

THE ASSOCIATIONS BETWEEN BLOOD AND URINARY CONCENTRATIONS OF METAL
METABOLITES, OBESITY, HYPERTENSION, TYPE 2 DIABETES, AND DYSLIPIDEMIA

SARAH SWAYZE

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Abstract

The objectives of the study were to determine if high concentrations of metals in blood or urine: 1) were associated with obesity and 2) influence the relationship between obesity and hypertension, type 2 diabetes and dyslipidemia, respectively. Data from the National Health and Examination Survey (NHANES Continuous 1999-2016) were used. We observed several associations between metal concentration, obesity and health. Blood lead had a linear and protective association with obesity (OR, 95% CI= 0.42, 0.37-0.47). In those with obesity, high blood lead was associated with lower risk of prevalent dyslipidemia and no effect of lead was found in those without obesity. We observed a curvilinear relationship between urinary antimony and obesity with the moderate group having the highest odds of obesity (OR=1.36, 1.16-1.59). However, the relationship between urinary antimony and prevalent hypertension and dyslipidemia risk was linear and positive. The impact of environmental factors on obesity and health may be complex and this study reinforces the heterogeneous relationship between various metals, obesity and metabolic disease.

Dedication

For my grandmother.
Who never stopped believing in me.

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Chapter 1.0 General Introduction

Obesity rates in the United States and worldwide have been increasing over the past 20 years.¹ Obesity is a well-known risk factor for other cardiometabolic diseases such as hypertension, type 2 diabetes and dyslipidemia.² Together, these diseases are a burden on the economy and the healthcare system.³ The current focus of obesity research has been on the influence of health behaviours such as diet and exercise, but there are other less studied factors that may influence obesity and the related cardiometabolic diseases.

Our environment and specifically the effect of heavy metal exposure is one such factor that has received less focus in recent times. While the health behaviours that influence obesity and the related cardiometabolic diseases are well understood, the potential role of metals in our drinking water, food and air are not well studied in the general population. In addition, due to the wide spread of technology and the use of metals in industrial processes, there is greater risk of exposure in the general population. While there is a significant amount of research into the occupational limits and risks associated with exposure to metals there is little research into the how these metals in our environment affect obesity rates and obesity related cardiometabolic risk factors.

Thus, the objective of this thesis will be to examine:

- 1) The relationship between the biomarkers of heavy metal exposure and obesity
- 2) Whether these biomarkers influence the relationship between obesity, hypertension, type 2 diabetes, and dyslipidemia.

Chapter 2.0 Literature Review

2.1 Introduction to Metals

Since ancient times heavy metals have been used in everything from makeup to pipes for plumbing. In modern times we have found even more uses for heavy metals from medicine to technology. The general population is at risk of exposure to heavy metals through several pathways including air pollution, water pollution, bioaccumulation and biomagnification. Despite metals being so ubiquitous in our environment, there has been little research into the potential health effects at exposure levels seen in the general public.

2.2 The Association Between Heavy Metal and Obesity

To date the research on heavy metals and their relationship with obesity is limited. Heavy metal poisoning is generally associated with weight loss not weight gain.^{4,5} However, barium is observed to be positively associated with higher body mass index and higher waist circumference, but this association has yet to be investigated in mouse models or longitudinal studies.⁶ Similarly, in mouse models, lead is positively associated with increased body weight in male mice offspring after maternal exposure⁷ and lead exposure is also associated with increased body weight in adult male mice.⁸ Conversely in humans, prenatal lead exposure is related to decreased birth weight and in a study of adults in the National Health and Examination Survey (NHANES 99-02), blood or urine lead concentration is negatively associated with body mass index and waist circumference.^{6,9} It is unclear whether modest lead exposure is associated with obesity in adults. Cadmium is potentially related to obesity and is also a known endocrine disruptor. In mouse models cadmium is associated with an increase in thyroid stimulating

hormones levels and a potential increase abdominal and general obesity in healthy adults and women who are overweight or have obesity.¹⁰⁻¹² However, in US adults examined in the National Health and Nutrition Examination Survey, cadmium exposure is negatively associated with body mass index and waist circumference.⁶ These conflicting observations in rodent versus human studies may be due to the differences in exposure levels as mouse models have exposure levels that are significantly higher than what a person would normally be exposed to within non-industrial conditions. It is unclear whether the relationship between heavy metals and obesity differs by exposure level.

2.3 The Association Between Heavy Metals and Hypertension

The relationship between heavy metal exposure and hypertension differs by the type of metal, and the length of exposure. For example, long term lead exposure induces hypertension in rats, while short term exposure had the opposite effect.¹³ In humans, high blood lead levels even below the occupational limits are associated with hypertension in perimenopausal and postmenopausal women.¹⁴ Long term accumulated blood and bone lead concentrations in men from the Normative Aging Study is associated with an increased risk of hypertension and may be an independent risk factor for developing hypertension.¹⁵ The relationship between cadmium and hypertension is less clear. In mouse models, there is a significant association between cadmium exposure and hypertension, but in epidemiological studies the relationship is inconsistent potentially due to lower exposure levels in human studies.^{16,17} For barium, mouse models demonstrate that chronic exposure is associated with a modest increase in blood pressure, but in humans there is no association in hypertension rates between those exposed to high barium levels in public drinking water and those with low exposure.^{18,19} To our knowledge, there is only one cross-sectional study that examines the relationship between antimony exposure and

hypertension risk. Shiue et al. demonstrates high antimony levels in urine are positively associated with hypertension.²⁰ A possible connection between hypertension, obesity, and metal exposure is potentially due to the nephrotoxic nature of metals and chronic kidney disease. Chronic kidney disease is associated with both obesity and hypertension leading to a potential connection between obesity, hypertension and metal exposure.^{21,22}

2.4 The Association Between Heavy Metals and Type 2 Diabetes

The relationship between type 2 diabetes and metals is complex and not well understood. There is no known direct causal link between metal exposure and type 2 diabetes. However, the association between uranium, type 2 diabetes and higher BMI has been reported previously in a study using NHANES data.²³ In mouse models even at low levels consistent with normal environmental exposure, uranium can act as an endocrine disruptor which is a potential cause for type 2 diabetes, but the mechanism of action between uranium exposure and type 2 diabetes is unknown.^{24,25} Nonetheless, a meta-analysis of epidemiological research including three studies on cadmium, found no evidence of any association between cadmium and the development of type 2 diabetes.²⁶ However, a later case-control study using data from the HUNT3 cohort survey, demonstrates strong associations between cadmium, type 2 diabetes risk and higher BMI.²⁷ Similarly, blood cadmium levels and BMI in Chinese steelworkers with diabetes are higher than their non-diabetic counterparts.²⁸ In the general Chinese population, high levels of cadmium, barium, antimony or lead are all associated with a higher BMI and higher risk of diabetes.²⁹ Higher urinary antimony and barium are also associated with greater insulin resistance in US adults.²³ To date, research has found that some metals such as uranium and cadmium may be positively related to higher BMI and type 2 diabetes risk but it is unclear whether heavy metal exposure may have a relationship with type 2 diabetes risk independent of BMI.

