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Urinary metals and adipokines in midlife women: The Study of Women's Health Across the nation (SWAN)

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ABSTRACT

Background: Information on the associations between metal exposures and adipokines in human populations is limited and results are inconsistent. We evaluated the associations between metals and adipokines.
Methods: Urinary concentrations of 15 metals (arsenic, barium, cadmium, cobalt, cesium, copper, mercury, manganese, molybdenum, nickel, lead, antimony, tin, thallium, and zinc) were measured in 1999–2000 among 1228 women of the Study of Women's Health Across the Nation Multi-Pollutant Study. Serum adipokines including high molecular weight (HMW)-adiponectin, leptin, and soluble leptin receptor (sOB-R) were measured at the follow-up visit (2002–2003). Linear regression models with adaptive elastic-net (AENET) were fit to identify metals associated with adipokines and to compute estimated percent changes in adipokines for one standard deviation increase in log-transformed urinary metal concentrations.
Results: After adjustment for confounders, urinary molybdenum was associated with a 5.54% higher level (95% CI: 1.36%, 9.90%), whereas cadmium was associated with a 4.53% lower level (95% CI: −8.17%, −0.76%) of HMW-adiponectin. Urinary molybdenum was also associated with a 5.95% lower leptin level (95% CI: −10.15%, −1.56%) and a 2.98% (95% CI: 0.69%, 5.32%) higher sOB-R level. Urinary cesium and lead were associated with a 3.58% (95% CI: −6.06%, −1.03%) and a 2.53% (95% CI: −4.80%, −0.21%) lower level of sOB-R, respectively.
Conclusions: Our findings suggest that molybdenum was associated with favorable profiles of HMW-adiponectin, leptin, and sOB-R. Exposures to cadmium, cesium, and lead were associated with adverse adipokine profiles.

1. Introduction

Obesity is a major public health concern. Approximately 42% of United States (U.S.) adults in 2017–2018 were obese (Hales et al., 2020). Obesity contributes to a high risk of chronic diseases including type 2 diabetes and cardiovascular disease (CVD) (Dixon, 2010). Adipose tissue is an active endocrine organ, and secretes biologically active proteins known as adipokines that are associated with these complications (Ouchi et al., 2011). Leptin is a pro-inflammatory, pro-thrombotic adipokine intimately involved in metabolic regulation and energy balance (Ouchi et al., 2011). Elevated leptin levels have been associated with hypertension, type 2 diabetes, coronary heart disease, and stroke in different populations (Hou and Luo, 2011; Liu et al., 2010; Sierra-Johnson et al., 2007; Wannamethee et al., 2007). Leptin binds to its receptor, the leptin receptor. The soluble leptin receptors (sOB-R) is the primary leptin-carrier protein in human circulation and is therefore an important regulator of leptin bioavailability and activity (Schaab and Kratzsch, 2015). On the contrary, adiponectin, the most abundant adipose tissue-specific adipokine in the circulation, improves insulin sensitivity and fatty acid oxidation, and promotes the production of anti-inflammatory cytokines (Ouchi et al., 2011). Of the various isoforms of adiponectin, high molecular weight (HMW) adiponectin

Abbreviations: AENET, adaptive elastic-net; BMI, body mass index; CVD, cardiovascular disease; ENET, elastic-net; FFQ, food frequency questionnaire; HMW, high molecular weight; ICP-MS, inductively coupled plasma-mass spectrometry; LOD, limit of detection; SD, standard deviation; sOB-R, soluble leptin receptor; SWAN, Study of Women's Health Across the Nation; SWAN-MPS, Study of Women's Health Across the Nation Multi-Pollutant Substudy.

