - stroke volume; *TFC2* - transferrin C2; TPR - total peripheral resistance; Zn – zinc;

References:

Afridi HI, Kazi TG, Kazi N, Kandhro GA, Baig JA, Shah AQ, Jamali MK, Arain MB. 2010a. Evaluation of toxic elements in scalp hair samples of myocardial infarction patients at different stages as related to controls. *Biol Trace Elem Res* 134(1): 1-12.

Afridi HI, Kazi TG, Kazi N, Sirajuddin, Kandhro GA, Baig JA, Shah AQ, Wadhwa SK, Khan S, Kolachi NF, Shah F, Jamali MK, Arain MB. 2010b. Evaluation of Status of Cadmium, Lead, and Nickel Levels in Biological Samples of Normal and Night Blindness Children of Age Groups 3-7 and 8-12 Years. *Biol Trace Elem Res* in press.

Al-Saleh I, Shinwari N, Mashhour A, Mohamed Gel D, Ghosh MA, Shammasi Z, Al-Nasser A. 2005. Is lead considered as a risk factor for high blood pressure during menopause period among Saudi women? *Int J Hyg Environ Health* 208(5): 341-356.

Apostoli P, Maranelli G, Dei Cas L, Micciolo R. 1990. Blood lead and blood pressure: a cross sectional study in a general population group. *Cardiologia* 35(7): 597-603.

Bakhtiarian A, Dizaji R, Mohaghegh A, Immami-Khansari F, Ghazi-Khansari M. 2006. The study of blood lead concentration in hypertensive and normotensive adults in Tehran's hospitals. *Journal of Medical Sciences* 6(1): 103-107.

Bost L, Primatesta P, Dong W, Poulter N. 1999. Blood lead and blood pressure: evidence from the Health Survey for England 1995. *J Hum Hypertens* 13(2): 123-128.

Chen A, Rhoads GG, Cai B, Salganik M, Rogan WJ. 2006. The effect of chelation on blood pressure in lead-exposed children: a randomized study. *Environ Health Perspect* 114(4): 579-583.

Cheng Y, Schwartz J, Vokonas PS, Weiss ST, Aro A, Hu H. 1998. Electrocardiographic conduction disturbances in association with low-level lead exposure (the Normative Aging Study). *Am J Cardiol* 82(5): 594-599.

Cheng Y, Schwartz J, Sparrow D, Aro A, Weiss ST, Hu H. 2001. Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension: the Normative Aging Study. *Am J Epidemiol* 153(2): 164-171.

Chu NF, Liou SH, Wu TN, Chang PY. 1999. Reappraisal of the relation between blood lead concentration and blood pressure among the general population in Taiwan. *Occup Environ Med* 56(1): 30-33.

Den Hond E, Nawrot T, Staessen JA. 2002. The relationship between blood pressure and blood lead in NHANES III. National Health and Nutritional Examination Survey. *J Hum Hypertens* 16(8): 563-568.

Dolenc P, Staessen JA, Lauwerys RR, Amery A. 1993. Short report: low-level lead exposure does not increase the blood pressure in the general population. Cadmibel Study Group. *J Hypertens* 11(5): 589-593.

Elmarsafawy SF, Jain NB, Schwartz J, Sparrow D, Nie H, Hu H. 2006. Dietary calcium as a potential modifier of the relationship of lead burden to blood pressure. *Epidemiology* 17(5): 531-537.

Elwood PC, Davey-Smith G, Oldham PD, Toothill C. 1988a. Two Welsh surveys of blood lead and blood pressure. *Environ Health Perspect* 78: 119-121.

Elwood PC, Yarnell JW, Oldham PD, Catford JC, Nutbeam D, Davey-Smith G, Toothill C. 1988b. Blood pressure and blood lead in surveys in Wales. *Am J Epidemiol* 127(5): 942-945.

Eum K-D, Nie LH, Schwartz J, Vokonas PS, Sparrow D, Hu H, Weisskopf MG. 2011. Prospective Cohort Study of Lead Exposure and Electrocardiographic Conduction Disturbances in the Department of Veterans Affairs Normative Aging Study. *Environ Health Perspect* in press.

Factor-Litvak P, Kline JK, Popovac D, Hadzialjevic S, Lekic V, Preteni-Rexhepi E, Capuni-Paracka S, Slavkovich V, Graziano J. 1996. Blood lead and blood pressure in young children. *Epidemiology* 7(6): 633-637.