2.5 The Association Between Heavy Metals and Dyslipidemia

The research on the relationship between dyslipidemia and metal exposure is sparse with very few studies examining the effects of metal exposure beyond exposure to lead and cadmium. Zhou et al. report that elevated blood cadmium in Chinese workers is positively associated with the prevalence of dyslipidemia and those in the higher quartiles of blood cadmium were more likely to have a higher BMI.³⁰ To our knowledge, the association with blood cadmium levels and dyslipidemia has not been reported in rodent models. Similarly, lead exposure at the occupational levels is positively associated with higher levels of total cholesterol and HDL cholesterol when compared to those exposed at lower levels.³¹ Conversely, rats exposed to lead had lower total, free and HDL cholesterol levels, but higher triglycerides than the controls.³² Current research suggests the higher levels of cadmium in blood are potentially positively related to dyslipidemia risk and higher BMI. Whereas higher blood lead levels in humans are associated with higher dyslipidemia risk but not BMI.

2.6 The Association Between Heavy Metals, Obesity, and the Related Health Effects

The intersection of metal exposure, obesity, and their associated health outcomes remains unclear. Commonly, studies regarding metal exposure and health risk adjust for body mass index or waist circumference, but these studies do not specifically examine those with obesity as a separate population which may unmask associations that are unique to those with obesity. As the prevalence of obesity increases it is imperative to examine how environmental exposures may affect this population.³³ Polycyclic aromatic hydrocarbon exposure is an example of an environmental pollutant that may have different associations with health risk in different weight categories. For example, individuals without obesity have a linear association between PAH and

hypertension, while within individuals with obesity, there is an inverted U-association wherein the highest risk is associated with the middle quintile for 3-fluorene.³⁴ This example illustrates how environmental exposures can have differential health risks within weight categories.

Chapter 3.0 Manuscript

3.1 The Associations between Blood and Urinary Concentrations of Metal Metabolites, Obesity, Hypertension, Type 2 Diabetes, and Dyslipidemia

There is no standard definition for categorizing heavy metals and the definition varies depending on the author and context.³⁵ Generally, heavy metals are a group of inorganic elements found on the periodic table with high densities, atomic weights or atomic numbers. Heavy metals are naturally occurring³⁶ and used in many different industries such as the mining, agricultural, medical and technological sectors.³⁷ The widespread use of heavy metals in industry has led to their presence throughout our environment. Heavy metals cannot be degraded or destroyed and are considered persistent environmental contaminants³⁸ and exposure to heavy metals is regulated in most of the western world at the federal level by agencies such as National Institute for Occupational Safety and Health and Occupational Safety and Health Administration. Exposure to heavy metals can occur through oral, dermal and respiratory routes³⁶ with the potential for exposure being higher in those working in industries that use heavy metals. This exposure can be measured at the source or using a variety of biomarkers such as concentration in hair or feces, or more commonly, through urine and blood. Health effects of heavy metals range from damage at the cellular level to widespread damage of the nervous system³⁸ with each metal having specific unique health effects. The exposure guidelines for heavy metals have been refined over the years, but historically, they were most commonly set to prevent cancer and neurodegenerative effects and generally do not consider other potential health outcomes like obesity or cardiometabolic conditions. The prevalence of obesity in the United States has increased over the past twenty years, making it prudent to examine whether there are health

effects of environmental pollutants such as heavy metals at levels more commonly observed in the general public, but below the legal limits.³⁹ The objective of this study is to gain insight into the relationship between the blood and urine measures of heavy metal exposure and obesity, and to determine if these measures influence the relationship between obesity, hypertension, type 2 diabetes, and dyslipidemia.

3.2 Methods

3.2.1 Participants

NHANES Continuous is a nationally representative cross-sectional survey biannually conducted in the United States from 1999 onwards.⁴⁰ NHANES Continuous samples approximately 5000 people per year gathering both interview data and physical examination data from across the country.⁴⁰ Participants were asked a variety of questions regarding their health, dietary information, demographics, and socioeconomic status. The examination portion of the survey consists of medical, dental, physiological tests and laboratory tests taken in mobile examination centers.⁴⁰ This study is an analysis of publicly available data and does not require ethics approval from our institutional review board.

Participants at least 20 years of age from the continuous National Health and Nutrition Examination Survey (NHANES Continuous) 1999-2016 with available metal metabolites data were included in this study. Beryllium and platinum were omitted due to inconsistencies in the method of measurement over the survey years. Participants were excluded from the study if they had a BMI under 18.5 kg/m², were pregnant or thought they might be pregnant, or had missing data for any of the variables of interest. Individuals determined to be potential influencers and extreme outliers during univariate analysis were excluded from the study.^{41,42} A domain

statement was used for each metal analysis and excluded those previously mentioned. The total sample before exclusions was (n=92,062) and the final sample size was dependent on each metal.

3.2.2 Survey Methods

Age, gender, ethnicity (White and Other), poverty income ratio, physical activity status (yes/no), smoking status (never, current, past), and dietary intake (calories) were obtained during the interview portion of the survey. BMI was calculated from height and weight data taken from the mobile examination centers. The cut off for obesity was defined as 30 kg/m^2 .⁴³

Metal Metabolites

Measures for blood cadmium and lead were collected during the mobile examination appointments by a trained phlebotomist.^{44,45} Samples were processed, frozen and shipped to the National Center for Environmental Health for analysis. Blood cadmium and lead measures for survey years 1999-2000 and 2001-2002 were analyzed simultaneously using adapted methods from Miller et al. (1987), Parsons et al. (1993) and Stoeppler et al. (1980).⁴⁵ Blood concentrations for all other survey years were determined using inductively coupled plasma mass spectrometry.² The urine samples were collected from participants for analysis for antimony, barium, cadmium, cesium, lead, uranium, molybdenum, thallium, tungsten and cobalt. Samples were processed, frozen and shipped to the National Center for Environmental Health for analysis. Urine concentrations were measured using inductively coupled plasma mass spectrometry.⁴⁶ Detailed laboratory procedures for the measurement of metal metabolites are described on the NHANES website.⁴⁶

Hypertension, Type 2 Diabetes, and Dyslipidemia

To measure blood pressure, each participant was asked to sit quietly for 5 minutes then three consecutive readings were taken, if one of the readings was incomplete or interrupted a fourth measure was taken and then averaged.⁴⁷ Hypertension was defined as having an average systolic pressure of 130 mmHg or higher, an average diastolic pressure of 80 mmHg or higher⁴⁸ or on medication for hypertension. Blood was drawn by a trained phlebotomist and shipped frozen to the University of Minnesota for testing.⁴⁹ Type 2 diabetes was defined as fasting plasma glucose levels greater than 7.0 mmol/L or A1C $\geq 6.5\%$ or an oral glucose tolerance test ≥ 11.1 mmol/L or they were taking medication for diabetes.⁵⁰ Dyslipidemia was defined as having any one of serum triglyceride levels ≥ 2.06 mmol/L, total cholesterol ≥ 6 mmol/L, HDL < 1.04 mmol/L for men, < 1.29 mmol/L for women or cholesterol medication.⁵¹ Medication data was compiled from the prescription drug questionnaire taken during the home interview.⁵²