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represents the most potent and biologically active form which has been considered a more useful marker than total adiponectin in prediction of insulin resistance, diabetes, and CVD (Nakashima et al., 2006; Peake et al., 2005; von Eynatten et al., 2008). The production of leptin is upregulated, while the production of adiponectin is downregulated in the obese state (Ouchi et al., 2011). A comprehensive understanding of the factors associated with adverse adipokine profiles is of great importance for understanding and ultimately preventing obesity-linked disorders. Growing evidence indicates that genetic, psychosocial, lifestyle and dietary factors play a role in alteration of adipokine profiles (Everson-Rose et al., 2018; Rokling-Andersen et al., 2007; Yu et al., 2012). However, the impact of environmental exposures on adipokine levels is still poorly understood.

Metals are widely dispersed in the environment and the general population can be exposed to a variety of metals through food, drinking water, and ambient air (Wang et al., 2019b). It is biologically plausible that both essential and non-essential metals may affect adipokine secretion. For instance, cadmium, a non-essential toxic metal, has been associated with a reduction in adipocyte size and abnormal adipokines expression in an animal study (Kawakami et al., 2013). In contrast, cobalt, an essential metal, has been linked with reduction of adipocyte size and improved adiponectin secretion in murine models (Kawakami et al., 2012). Information on the associations between metals and adipokines in human populations, however, is limited and available mainly in pregnant women and children (Ashley-Martin et al., 2015; Gossai et al., 2015; Kupsco et al., 2019). Only a few studies have explored the associations in adults and yield inconsistent findings (Ochoa-Martínez et al., 2019; Olusi et al., 2003; Valcke et al., 2019). Additionally, people are exposed to multiple metals in the environment but most previous studies have focused on individual metals. Studies of individual metals are prone to confounding by co-exposure to other metals, which are frequently correlated due to common environmental sources or similarities in metabolic pathways (Wang et al, 2018, 2019c). Furthermore, it is largely unknown whether midlife women, who are accompanied by unfavorable changes in body composition and abdominal fat deposition (Greendale et al., 2019), may be susceptible to the potential effects of metal exposures on adipokines.

In this study, we examined the associations of 15 urinary metal concentrations with prospectively-assessed serum levels of adipokines including HMW adiponectin, leptin, and sOB-R, in the Study of Women's Health Across the Nation (SWAN), a multi-site, multi-ethnic prospective cohort study of midlife women. We examined associations with individual metals as well as exposure to multiple metals as an initial exploratory inquiry of potential environmental exposures linked to adipokines.

2. Materials and methods

2.1. Study population

SWAN is a community based, multi-center, multi-ethnic longitudinal study designed to investigate psychosocial changes that occur during the menopausal transition and their effects on subsequent health endpoints (Sowers et al., 2000). From 1996 to 1997, 3302 women were enrolled from seven study sites; each site recruited White women and Black women were recruited at the Boston, MA, Pittsburgh, PA, southeast Michigan, MI, and Chicago, IL site; Hispanic women from the Newark, NJ site; Chinese women from the Oakland, CA site; and Japanese women from the Los Angeles, CA site. Eligibility criteria for enrollment into SWAN included: age 42–52 years, intact uterus and at least one ovary, no use of exogenous hormones affecting ovarian function in the past 3 months, at least one menstrual period in the previous 3 months, and self-identification with a site's designated racial/ethnic groups. The institutional review board at each participating site approved the study protocol and all participants provided written, signed informed consent.

Urinary metal concentrations were measured in 1400 women from the Michigan, Boston, Oakland, Los Angeles, and Pittsburgh sites that participated in the SWAN Multi-Pollutant Substudy (SWAN-MPS) (Ding et al., 2020; Wang et al., 2019b). Metal concentrations were measured in urine samples from the SWAN Repository collected at the third SWAN follow-up visit (1999–2000). After excluding 101 women with missing information on adipokines and 71 women who had no information on key covariates, data from 1228 women were available for the current analysis. An overview of our analytic sample is shown in Figure S1.