Factor-Litvak P, Wasserman G, Kline JK, Graziano J. 1999. The Yugoslavia Prospective Study of environmental lead exposure. *Environ Health Perspect* 107(1): 9-15.

Gartside PS. 1988. The relationship of blood lead levels and blood pressure in NHANES II: additional calculations. *Environ Health Perspect* 78: 31-34.

Gerr F, Letz R, Stokes L, Chettle D, McNeill F, Kaye W. 2002. Association between bone lead concentration and blood pressure among young adults. *Am J Ind Med* 42(2): 98-106.

Glenn BS, Stewart WF, Links JM, Todd AC, Schwartz BS. 2003. The longitudinal association of lead with blood pressure. *Epidemiology* 14(1): 30-36.

Grandjean P, Hollnagel H, Hedegaard L, Christensen JM, Larsen S. 1989. Blood lead-blood pressure relations: alcohol intake and hemoglobin as confounders. *Am J Epidemiol* 129(4): 732-739.

Guallar E, Silbergeld EK, Navas-Acien A, Malhotra S, Astor BC, Sharrett AR, Schwartz BS. 2006. Confounding of the relation between homocysteine and peripheral arterial disease by lead, cadmium, and renal function. *Am J Epidemiol* 163(8): 700-708.

Gump BB, Stewart P, Reihman J, Lonky E, Darvill T, Matthews KA, Parsons PJ. 2005. Prenatal and early childhood blood lead levels and cardiovascular functioning in 9(1/2) year old children. *Neurotoxicol Teratol* 27(4): 655-665.

Gump BB, Reihman J, Stewart P, Lonky E, Darvill T, Matthews KA. 2007. Blood lead (Pb) levels: a potential environmental mechanism explaining the relation between socioeconomic status and cardiovascular reactivity in children. *Health Psychol* 26(3): 296-304.

Gump BB, Mackenzie JA, Bendinskas K, Morgan R, Dumas AK, Palmer CD, Parsons PJ. 2011. Low-level Pb and cardiovascular responses to acute stress in children: the role of cardiac autonomic regulation. *Neurotoxicol Teratol* 33(2): 212-219.

Hense HW, Filipiak B, Keil U. 1993. The association of blood lead and blood pressure in population surveys. *Epidemiology* 4(2): 173-179.

Hense HW, Filipiak B, Keil U. 1994. Alcohol consumption as a modifier of the relation between blood lead and blood pressure. *Epidemiology* 5(1): 120-123.

Hu H, Aro A, Payton M, Korrick S, Sparrow D, Weiss ST, Rotnitzky A. 1996. The relationship of bone and blood lead to hypertension. The Normative Aging Study. *Jama* 275(15): 1171-1176.

Ishida M, Ishizaki M, Yamada Y. 1996. Decreases in postural change in finger blood flow in ceramic painters chronically exposed to low level lead. *Am J Ind Med* 29(5): 547-553.

Jain NB, Potula V, Schwartz J, Vokonas PS, Sparrow D, Wright RO, Nie H, Hu H. 2007. Lead levels and ischemic heart disease in a prospective study of middle-aged and elderly men: the VA Normative Aging Study. *Environ Health Perspect* 115(6): 871-875.

Jhun HJ, Kim H, Paek DM. 2005. The association between blood metal concentrations and heart rate variability: a cross-sectional study. *Int Arch Occup Environ Health* 78(3): 243-247.

Kaewboonchoo O, Saleekul S, Powwattana A, Kawai T. 2007. Blood lead level and blood pressure of bus drivers in Bangkok, Thailand. *Ind Health* 45(4): 590-594.

Kaewboonchoo O, Morioka I, Saleekul S, Miyai N, Chaikittiporn C, Kawai T. 2010. Blood lead level and cardiovascular risk factors among bus drivers in Bangkok, Thailand. *Ind Health* 48(1): 61-65.

Kim KR, Lee SW, Paik NW, Choi K. 2008. Low-level lead exposure among South Korean lead workers, and estimates of associated risk of cardiovascular diseases. *J Occup Environ Hyg* 5(6): 399-416.

Korrick SA, Hunter DJ, Rotnitzky A, Hu H, Speizer FE. 1999. Lead and hypertension in a sample of middle-aged women. *Am J Public Health* 89(3): 330-335.