3.2.3 Statistical Analysis

Participant characteristics are presented by metal concentration category with differences between groups examined using chi-square tests for categorical variables and t-tests for continuous variables. Metal concentrations are reported as the geometric means with standard error (SE). Continuous variables are presented as means with SE, and categorical variables as prevalence and SE. Logistic regression was performed to determine the relationship between obesity and quintile groups for metal concentration while adjusting for age, gender, ethnicity, smoking status, physical active status, poverty income ratio, and creatinine for the urine measures. Concentration categories were defined by grouping quintiles with similar associations with obesity upon visual inspection. In instances where the metals appeared to have no association or a linear association with obesity, the bottom 80% was defined as low and the

remaining 20% were considered high. In cases where the relationship between metal concentration and obesity was curvilinear the concentration categories were split into lowest 40%, moderate 40% and highest 20% based on visual inspection.

Adjusted logistic regression analyses were performed to examine the relationship between obesity, hypertension, type 2 diabetes, dyslipidemia, and metal concentration category respectively. Models included obesity and metal concentration main effect and interaction terms adjusting for age, gender, ethnicity, smoking status, physical active status, poverty income ratio, and creatinine for the urine measures. Due to the complex nature of the NHANES survey design, all statistical analyses were performed using SAS 9.4 survey procedures with domain statements and weighted to be representative of the United States population. Sample weights for the blood metal analysis were calculated using the mobile examination center weights and the urine metal analysis were calculated using the metals subsample weights. Statistical significance was set at $P \leq 0.05$.

3.3 Results

Unadjusted group differences were observed between the BMI groups for molybdenum, thallium, tungsten and cobalt in the univariate analysis. However, when adjusting for age, sex, ethnicity, smoking status, poverty income ratio, dietary intake and physical activity in the multivariate analysis there was no evidence any evidence statistically significant or clinically meaningful differences and these metals were thus omitted from the final analysis.

([Supplementary Table 1 and 2](#)). Participant characteristics are shown by urinary and blood metal concentration in [Table 1](#). Individuals in the high metal concentration groups tended to be younger than the low metal concentration groups ($P<0.001$), while both high blood and urinary cadmium and lead groups were significantly older ($p<0.001$). The high concentration groups were more likely to be male and have a higher prevalence of current smokers.

The relationship between metal concentration and obesity is outlined in [Figure 1](#). A high concentration of urinary barium (OR, 95% CI=1.22, 1.04-1.44) was positively associated with the odds of prevalent obesity. A moderate concentration of urinary antimony (OR=1.36, 1.16-1.59) was also positively associated with prevalent obesity, however, the relationship between obesity and urinary antimony was curvilinear with the high concentration having a similar association with obesity as the reference group. There was a negative relationship between obesity and urinary cesium (OR=0.74, 0.59-0.94), urinary cadmium (OR=0.52, 0.43-0.63), urinary lead (OR=0.45, 0.37-0.56), blood cadmium (OR=0.52, 0.46-0.59) and blood lead (OR=0.42, 0.37-0.47).

[Table 2](#) presents the weighted prevalence of hypertension, type 2 diabetes, and dyslipidemia stratified by metal concentration category. High metal concentration was generally

associated with lower prevalence rates type 2 diabetes but higher prevalence rates of hypertension and dyslipidemia.

[Figure 2](#) outlines the associations between metal concentration, obesity and hypertension with adjustment for age, sex, ethnicity, smoking status, poverty income ratio, dietary intake and physical activity. For hypertension, there was a trend for a significant interaction for urinary barium and obesity (Urinary Barium x Obesity, $p=0.06$), specifically obesity was associated with higher prevalent risk of hypertension where the effect was larger in those with higher levels of urinary barium. For hypertension, there was a significant interaction for blood lead and obesity (Blood Lead x Obesity, $p=0.001$), where high blood lead in those without obesity was associated with higher risk of hypertension but no difference in risk in those with obesity. Although the pattern of association between urinary lead and hypertension was similar to those with blood lead, the group differences for urinary lead failed to reach statistical significance (Urinary Lead x Obesity, $p=0.09$ Urinary Lead, $p=0.88$). A moderate concentration of urinary antimony was associated with a 15% higher risk of hypertension while a high concentration of urinary antimony was associated with 39% higher odds of hypertension, independent of obesity ([Fig 2](#)). Conversely, a high concentration of urinary cesium was associated with a 20% lower risk of prevalent hypertension independent of obesity ([Fig 2](#)). For all other metals, there were no significant associations with hypertension ($P>0.05$).

[Figure 3](#) outlines the associations between metal concentration, obesity and type 2 diabetes with adjustment for covariates. For type 2 diabetes, there was a negative association between blood lead and obesity, wherein the difference between blood lead groups was smaller in those without obesity (blood lead x obesity, $p=0.04$). ([Fig 3](#)). Similarly, urinary lead was associated with a 21% lower odds of type 2 diabetes, but with no differences by obesity status

(Fig 3). High urinary uranium was associated with a 30% higher odds of type 2 diabetes, independent of obesity. Conversely, high blood measures of cadmium were associated with an 18% lower odds of type 2 diabetes, independent of obesity (Fig 3, $p<0.05$). Urinary cadmium and all other metals were not significantly associated with type 2 diabetes ($P>0.05$).

Figure 4 outlines the associations between metal concentration, obesity and dyslipidemia with adjustment for covariates. For dyslipidemia there was a trend for a significant interaction for urinary barium and obesity (Urinary Barium x Obesity, $p=0.08$) wherein obesity was associated with higher prevalent risk of dyslipidemia with the effect being larger in those with higher levels of urinary barium than low barium. For dyslipidemia there was a significant interaction for blood lead and obesity (Blood Lead x Obesity, $p=0.02$) wherein having obesity was associated with higher risk of prevalent dyslipidemia, with the effect being larger in those with lower levels of blood lead than high lead (Fig 4). A moderate and high concentration of urinary antimony was associated with a 16% and 31% higher risk of dyslipidemia than low antimony respectively, independent of obesity (Fig 4). For all other metals there were no evidence of significant associations with dyslipidemia ($P>0.05$).