2.2. Exposure: urinary metals

High-resolution inductively-coupled plasma mass spectrometry (ICP-MS) (Thermo Scientific iCAP RQ, Waltham, MA) was used to determine concentrations of 15 metals (arsenic, barium, cadmium, cobalt, cesium, copper, mercury, manganese, molybdenum, nickel, lead, antimony, tin, thallium, and zinc) in first morning spontaneously voided urine samples at the Applied Research Center of NSF International (Ann Arbor, Michigan). The laboratory methods and quality control procedures of urinary metals measurements have been described previously (Wang et al., 2019b). The limits of detection (LOD) and detection rates are presented in Table S1. For participants with metal concentrations below the limit of detection, a value equal to the limit of detection divided by the square root of 2 was assigned. Pairwise Spearman correlations among urinary metal concentrations were calculated.

2.3. Outcome: adipokines

HMW adiponectin, leptin, and sOB-R were assayed in duplicate at the University of Michigan using 12-h fasted serum samples collected at the sixth SWAN follow-up visit (2002–2003). The assays used commercially available colorimetric enzyme immunoassay kits (leptin, adiponectin, and HMW adiponectin, Millipore, St. Charles, MO and sOB-R, R&D systems, Minneapolis, MN). The mean coefficient of variation for duplicate samples for each participant and lower limit of detection, respectively, were 4.0%, 0.78 ng/mL for adiponectin; 8.1%, 0.5 ng/ml for HMW adiponectin; 4.0%, 0.5 ng/mL for leptin; and 3.7%, 0.31 ng/ml for sOB-R.

2.4. Covariates

Information on age, self-defined race/ethnicity (White, Black, Chinese, and Japanese), education (≤high school, some college, or college degree/post-college), smoking status (current, former, and never), physical activity, and menopausal status were obtained from standardized interviews. Physical activity during the previous 12 months was evaluated using a modified version of the Kaiser Physical Activity Survey (Sternfeld et al., 2000), which consists of 38 questions with primarily Likert-scale responses about physical activity in various domains, including sports/exercise, household/caregiving, and daily routine. Domain-specific indices were derived by averaging the ordinal responses to questions in each domain, resulting in values from 1 to 5. Thus, the total physical activity score ranged from 3 to 15 with 15 indicating the highest level of activity. Waist circumference was measured by a trained technician with a non-stretchable tape to the nearest 0.1 cm at the narrowest part of the torso. Urinary specific gravity was determined using a handheld digital refractometer (ATAGO model PAL-10S, Tokyo, Japan) as a marker of urine dilution. All the covariates were measured at the SWAN-MPS baseline.

2.5. Statistical analysis

We used multivariable linear regression models to evaluate the associations of each urinary metal concentration with each adipokine (single metal models). Given the highly skewed distributions of HMW adiponectin, leptin, sOB-R, and urinary metal concentrations, logarithmic transformations with natural base were applied so that shapes of

exposure-outcome relationships more closely approximated log-linear. To better compare the associations of different metals, each urinary metal concentration was z-standardized by subtracting its mean divided by its standard deviation (SD). Potential confounders considered in multivariate adjustments included baseline values of age, race/ethnicity, study site, education level, smoking, alcohol drinking, physical activity score, menopausal status, and waist circumference (as a surrogate measure of central obesity). Log-transformed urine specific gravity was also adjusted in models to account for urine dilution. The impacts of possible outliers on the coefficient estimates were checked by excluding observations that have Cook's distances greater than 4 times the means and consistent results were observed.