Kuo HW, Lai LH, Chou SY, Wu FY. 2006. Association between blood lead level and blood pressure in aborigines and others in central Taiwan. *Int J Occup Environ Health* 12(3): 222-227.

Lawes CMM, Vander Hoorn S, Law MR, Elliot P, MacMahon S, Rodgers A. 2003. High Blood Pressure. In *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors*. 1. Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. Geneva: World Health Organization. 305-413.

Lin JL, Lin-Tan DT, Hsu CW, Yen TH, Chen KH, Hsu HH, Ho TC, Hsu KH. 2011. Association of blood lead levels with mortality in patients on maintenance hemodialysis. *Am J Med* 124(4): 350-358.

Magri J, Sammut M, Savona-Ventura C. 2003. Lead and other metals in gestational hypertension. *Int J Gynaecol Obstet* 83(1): 29-36.

Martin D, Glass TA, Bandeen-Roche K, Todd AC, Shi W, Schwartz BS. 2006. Association of blood lead and tibia lead with blood pressure and hypertension in a community sample of older adults. *Am J Epidemiol* 163(5): 467-478.

Menditto A, Morisi G, Spagnolo A, Menotti A. 1994. Association of blood lead to blood pressure in men aged 55 to 75 years: effect of selected social and biochemical confounders. NFR Study Group. *Environ Health Perspect* 102 Suppl 9: 107-111.

Menke A, Muntner P, Batuman V, Silbergeld EK, Guallar E. 2006. Blood lead below 0.48 micromol/L (10 microg/dL) and mortality among US adults. *Circ* 114(13): 1388-1394.

Moller L, Kristensen TS. 1992. Blood lead as a cardiovascular risk factor. *Am J Epidemiol* 136(9): 1091-1100.

Morris C, McCarron DA, Bennett WM. 1990. Low-level lead exposure, blood pressure, and calcium metabolism. *Am J Kidney Dis* 15(6): 568-574.

Muntner P, Menke A, DeSalvo KB, Rabito FA, Batuman V. 2005. Continued decline in blood lead levels among adults in the United States: the National Health and Nutrition Examination Surveys. *Arch Intern Med* 165(18): 2155-2161.

Nash D, Magder L, Lustberg M, Sherwin RW, Rubin RJ, Kaufmann RB, Silbergeld EK. 2003. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. *Jama* 289(12): 1523-1532.

Navas-Acien A, Selvin E, Sharrett AR, Calderon-Aranda E, Silbergeld E, Guallar E. 2004. Lead, cadmium, smoking, and increased risk of peripheral arterial disease. *Circ* 109(25): 3196-3201.

Navas-Acien A, Schwartz BS, Rothenberg SJ, Hu H, Silbergeld EK, Guallar E. 2008. Bone lead levels and blood pressure endpoints: a meta-analysis. *Epidemiology* 19(3): 496-504.

Nawrot TS, Thijs L, Den Hond EM, Roels HA, Staessen JA. 2002. An epidemiological re-appraisal of the association between blood pressure and blood lead: a meta-analysis. *J Hum Hypertens* 16(2): 123-131.

Nordberg M, Winblad B, Fratiglioni L, Basun H. 2000. Lead concentrations in elderly urban people related to blood pressure and mental performance: results from a population-based study. *Am J Ind Med* 38(3): 290-294.

Orssaud G, Claude JR, Moreau T, Lellouch J, Juguet B, Festy B. 1985. Blood lead concentration and blood pressure. *Br Med J (Clin Res Ed)* 290(6463): 244.

Park SK, Schwartz J, Weisskopf M, Sparrow D, Vokonas PS, Wright RO, Coull B, Nie H, Hu H. 2006. Low-level lead exposure, metabolic syndrome, and heart rate variability: the VA Normative Aging Study. *Environ Health Perspect* 114(11): 1718-1724.

Park SK, O'Neill MS, Vokonas PS, Sparrow D, Wright RO, Coull B, Nie H, Hu H, Schwartz J. 2008. Air pollution and heart rate variability: effect modification by chronic lead exposure. *Epidemiology* 19(1): 111-120.

Park SK, Hu H, Wright RO, Schwartz J, Cheng Y, Sparrow D, Vokonas PS, Weisskopf MG. 2009. Iron metabolism genes, low-level lead exposure, and QT interval. *Environ Health Perspect* 117(1): 80-85.