Table 1 Participant Characteristics by Metal

Weighted	Urinary Barium		Urinary Cesium		Urinary Antimony			Urinary Uranium	
	Low Concentration	High Concentration	Low Concentration	High Concentration	Low Concentration	Moderate Concentration	High Concentration	Low Concentration	High Concentration
N	9818	2438	9860	2502	5100	4740	2440	9099	2213
Metal Concentration, ng/ml*	0.88±0.01	4.76±0.06	3.3±0.03	10.3±0.07	0.03±0.01	0.08±0.01	0.23±0.01	0.004±0.01	0.028±0.01
Age, years	47.3±0.3	45.0±0.4*	46.9±0.3	46.2±0.4	49.1±0.4	46.2±0.3	42.8±0.4*	47.1±0.3	46.2±0.5
BMI, kg/m ²	28.6±0.1	29.5±0.2*	28.7±0.1	29.1±0.2*	28.1±0.1	29.5±0.1	29.0±0.2*	28.7±0.1	29.3±0.2*
Obesity, %	32.8(0.7)	39.4(1.3)*	33.6(0.7)	36.(1.3)*	30.2(0.9)	38.6(1.0)*	34.8(1.3)*	34.3(0.8)	36.7(1.5)
Sex, % male	47.7(0.6)	55.8(1.2)*	48.2(0.6)	54.5(1.1)*	43.6(0.8)	51.5(0.9)*	58.8(0.9)*	48.5(0.6)	54.2(1.4)*
White Ethnicity, %	68.8(1.2)	76.8(1.2)*	70.4(1.2)	71.7(1.4)	74.0(1.3)	69.1(1.4)*	66.4(1.7)*	71.5(1.2)	65.9(2.3)*
Current Smoker, %	21.0(0.6)	24.1(1.2)*	21.3(0.6)	23.3(1.0)*	17.4(0.7)	23.4(0.9)*	28.0(1.2)*	20.1(0.5)	27.7(1.3)*
Intake, Kcal/day	2153±12	2322±24*	2182±12	2205±25	2128±17	2192±18	2341±27*	2183±12	2226±27
Physically Active, %	81.3(0.6)	84.1(0.9)*	81.4(0.6)	84.3(0.9)*	82.3(0.8)	81.7(0.8)	82.0(1.0)	82.8(0.6)	77.3(1.2)*
Weighted	Blood Cadmium		Urinary Cadmium		Blood Lead		Urinary Lead		
	Low Concentration	High Concentration	Low Concentration	High Concentration	Low Concentration	High Concentration	Low Concentration	High Concentration	
N	25577	6435	9944	2318	25664	6348	9851	2511	
Metal Concentration, ng/ml*	2.4±0.02	11.2±0.09	0.16±0.01	1.01±0.01	0.05±0.01	0.18±0.01	0.4±0.01	1.8±0.02	
Age, years	46.8±0.2	47.9±0.3*	45.4±0.3	54.1±0.4*	45.5±0.2	55.0±0.3*	46.5±0.3	50.0±0.4*	
BMI, kg/m ²	29.0±0.7	27.7±0.1*	28.9±0.1	28.5±0.2	29.0±0.1	27.6±0.1*	29.0±0.1	28.2±0.2*	
Obesity, %	36.1(0.5)	28.9(0.7)*	34.6(0.7)	33.3(1.3)	36.2(0.5)	27.4(0.8)*	34.9(0.7)	31.4(1.3)*	
Sex, % male	50.0(0.3)	48.4(0.7)*	50.2(0.6)	46.1(1.4)*	46.0(0.3)	69.4(0.8)*	46.9(0.6)	62.9(1.3)*	
White Ethnicity, %	71.4(1.1)	72.4(1.4)*	71.5(1.2)	66.4(1.6)*	72.3(1.1)	68.3(1.5)*	72.1(1.2)	64.0(1.6)*	
Current Smoker, %	9.5(0.3)	75.0(0.8)*	18.3(0.5)	39.8(1.5)*	19.8(0.4)	33.6(0.8)*	19.8(0.5)	31.0(1.4)*	
Intake, Kcal/day	2201±9	2202±18	2221±12	2035±26*	2192±10	2247±20*	2184±12	2231±27*	
Physically Active, %	83.0(0.4)	77.4(0.7)*	83.2(0.6)	75.6(1.1)*	82.7(0.4)	78.2(0.7)*	82.2(0.6)	81.0(1.0)	

For continuous variables weighted mean ±SE are reported, and for categorical variables weighted prevalence (SE) are reported.

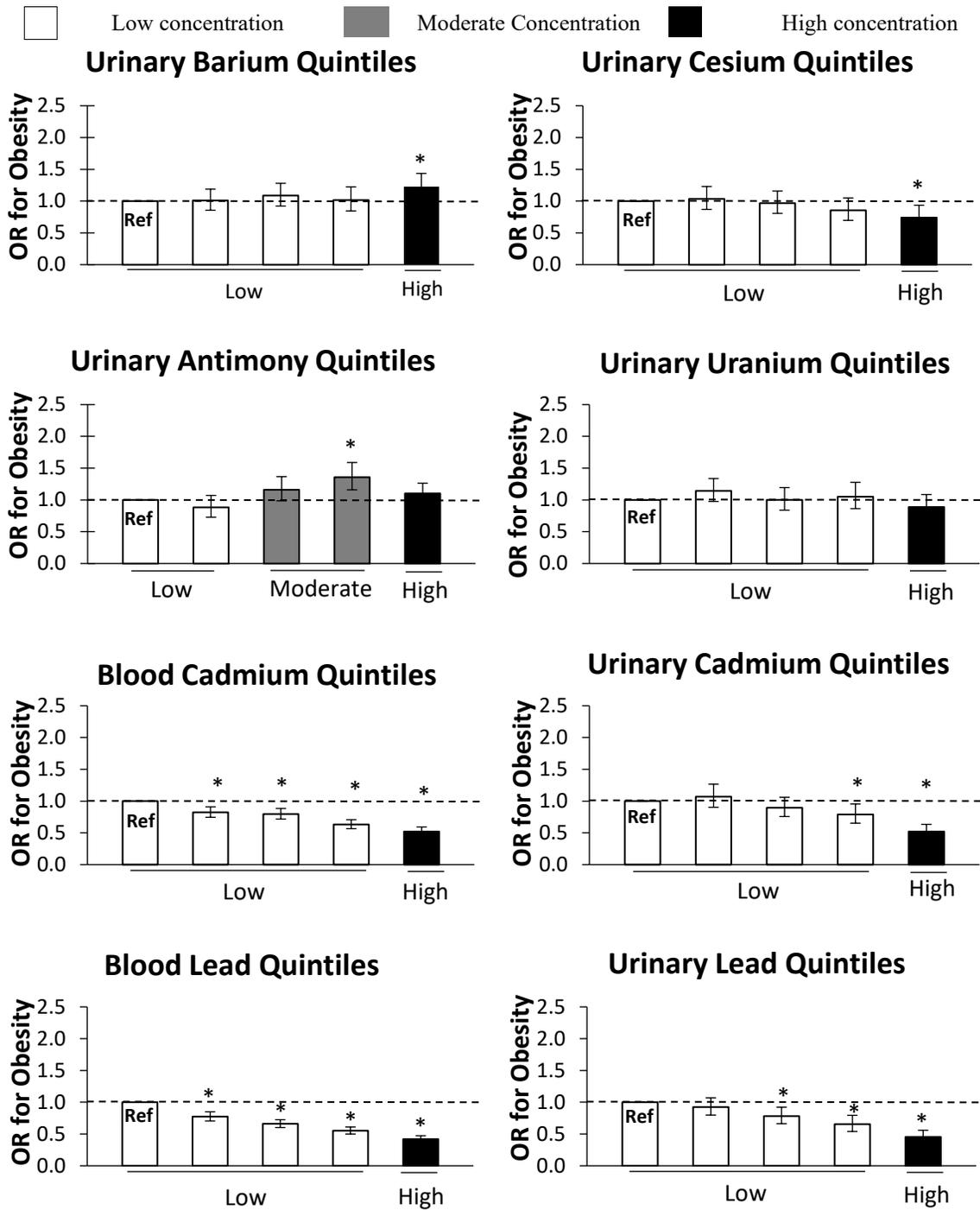
*Metal Concentration presented as geometric mean ±SE.