To evaluate the association between exposure to multiple metals and adipokine levels, adaptive elastic-net (AENET), a machine learning algorithm designed for analyzing high-dimensional data, was applied (Zou and Zhang, 2009). Simultaneously incorporating all metal predictors into the same linear regression model is prone to over-fitting and does not work well in the presence of potentially high-dimensional predictors or when predictors are highly correlated (multicollinearity). To address this problem, elastic-net (ENET), a shrinkage regression method, has been introduced (Zou and Hastie, 2005). ENET performs variable selection by shrinking coefficients of "unimportant" predictors towards exact zeroes, and has the ability to handle the complex correlations between predictor variables (Zou and Hastie, 2005). AENET is an adaptive version of ENET that not only deals with the collinearity problem over ENET but satisfies the asymptotic normality assumption that allows us to conduct statistical inference and hypothesis testing by providing large sample standard errors and p-values (Zou and Zhang, 2009). AENET was proved satisfactory in terms of the statistical performance and epidemiologic interpretability (Park et al., 2017; Wang et al, 2018, 2020b). In our analysis, all 15 z-standardized log-transformed urinary metal concentrations were included in the same AENET model. The simultaneous inclusion of all metals in the same AENET model controlled for confounding due to co-exposure to other metals in mixtures. AENET shrinks coefficients of "unimportant" metals towards exact zeroes while handling the complex correlations. It should be noted that AENET performs variable selection by shrinking certain coefficients to zero but not based on p-values of coefficients. The same covariates used in individual metal analysis were adjusted ("forced") in the models. AENET penalized parameters were ascertained based on 10-fold cross-validation for minimal prediction errors. The R package 'gcdnet' was used to implement AENET (Yi and Zou, 2017).

Due to the role of sOB-R in regulation of circulating level of leptin, we additionally adjusted sOB-R in models in evaluation of associations between metals and leptin level in the sensitivity analysis. All analyses were conducted using R, version 3.6.3 (www.R-project.org).

3. Results

3.1. Participant characteristics

Characteristics of the study population are presented in Table 1. The median (interquartile range, IQR) age of 1228 women was 49.5 (47.7, 51.6) years. Most women had a college degree or higher (51.0%), had never smoked (62.9%), and were pre-menopausal (70.4%) at SWAN-MPS baseline (1999–2000). The median (IQR) of serum adipokine levels at the sixth SWAN follow-up visit (2002–2003) was 6.8 (4.5, 10.5) μg/mL for HMW-adiponectin, 16.4 (9.0, 29.1) ng/mL for leptin, and 29.9 (24.0, 37.4) ng/mL for sOB-R. The distributions and detection rates of all 15 urinary metal concentrations are shown in Table S1. All metals were positively correlated with each other (Figure S2).

3.2. Single metals and adipokines

In the single metal models, molybdenum and antimony concentrations from 1999 to 2000 were significantly positively associated with HMW-adiponectin at in 2002–2003 (Table 2). After multivariable adjustment for age, race/ethnicity, study site, education, waist circumference, smoking, physical activity, menopausal status, and urine specific gravity, a one standard deviation (SD) increase in log-transformed urinary metal concentration was associated with 5.11% (95% CI: 1.12%, 9.25%) higher HMW-adiponectin level for molybdenum, and 3.95% (95% CI: 0.23%, 7.82%) for antimony. Urinary molybdenum and lead were inversely associated with leptin levels. A one SD increase in log-transformed urinary metal concentration was associated with 6.14% (95% CI: −10.33%, −1.76%) lower leptin level for molybdenum, and 4.38% (95% CI: −8.51%, −0.06%) for lead. Finally, urinary cobalt, cesium, mercury, nickel, and lead were inversely associated with level of sOB-R. A one SD increase in log-transformed urinary metal concentration was associated with 2.40% (95% CI: −4.51%, −0.24%) lower sOB-R level for cobalt, 3.55% (95% CI: −5.82%, −1.22%) for cesium, 2.05% (95% CI: −4.03%, −0.02%) for mercury, 2.47% (95% CI: −4.77%, −0.11%) for nickel, and 2.63% (95% CI: −4.66%, −0.55%) for lead.

Table 1
Descriptive characteristics of the study population (N = 1228).