Perlstein T, Weuve J, Schwartz J, Sparrow D, Wright R, Litonjua A, Nie H, Hu H. 2007. Cumulative community-level lead exposure and pulse pressure: the normative aging study. *Environ Health Perspect* 115(12): 1696-1700.

Peters JL, Kubzansky L, McNeely E, Schwartz J, Spiro A, 3rd, Sparrow D, Wright RO, Nie H, Hu H. 2007. Stress as a potential modifier of the impact of lead levels on blood pressure: the normative aging study. *Environ Health Perspect* 115(8): 1154-1159.

Pizent A, Jurasovie J, Telisman S. 2001. Blood pressure in relation to dietary calcium intake, alcohol consumption, blood lead, and blood cadmium in female nonsmokers. *J Trace Elem Med Biol* 15(2-3): 123-130.

Pocock SJ, Shaper AG, Ashby D, Delves T, Whitehead TP. 1984. Blood lead concentration, blood pressure, and renal function. *Br Med J (Clin Res Ed)* 289(6449): 872-874.

Pocock SJ, Shaper AG, Ashby D, Delves HT, Clayton BE. 1988. The relationship between blood lead, blood pressure, stroke, and heart attacks in middle-aged British men. *Environ Health Perspect* 78: 23-30.

Proctor SP, Rotnitzky A, Sparrow D, Weiss ST, Hu H. 1996. The relationship of blood lead and dietary calcium to blood pressure in the normative aging study. *Int J Epidemiol* 25(3): 528-536.

Rabinowitz M, Bellinger D, Leviton A, Needleman H, Schoenbaum S. 1987. Pregnancy hypertension, blood pressure during labor, and blood lead levels. *Hypertension* 10(4): 447-451.

Rothenberg SJ, Manalo M, Jiang J, Cuellar R, Reyes S, Sanchez M, Diaz M, Khan F, Aguilar A, Reynoso B, Juaregui M, Acosta S, Johnson C. 1999. Blood lead level and blood pressure during pregnancy in South Central Los Angeles. *Arch Environ Health* 54(6): 382-389.

Rothenberg SJ, Kondrashov V, Manalo M, Jiang J, Cuellar R, Garcia M, Reynoso B, Reyes S, Diaz M, Todd AC. 2002. Increases in hypertension and blood pressure during pregnancy with increased bone lead levels. *Am J Epidemiol* 156(12): 1079-1087.

Schober SE, Mirel LB, Graubard BI, Brody DJ, Flegal KM. 2006. Blood lead levels and death from all causes, cardiovascular disease, and cancer: results from the NHANES III mortality study. *Environ Health Perspect* 114(10): 1538-1541.

Schuhmacher M, Bosque MA, Domingo JL, Corbella J. 1994. Effects of chronic lead and cadmium exposure on blood pressure in occupationally exposed workers. *Biol Trace Elem Res* 41(3): 269-278.

Schwartz J. 1991. Lead, blood pressure, and cardiovascular disease in men and women. *Environ Health Perspect* 91: 71-75.

Scinicariello F, Yesupriya A, Chang MH, Fowler BA. 2010. Modification by ALAD of the association between blood lead and blood pressure in the U.S. population: results from the Third National Health and Nutrition Examination Survey. *Environ Health Perspect* 118(2): 259-264.

Scinicariello F, Abadin HG, Edward Murray H. 2011. Association of low-level blood lead and blood pressure in NHANES 1999-2006. *Environ Res*.

Sharp DS, Osterloh J, Becker CE, Bernard B, Smith AH, Fisher JM, Syme SL, Holman BL, Johnston T. 1988. Blood pressure and blood lead concentration in bus drivers. *Environ Health Perspect* 78: 131-137.

Sharp DS, Benowitz NL, Osterloh JD, Becker CE, Smith AH, Syme SL. 1990. Influence of race, tobacco use, and caffeine use on the relation between blood pressure and blood lead concentration. *Am J Epidemiol* 131(5): 845-854.

Sirivarasai J, Kaojarern S, Wananukul W, Deechakwan W, Srisomerarn P. 2004. Non-occupational lead and cadmium exposure and blood pressure in Thai men. *Asia Pac J Public Health* 16(2): 133-137.