Obesity Defined as BMI ≥30 kg/m²

BMI, Body Mass Index; Kcal, Kilocalories.

* P<0.05 different from low concentration group.

Figure 1 - Weighted and Adjusted Odds Ratios for Obesity and Metal Concentration Category



* Significantly different from the reference group, $P \leq 0.05$.

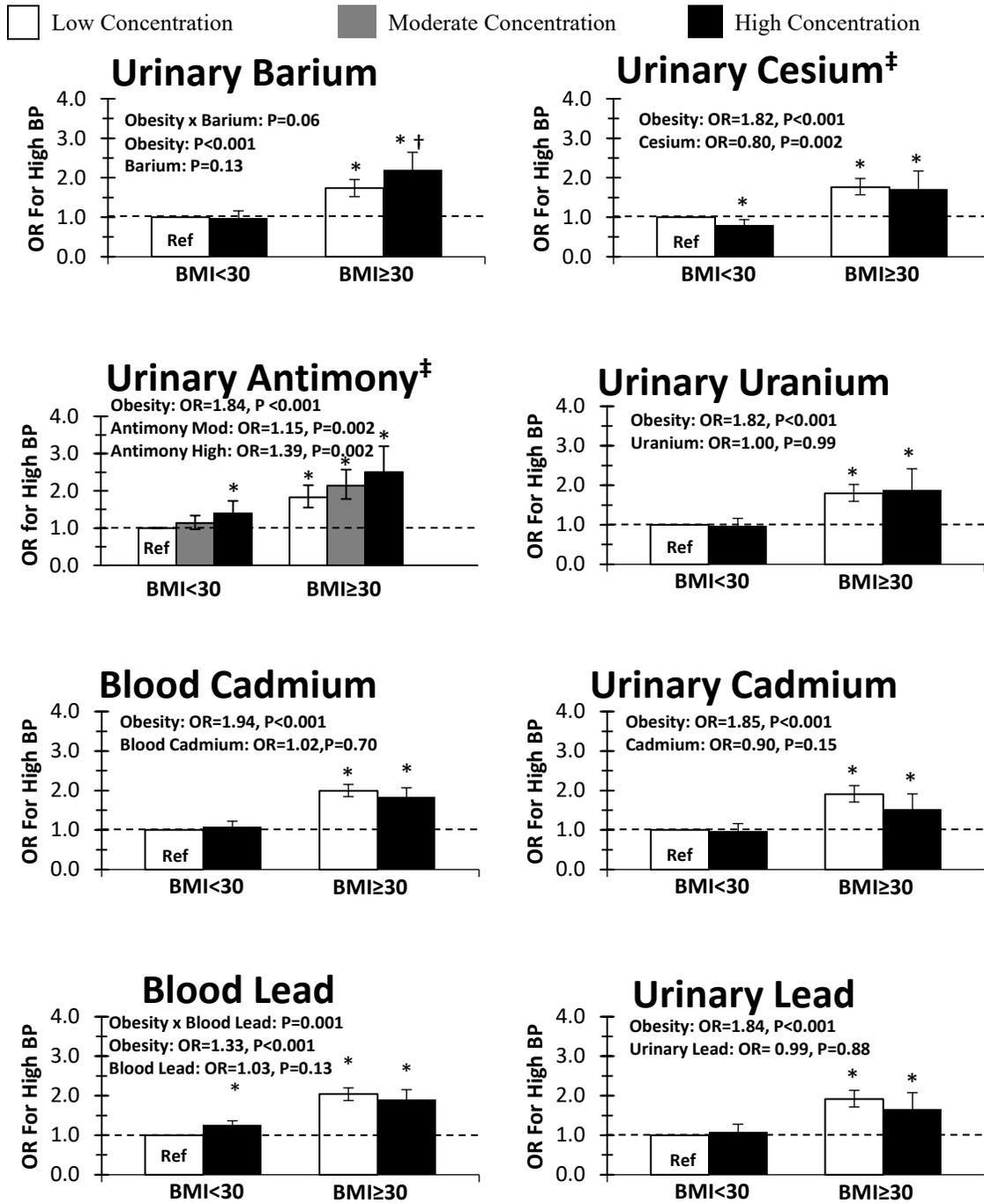
Weighted and adjusted for age, sex, poverty income ratio, ethnicity, smoking status, urinary creatinine, calories consumed per day, and physical activity status.

Table 2 Weighted Prevalence Rates for Hypertension, Type 2 Diabetes and Dyslipidemia by Metal metabolite

	Urinary Barium		Urinary Cesium		
	Low Concentration	High Concentration	Low Concentration	High Concentration	
Hypertension, %	36.4(0.6)	36.1(1.2)	37.0(0.6)	33.8(1.1)*	
Type 2 Diabetes, %	10.1(0.4)	8.2(0.6)*	10.1(0.4)	8.3(0.7)*	
Dyslipidemia, %	52.6(0.7)	57.2(1.3)*	53.3(0.7)	54.7(1.3)	
	Urinary Antimony			Urinary Uranium	
	Low Concentration	Moderate Concentration	High Concentration	Low Concentration	High Concentration
Hypertension, %	36.5(0.9)	36.6(1.0)	31.2(1.3)	35.5(0.7)	35.4(1.4)
Type 2 Diabetes, %	9.5(0.5)	10.3(0.5)	8.8(0.7)	9.5(0.4)	11.6(0.9) *
Dyslipidemia, %	50.1(0.9)	55.6(1.0)*	57.4(1.2) *	51.9(0.7)	55.9(1.5) *
	Blood Cadmium		Urinary Cadmium		
	Low Concentration	High Concentration	Low Concentration	High Concentration	
Hypertension, %	36.7(0.5)	36.8(0.8)	34.8(0.6)	44.0(1.3) *	
Type 2 Diabetes, %	10.1(0.3)	9.4(0.4)	9.1(0.3)	12.9(0.8) *	
Dyslipidemia, %	52.2(0.5)	58.2(0.9) *	52.2(0.7)	61.1(1.3) *	
	Blood Lead		Urinary Lead		
	Low Concentration	High Concentration	Low Concentration	High Concentration	
Hypertension, %	34.3(0.5)	49.4(1.0) *	35.4(0.6)	41.2(1.4) *	
Type 2 Diabetes, %	9.9(0.3)	10.2(0.5)	9.7(0.4)	9.7(0.7)	
Dyslipidemia, %	53.0(0.5)	55.3(0.9) *	52.6(0.7)	58.9(1.3) *	