Characteristics[a]	Median (IQR) or N (%)
Age, years	49.5 (47.7, 51.6)
Race/ethnicity	
White	631 (51.4)
Black	257 (20.9)
Chinese	149 (12.1)
Japanese	191 (15.6)
Study site	
Michigan	213 (17.4)
Boston	196 (16.0)
Oakland	268 (21.8)
Los Angeles	341 (27.8)
Pittsburgh	210 (17.1)
Education	
High school or less	215 (17.5)
Some College[b]	387 (31.5)
College and above	626 (51.0)
Smoking status	
Never smoked	772 (62.9)
Former smoker	336 (27.4)
Current smoker	120 (9.8)
Waist circumference, cm	81.8 (73.4, 94.2)
Physical activity score	7.9 (6.6, 9.0)
Menopausal status	
Pre-menopausal	865 (70.4)
Post-menopausal	170 (13.8)
Unknown[c]	193 (15.7)
High molecular weight adiponectin, μg/mL	6.8 (4.5, 10.5)
Leptin, ng/mL	16.4 (9.0, 29.1)
Soluble leptin receptor, ng/mL	29.9 (24.0, 37.4)

IQR: interquartile range.
[a] High molecular weight adiponectin, leptin, and soluble leptin receptor were measured at the sixth SWAN follow-up visit (2002–2003). All other characteristics were measured at the SWAN-MPS baseline (1999–2000).
[b] Some college indicates that a person has attended college but that they did not receive any degree.
[c] Menopausal status unknown due to hormone therapy or hysterectomy.

3.3. Multiple metals and adipokines

Table 3 summarizes the associations between exposure to multiple metals and adipokine levels. Of the 15 metal predictors in the AENET model, only cadmium, molybdenum, and antimony were associated with HMW-adiponectin level; the beta coefficients for all other metals were shrunk to zero. The associations between cadmium and molybdenum and HMW-adiponectin were statistically significant. After multiple adjustment for covariates, a one SD increase in log-transformed urinary metal concentration was associated with 4.53% (95% CI: −8.17%, −0.76%) lower HMW-adiponectin level for cadmium, and 5.54% (95% CI: 1.36%, 9.90%) higher level for molybdenum.

Table 2
Associations (β for 1-SD increase in log-transformed urinary metal concentrations) between individual metals and serum adipokine level in multivariable-adjusted linear regressions.

Metals[a]	Percentage change (95% CI) in adipokine levels for 1-SD increase in log-transformed urinary metal concentrations)		
	HMW-adiponectin[b]	Leptin[b]	sOB-R[b]
Arsenic	0.37 (−3.22, 4.09)	−2.53 (−6.64, 1.75)	−1.63 (−3.64, 0.41)
Barium	−2.49 (−5.73, 0.86)	−3.56 (−7.33, 0.37)	−0.94 (−2.82, 0.97)
Cadmium	−2.85 (−6.42, 0.85)	−2.93 (−7.13, 1.46)	−0.21 (−2.30, 1.93)
Cobalt	1.34 (−2.51, 5.33)	−3.95 (−8.24, 0.54)	**−2.40 (-4.51, -0.24)**
Cesium	−1.73 (−5.81, 2.52)	1.02 (−3.91, 6.21)	**−3.55 (-5.82, -1.22)**
Copper	0.70 (−3.37, 4.95)	−0.79 (−5.51, 4.17)	−0.52 (−2.82, 1.83)
Mercury	−2.53 (−5.99, 1.05)	−1.94 (−6.04, 2.34)	**−2.05 (-4.03, -0.02)**
Manganese	0.81 (−2.44, 4.16)	−2.55 (−6.25, 1.29)	1.00 (−0.86, 2.88)
Molybdenum	**5.11 (1.12, 9.25)**	**−6.14 (-10.33, -1.76)**	2.20 (−0.01, 4.46)
Nickel	−2.02 (−6.07, 2.21)	−3.68 (−8.37, 1.24)	**−2.47 (-4.77, -0.11)**
Lead	0.42 (−3.27, 4.25)	**−4.38 (-8.51, -0.06)**	**−2.63 (-4.66, -0.55)**
Antimony	**3.95 (0.23, 7.82)**	−2.55 (−6.67, 1.75)	0.13 (−1.92, 2.22)
Tin	0.66 (−2.77, 4.21)	−2.00 (−5.94, 2.09)	−1.46 (−3.37, 0.50)
Thallium	−0.89 (−4.38, 2.72)	−1.99 (−6.05, 2.24)	1.00 (−1.03, 3.06)
Zinc	−1.78 (−5.75, 2.36)	−0.21 (−4.96, 4.78)	0.61 (−1.71, 2.98)

SD: standard deviation; HMW: high molecular weight; sOB-R: soluble leptin receptor.
[a] All urinary metal concentrations were log-transformed and standardized.
[b] All linear regression models were adjusted for age, race/ethnicity, study site, education, waist circumference, smoking, physical activity, menopausal status, and urinary specific gravity.