Sokas RK, Simmens S, Sophar K, Welch LS, Liziewski T. 1997. Lead levels in Maryland construction workers. *Am J Ind Med* 31(2): 188-194.

Sowers M, Jannausch M, Scholl T, Li W, Kemp FW, Bogden JD. 2002. Blood lead concentrations and pregnancy outcomes. *Arch Environ Health* 57(5): 489-495.

Staessen J, Yeoman WB, Fletcher AE, Markowe HL, Marmot MG, Rose G, Semmence A, Shipley MJ, Bulpitt CJ. 1990. Blood lead concentration, renal function, and blood pressure in London civil servants. *Br J Ind Med* 47(7): 442-447.

Staessen J, Sartor F, Roels H, Bulpitt CJ, Claeys F, Ducoffre G, Fagard R, Lauwerijs R, Lijnen P, Rondia D, Thijs L, Amery A. 1991. The Association between Blood-Pressure, Calcium and Other Divalent-Cations - a Population Study. *Journal of Human Hypertension* 5(6): 485-494.

Staessen J. 1995. Low-level lead exposure, renal function and blood pressure. *Verh K Acad Geneeskd Belg* 57(6): 527-574.

Staessen JA, Roels H, Fagard R. 1996. Lead exposure and conventional and ambulatory blood pressure: a prospective population study. PheeCad Investigators. *Jama* 275(20): 1563-1570.

Telisman S, Jurasovic J, Pizent A, Cvitkovic P. 2001. Blood pressure in relation to biomarkers of lead, cadmium, copper, zinc, and selenium in men without occupational exposure to metals. *Environ Res* 87(2): 57-68.

Vigeh M, Yokoyama K, Mazaheri M, Beheshti S, Ghazizadeh S, Sakai T, Morita Y, Kitamura F, Araki S. 2004. Relationship between increased blood lead and pregnancy hypertension in women without occupational lead exposure in Tehran, Iran. *Arch Environ Health* 59(2): 70-75.

Vupputuri S, He J, Muntner P, Bazzano LA, Whelton PK, Batuman V. 2003. Blood lead level is associated with elevated blood pressure in blacks. *Hypertension* 41(3): 463-468.

Weisskopf MG, Jain N, Nie H, Sparrow D, Vokonas P, Schwartz J, Hu H. 2009. A prospective study of bone lead concentration and death from all causes, cardiovascular diseases, and cancer in the Department of Veterans Affairs Normative Aging Study. *Circ* 120(12): 1056-1064.

Wells EM, Navas-Acien A, Herbstman JB, Apelberg BJ, Silbergeld EK, Caldwell KL, Jones RL, Halden RU, Witter FR, Goldman LR. 2011. Low Level Lead Exposure and Elevations in Blood Pressure During Pregnancy. *Environ Health Perspect* 119(5): 664-669.

Wolf C, Wallnofer A, Waldhor T, Vutuc C, Meisinger V, Rudiger HW. 1995. Effect of lead on blood pressure in occupationally nonexposed men. *Am J Ind Med* 27(6): 897-903.

Yazbeck C, Thiebaugeorges O, Moreau T, Goua V, Debotte G, Sahuquillo J, Forhan A, Foliguet B, Magnin G, Slama R, Charles MA, Huel G. 2009. Maternal blood lead levels and the risk of pregnancy-induced hypertension: the EDEN cohort study. *Environ Health Perspect* 117(10): 1526-1530.

Zeller I, Knoflach M, Seubert A, Kreutmayer SB, Stelzmuller ME, Wallnoefer E, Blunder S, Frotschnig S, Messner B, Willeit J, Debbage P, Wick G, Kiechl S, Laufer G, Bernhard D. 2010. Lead contributes to arterial intimal hyperplasia through nuclear factor erythroid 2-related factor-mediated endothelial interleukin 8 synthesis and subsequent invasion of smooth muscle cells. *Arterioscler Thromb Vasc Biol* 30(9): 1733-1740.

Zhang A, Park SK, Wright RO, Weisskopf MG, Mukherjee B, Nie H, Sparrow D, Hu H. 2010. HFE H63D Polymorphism as a Modifier of the Effect of Cumulative Lead Exposure on Pulse Pressure: the Normative Aging Study. *Environ Health Perspect* 118(9): 1261-1266.