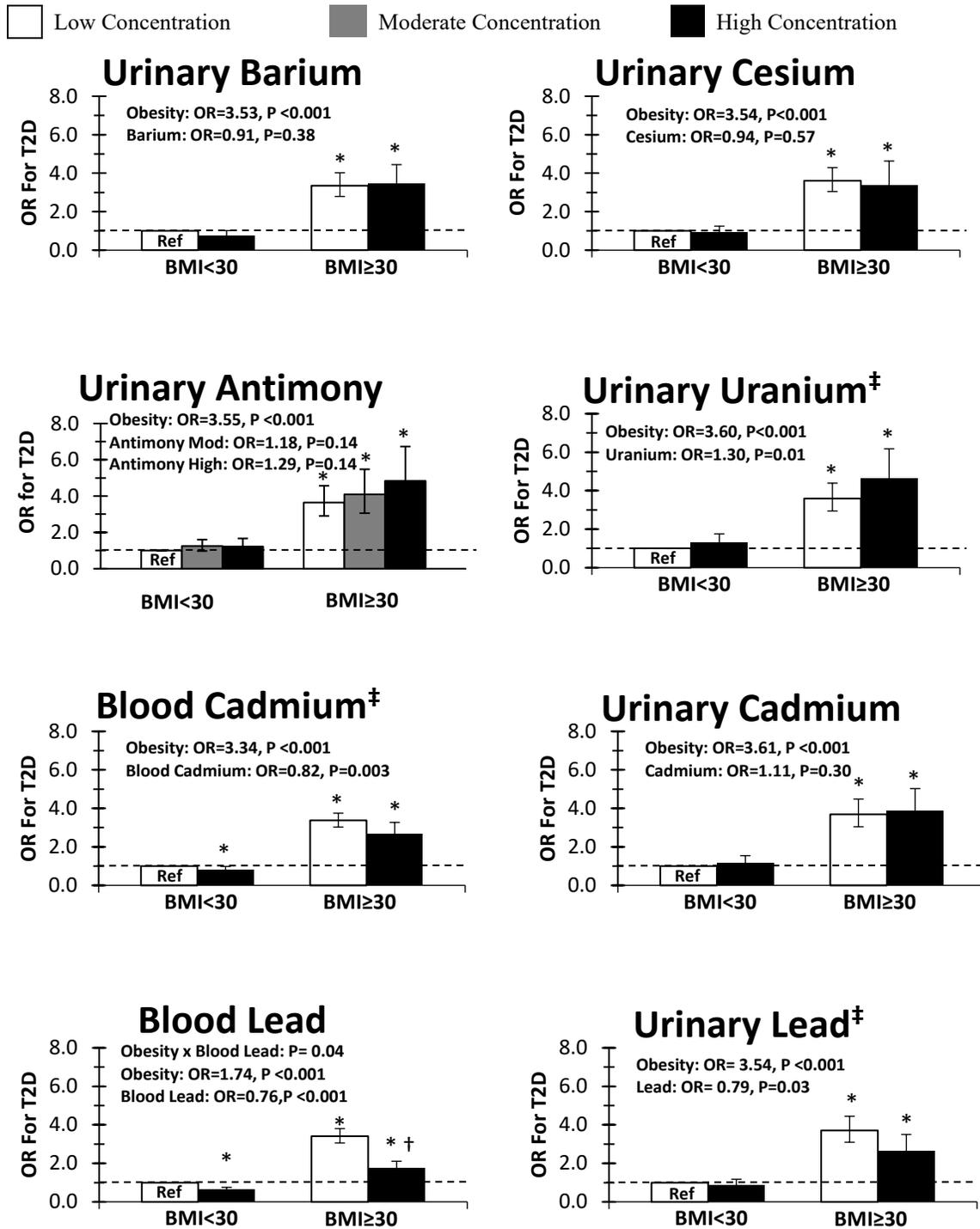
Weighted prevalence (SE) reported.
 * P ≤ 0.05 different from low concentration group.

Figure 2- Weighted and Adjusted Odds Ratios for Hypertension, Obesity status and Metal Concentration Category



* Significantly different from the reference group, $P \leq 0.05$. † Metal group significantly different within BMI group, $P \leq 0.05$.
 ‡ Significant Metal Main Effect ($P < 0.05$).
 Obesity main effect significant in all models ($P < 0.05$).
 Weighted and adjusted for age, sex, poverty income ratio, ethnicity, smoking status, urinary creatinine, calories consumed per day, and physical activity status.

Figure 3- Weighted and Adjusted Odds Ratios for Type 2 Diabetes, Obesity status and Metal Concentration Category



* Significantly different from the reference group, $P \leq 0.05$.