For leptin, barium and molybdenum were selected in the AENET model. A statistically significant inverse association was observed between molybdenum and leptin; a one SD increase in log-transformed urinary molybdenum was associated with 5.95% (95% CI: −10.15%, −1.56%) lower leptin level after adjustment for covariates.

For sOB-R, 6 metals including cobalt, cesium, manganese, molybdenum, lead, and thallium were selected in the AENET model, while statistically significant associations were observed for cesium, molybdenum, and lead. After adjusting for all covariates, a one SD increase in urinary metal concentration was associated with 3.58% (95% CI: −6.06%, −1.03%) lower sOB-R for cesium, and 2.53% (95% CI: −4.80%, −0.21%) lower level for lead, respectively. In contrast, a one SD increase in urinary molybdenum was associated with 2.98% (95% CI: 0.69%, 5.32%) higher sOB-R.

3.4. Molybdenum and adipokines by racial/ethnic groups

For molybdenum that was significantly associated with adiponectin, leptin, and sOB-R, we further evaluated the associations by racial/ethnic groups (White vs. Black vs. Asian including both Chinese and Japanese) (Table S2). A stronger positive association between molybdenum and leptin was observed in Asian compared to white or black women. Inverse associations of molybdenum with adiponectin and sOB-R levels were observed in black women, though they were not statistically significant.

3.5. Sensitivity analysis

In an AENET model evaluating the association between leptin and multiple metals after further adjusting for sOB-R level, urinary molybdenum was the only metal retained in the model. The estimate was attenuated compared to that in the model without sOB-R adjustment, such that a one SD increase in urinary molybdenum concentration was associated with 3.71% (95% CI: −7.95%, 0.72%) lower leptin level.

Table 3
Associations (β for 1-SD increase in log-transformed urinary metal concentrations) between multiple metals and serum adipokine level in adaptive elastic-net.

Metals[a]	Percentage change (95% CI) in adipokine levels for 1-SD increase in log-transformed urinary metal concentrations)		
	HMW-adiponectin[b]	Leptin[b]	sOB-R[b]
Arsenic	–[c]	–	–
Barium	–	−2.36 (−6.17, 1.62)	–
Cadmium	**−4.53 (-8.17, -0.76)**	–	–
Cobalt	–	–	−1.79 (−4.02, 0.49)
Cesium	–	–	**−3.58 (-6.06, -1.03)**
Copper	–	–	–
Mercury	–	–	–
Manganese	–	–	1.20 (−0.78, 3.22)
Molybdenum	**5.54 (1.36, 9.90)**	**−5.95 (-10.15, -1.56)**	**2.98 (0.69, 5.32)**
Nickel	–	–	–
Lead	–	–	**−2.53 (-4.80, -0.21)**
Antimony	3.20 (−0.54, 7.09)	–	–
Tin	–	–	–
Thallium	–	–	2.21 (−0.02, 4.48)
Zinc	–	–	–

SD: standard deviation; HMW: high molecular weight; sOB-R: soluble leptin receptor.
[a] All urinary metal concentrations were log-transformed and standardized.
[b] All linear regression models were adjusted for age, race/ethnicity, study site, education, waist circumference, smoking, physical activity, menopausal status, and urinary specific gravity.
[c] Coefficient were shrunk to zero in the adaptive elastic-net models.