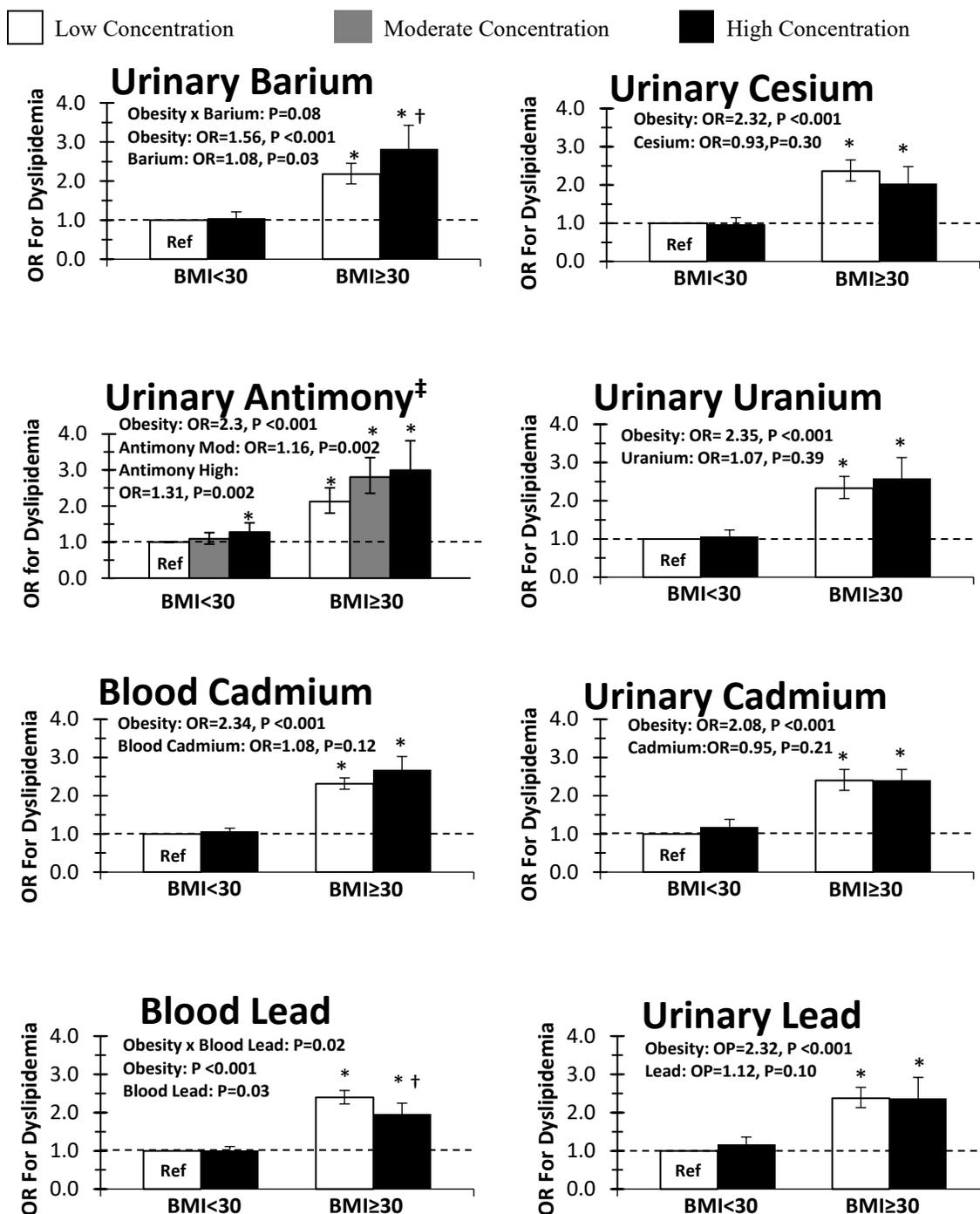
† Metal group significantly different within BMI group, $P \leq 0.05$.

‡ Significant Metal Main Effect ($P < 0.05$).

Obesity main effect significant in all models ($P < 0.05$).

Weighted and adjusted for age, sex, poverty income ratio, ethnicity, smoking status, urinary creatinine, calories consumed per day, and physical activity status.

Figure 4- Weighted and Adjusted Odds Ratios for Dyslipidemia, Obesity status and Metal Concentration Category



* Significantly different from the reference group, $P \leq 0.05$.

† Metal group significantly different within BMI group, $P \leq 0.05$.

‡ Significant Metal Main Effect ($P < 0.05$).

Obesity main effect significant in all models ($P < 0.05$).

Weighted and adjusted for age, sex, poverty income ratio, ethnicity, smoking status, urinary creatinine, calories consumed per day, and physical activity status.

3.4 Discussion

3.4.1 Key findings

Our study examined the relationship between heavy metal concentration and obesity and whether metal concentration is associated with obesity, hypertension, type 2 diabetes and dyslipidemia in the general population. We observed both positive, negative and null relationships between metal concentration and obesity. Further, metal concentration is associated with both better and worse health profiles for a given level of obesity. Thus, the impact of single factors on obesity and health may be complex and reinforces the hypothesis of a heterogeneous relationship between heavy metals, obesity and metabolic disease.

3.4.2 Obesity

While exposure to metals such as lead has been known to be associated with weight loss, our study and previous reports⁵³, suggest there may be both positive and negative associations between metal concentration and prevalent obesity. The negative association between metals and body weight are well established. Accordingly, we also report that metals such as lead, cadmium and cesium were strongly negatively associated with obesity.^{6,54,55} Conversely, we and a previous study using NHANES data from 1999-2002, suggest that high levels of barium are associated with higher BMI.⁶ Further, in contrast to a previous report by Padilla et al.⁶ showing no evidence of an association, we observed a curvilinear relationship between antimony and obesity with the moderate concentration group having the highest risk of obesity. Thus, the direction and pattern of association between metals and obesity may differ depending on the metal in questions. Further, it is important to remember that there may be other negative health effects associated

with even modest exposure to these metals that may also influence the association between obesity and cardiometabolic health effects.

3.4.3 Hypertension

While relatively little is reported regarding the association between heavy metals and cardiometabolic risk factors, obesity is a well-known independent risk factor for several cardiometabolic risk factors. Our study suggests that heavy metals may be associated with cardiometabolic risk factors through differences in obesity but may also be an independent risk factor. We observe that depending on the metal, there may be a positive or negative association with hypertension. For example, antimony and barium was positively associated with prevalent hypertension, independent of obesity. This is consistent with previous literature in rats suggesting barium exposure adversely affects average systolic blood pressure.¹⁸ However, an older study published in 1981 report no differences in hypertension rates in communities with high and low levels of barium in their drinking water.¹⁹ This study did not report BMI or obesity status, and given that we observe a greater effect of barium on hypertension in those with obesity, these differences may reflect the likely lower prevalence of obesity in this older study. Conversely, we observed that across all weight categories, cesium was associated with lower risk of prevalent risk of hypertension. This is in contrast to Shiue et al.⁵⁶ who report a positive association between cesium and prevalent hypertension risk when using a substantively smaller dataset of only the NHANES data from 2011-12. Lead exposure has long been known associated with weight loss and hypertension.^{57,58} However, our study demonstrates that the association between lead and hypertension may be dependent on obesity status. Consistent with past literature, we demonstrate a positive association between lead and hypertension in lean

individuals, whereas there was a negative association between lead and hypertension in those with obesity.^{59,60} Reasons for these findings are unclear and warrant further investigation.

3.4.4 Type 2 diabetes

In terms of type 2 diabetes, only three metals demonstrate significant associations, but in differing directions. Consistent with a previous study using a smaller subset of NHANES data (1999-2010), we showed that uranium is associated with higher prevalent diabetes risk.²³ In mouse models, even at low levels consistent with normal environmental exposure, uranium can act as an endocrine disruptor which is a potential cause for type 2 diabetes, though the mechanism of action is as yet unknown.^{24,25} Conversely, we demonstrate that high lead and cadmium were negatively associated with prevalent diabetes. The published research is conflicted^{26,28,61}, however, it is interesting to note that in this study, both lead and cadmium were also negatively associated with obesity. Nevertheless, cadmium exposure even at these low levels may still cause kidney damage which may complicate other health profiles.⁶²⁻⁶⁴ Thus, it is clear that obesity and type 2 diabetes risk may be associated with certain metal exposures, and metal exposures may also alter how obesity relates with type 2 diabetes.