4. Discussion

We examined the associations between urinary concentrations of 15 metals and serum levels of 3 adipokines in a prospective cohort of 1228 women. Using the AENET method, which is able to analyze multiple metal exposures, we found that cadmium was associated with lower HMW-adiponectin, while molybdenum was associated with higher HMW-adiponectin. Molybdenum was also associated with lower leptin levels. For sOB-R, cesium and lead were associated with lower levels, whereas molybdenum was associated with higher levels. Therefore, our data raise the possibility that metals may impact adipokines profiles.

To our knowledge, this study is the first to examine the associations of exposure to a suite of 15 metals with adipokines in adults. The statistical approaches we used here acknowledged the reality that people are exposed to multiple metals and not individual ones in isolation (Wang et al., 2019b), and accounted for the high degree of correlation between urinary metal concentrations that may lead to the collinearity problem if all metal predictors were simultaneously included in the same linear regression model (Wang et al, 2018, 2019c; Zou and Zhang, 2009). There are also discrepancies between single metal models (linear regressions) and multiple metal models (AENET models) in our study, which may be attributed to confounding due to co-exposure to other metal components (Weisskopf et al., 2018). For example, antimony was modestly correlated with all other metals. Effect estimate for the association between antimony and HMW-adiponectin in single-metal linear regression changed by 20% in the AENET model, suggesting that the association may be confounded by other metals. In contrast, cadmium was not associated with HMW-adiponectin in single-metal model;

however, it was significantly associated with HMW-adiponectin in the AENET model with the effect estimate changed by greater than 50%. These findings highlight the importance of controlling for confounding due to co-exposures, particularly with colinear and high-dimensional environmental exposure data.

One robust finding from our analysis was that urinary molybdenum was associated with favorable adipokine profiles, including higher levels of HMW-adiponectin and sOB-R, and lower levels of leptin. Molybdenum is an essential element for enzymes including sulfite oxidase, xanthine oxidase, aldehyde oxidase, and mitochondrial amidoxime reducing component in humans (Schwarz, 2016). The general population is exposed to it primarily through food (legumes, whole grains, milk), and urinary molybdenum reflects long-term exposure (ATSDR, 2017). Leptin exerts its effects by binding to the leptin receptors (Schaab and Kratzsch, 2015). In humans, several isoforms of leptin receptors with identical extracellular domains but variable intracellular domains are produced through posttranscriptional alternative mRNA splicing (Schaab and Kratzsch, 2015). sOB-R is exclusively produced through proteolytic cleavage of the extracellular domain of membrane-anchored leptin receptors, and provides the primary leptin binding capacity in human circulation which modulates the bioavailability of the leptin (Schaab and Kratzsch, 2015). Serum sOB-R level has been proposed to reflect the amount of membrane-anchored receptors, and a decrease of sOB-R accompanied by a concurrent increase of leptin concentration may reflect the state of leptin resistance, a condition characterized by decreased leptin biological effects attributed to the impaired or absent leptin sensitivity (Schaab and Kratzsch, 2015). We observed that molybdenum was associated with lower leptin but higher sOB-R levels, suggesting a possible beneficial effect of molybdenum on leptin resistance. We also observed that the association between molybdenum and leptin was slightly attenuated after further adjustment for sOB-R at follow-up. This finding, which warrants further investigation, raises interesting questions regarding the role of molybdenum in the leptin resistance. On the one hand, the attenuated association suggests that the effect of molybdenum on leptin levels may be not independent of sOB-R. On the other hand, sOB-R could be a surrogate of fat mass at follow-up. Thus, it is possible that molybdenum influence leptin metabolism through its impact on adiposity. Though no identified literature has examined the relationship between molybdenum and adipokines, an epidemiologic study has reported an inverse relationship between molybdenum and obesity in the U.S. general population (Wang et al., 2018). An inverse association between molybdenum and adiposity has also been reported in a most recent study using the systematic exposome approach (Vrijheid et al., 2020). Favorable associations between molybdenum and glucose homeostasis have also been observed in our recent SWAN study (Wang et al., 2020b). A study of mice also reported beneficial effects of molybdenum including improved glucose tolerance, replenished glycogen stores, and corrected lipogenic enzyme gene expression, likely through its insulin-mimic actions (Tanju Özcelikay et al., 1996). In light of evidence that insulin may play a role in the regulation of adipokines (Chan et al., 2002), the observed findings of molybdenum and adipokines may also be attributed to its effect on insulin homeostasis. Further work is necessary to confirm our findings and clarify the biological mechanisms underlying these potential pathways. In this study, the strongest inverse association between molybdenum and leptin was observed in Asian women, possibly due to the higher concentrations of molybdenum found in both Chinese and Japanese women, independent of other sociodemographic factors such as geographic locations and socioeconomic status, that have been reported in SWAN previously (Wang et al., 2019b).