3.4.5 Dyslipidemia

There have been very few studies reporting the relationship between dyslipidemia risk and metal exposure. While our results show that while the relationship between antimony and obesity is curvilinear, there is a strong linear relationship with dyslipidemia. Barium was also associated with higher risk of prevalent dyslipidemia only in those with obesity suggesting that metals such as barium may further exacerbate cardiometabolic risk in those with obesity. Conversely, our study also suggests high blood lead levels are associated with lower risk of

prevalent dyslipidemia in those with obesity. Interestingly, higher levels of blood lead were negatively associated with obesity. However, lead exposure at occupational levels in those with a without obesity were reported to be associated with higher total cholesterol and HDL cholesterol³¹ suggesting the role of heavy metal and dyslipidemia may differ between lean populations and populations with obesity.

3.5 Strength and Limitations

There are several strengths and limitations worth mentioning. First, this study used a large dataset weighted to be representative of the United States population from the continuous National Health and Examination Survey (NHANES). However, due to the cross-sectional nature of the survey design causality cannot be established. The use a single time point measure of urine and blood for the metals may not fully estimate participant exposure to these metals. Future longitudinal studies are needed to validate these findings.

3.6 Conclusion

In summary, our study observed both negative and positive associations between heavy metal and health risk factors within the general population of the United States ([Table 3](#)). Our study suggests that heavy metals and obesity have a potentially complex relationship with health profiles within the general population and a need for more investigation into the health effects of environmental exposure at levels seen in the general public.

Table 3 Summary of Results for all Outcomes				
	Obesity	Hypertension	Type 2 Diabetes	Dyslipidemia
Urinary Barium	↑	↑	↔	↑
Urinary Cesium	↓	↓	↔	↔
Urinary Antimony	↑&↓	↑	↔	↑
Urinary Uranium	↔	↔	↑	↔
Blood Cadmium	↓	↔	↓	↔
Urinary Cadmium	↓	↔	↔	↔
Blood Lead	↓	↑	↓	↓
Urinary Lead	↓	↔	↓	↔
↑ = Higher Risk; ↓ = Lower Risk; ↔ = No Association; ↑&↓ = Curvilinear association				

Chapter 4.0 Final Thoughts

Given the results of our study, there is a potential complex relationship between environmental exposures, obesity, and the comorbidities associated with obesity in the general U.S. population. However, as obesity rates increase across the world, industry thrives in developing nations, and the life span of technology becomes shorter a lack of strong environmental protections and increased levels of e-waste leave many countries vulnerable to negative health effects.⁶⁵⁻⁶⁷ Parts of Asia and Africa have seen rapid industrialization since the latter half of the 20th century, but the development and enforcement of environmental health standards has been deficient over this time.⁶⁷⁻⁶⁹ These environmental protections are meant not only to safeguard the wellbeing of workers, but to keep the general population safe from environmental contaminants. According to a report from the Earth Institute at Columbia University, the United States and other wealthy nations exports about 23% of their e-waste to developing countries where there is no proper recycling, leading to exposure to the general public.^{70,71} During the same period, obesity rates have increased and the potential role of heavy metals has been largely ignored. We demonstrate that heavy metals may influence both obesity risk and obesity related cardiometabolic risk factors. Thus, the potential nexus of weight related health outcomes and exposure to environmental pollutants requires further study.

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Supplementary Tables

Supplementary Table 1 Participant Characteristics by Metal								
Weighted	Urinary Molybdenum		Urinary Cobalt		Urinary Thallium		Urinary Tungsten	
	Low Concentration	High Concentration	Low Concentration	High Concentration	Low Concentration	High Concentration	Low Concentration	High Concentration
N	9777	2495	9980	2382	9847	2481	9851	2442
Metal Concentration, ng/ml*	27.50 ±0.32	119.38 ±1.02	0.26 ±0.01	1.02 ±0.01	0.12 ±0.01	0.37 ±0.01	0.05 ±0.01	0.30 ±0.01
Age, years	47.3 ±0.3	44.5 ±0.4*	47.1 ±0.3	45.4 ±0.4*	47.9 ±0.3	42.6 ±0.4*	47.7 ±0.3	43.1 ±0.5*
BMI, kg/m²	28.7 ±0.1	29.1 ±0.2	28.7 ±0.1	29.4 ±0.2*	28.7 ±0.1	29.3 ±0.2*	28.6 ±0.1	29.5 ±0.2*
Obesity, %	33.8 (0.7)	36.9 (1.5)*	32.9 (0.7)	40.3 (1.3)*	33.2 (0.7)	38.3 (1.2)*	33.4 (0.7)	37.9 (1.5)*
Sex, % male	47.5 (0.6)	58.1 (1.2)*	52.4 (0.6)	37.1 (1.2)*	48.0 (0.7)	55.3 (1.2)*	47.7 (0.6)	57.0 (1.3)*
White Ethnicity, %	71.9 (1.2)	65.6 (1.5)*	71.2 (1.2)	31.5 (1.5)*	71.9 (1.2)	66.0 (1.6)*	71.7 (1.2)	66.6 (1.4)*
Current Smoker, %	21.6 (0.6)	22.4 (1.0)	21.3 (0.6)	23.5 (1.1)	21.7 (0.6)	21.7 (1.1)	20.6 (0.6)	26.0 (1.2)*
Intake, Kcal/day	2157 ±12	2331 ±29*	2214 ±12	2096 ±25*	2159 ±12	2310 ±25*	2162 ±12	2316 ±30*
Physically Active, %	81.9 (0.6)	82.3 (0.9)	82.6 (0.6)	79.3 (0.9)*	80.9 (0.6)	86.2 (0.8)*	82.1 (0.6)	81.6 (1.0)

For continuous variables weighted mean ±SE are reported, and for categorical variables weighted prevalence (SE) are reported.
 *Metal Concentration presented as geometric mean ±SE.
 Obesity Defined as BMI ≥30 kg/m²
 BMI, Body Mass Index; Kcal, Kilocalories.
 * P≤0.05 different from low concentration group.

Supplementary Table 2						
Weighted and Adjusted Odds Ratios for Quintiles of Urinary Metals and Obesity						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}
Metabolite:		OR(95% CL)	OR(95% CL)	OR(95% CL)	OR(95% CL)	
Molybdenum	1 (Referent)	1.04 (0.91,1.21)	1.08(0.92,1.20)	1.03 (0.86,1.23)	0.88 (0.73,1.07)	0.15
Cobalt	1 (Referent)	1.02 (0.88,1.18)	1.09(0.92,1.29)	0.93 (0.77,1.11)	1.01 (0.85,1.20)	0.36
Thallium	1 (Referent)	1.12 (0.96,1.31)	0.99(0.84,1.17)	1.08(0.88,1.31)	1.00 (0.83,1.21)	0.40
Tungsten	1 (Referent)	1.07 (0.90,1.26)	1.21(1.05,1.40)	1.10(0.94,1.28)	1.08 (0.89,1.32)	0.12

Weighted and adjusted for age, sex, poverty income ratio, ethnicity, smoking status, urinary creatinine, calories consumed per day, and physical activity status.