Our analysis detected a negative association between urinary lead and sOB-R. Lead is stored in bones for decades and bone lead has been considered a proxy for cumulative exposure to lead (Ding et al, 2016, 2018; Wang et al., 2019a). Urinary lead adjusted for urine dilution, rather than whole blood lead, has been found to closely reflect lead mobilized from the bone (Wang et al., 2019a). Given the fact that midlife women may experience an increased bone turnover rate (Hernandez-Avila et al., 2000), the observed association could be attributed in part to a greater mobilization of lead from bone into the circulation. Currently, no studies have investigated the relation between lead exposure and sOB-R. The scope of the biological mechanism underlying the association of lead with sOB-R is also still largely unknown. Oxidative stress has known adverse impacts on adipokine gene expression in murine models (Kamigaki et al., 2006). Lead is a well-known inducer of oxidative stress (Ahamed and Siddiqui, 2007), thus, this is one pathway by which lead may impact adipokine levels. Alternatively, lead may affect sOB-R through the disruption of secretion and physiological activity of estradiol and testosterone (Iavicoli et al., 2009), which have been suggested to serve as regulators of sOB-R in human studies (Chan et al., 2002; Wildman et al., 2013).

Another finding of our analysis was an inverse association between urinary cadmium and HMW-adiponectin. Urinary cadmium reflects long-term exposures (Vacchi-Suzzi et al., 2016). Studies on exposure to cadmium and adiponectin are limited and the results are mixed. Similar to our findings, a cross-sectional study of 70 Canadian adults reported an inverse correlation between urinary cadmium and plasma adiponectin (Valcke et al., 2019). However, in a Canadian birth cohort study, no association between maternal blood cadmium and cord blood adiponectin level was observed (Ashley-Martin et al., 2015). In human circulation, the low molecular weight and HMW forms are the most abundant, and the HMW form of adiponectin is the most biologically active (Nakashima et al., 2006; von Eynatten et al., 2008). To our knowledge, this is the first report of an association between cadmium and HMW-adiponectin. Thus, the failure of previous studies to examine HMW adiponectin may also partly underlie discrepant results. The association between cadmium and adiponectin is biologically plausible. In a study of mice, cadmium treatment significantly decreased adipocyte size and lowered adiponectin expression (Kawakami et al., 2013). Although adipocyte size recovered in 6 weeks after cessation of cadmium treatment in mice, the expression of adiponectin remained low. In the same study, cadmium was demonstrated to increase macrophage infiltration of white adipose tissue through up-regulation of monocyte chemoattractant protein-1 expression, suggesting a role in the dysregulation of adipokine levels (Kawakami et al., 2013).

Our study also found a positive association between urinary cesium and sOB-R. We were unable to locate any other biological or epidemiologic studies of cesium and adipokines. A previous study conducted in the U.S. general population found that cesium was not associated with obesity (Wang et al., 2018). In SWAN, cesium was not associated with either glucose homeostasis or the incidence of diabetes (Wang et al., 2020a, 2020b).

This study has several strengths. First, the prospective measure of adipokines minimized the possibility of reverse causation. Second, we measured a panel of 15 metals, which allowed us to assess a large number of associations as an initial exploratory inquiry of environmental factors affecting adipokine profiles. Third, for the first time, we used AENET to investigate the associations between exposure to multiple metals and adipokines in adults while accounting for statistical challenges such as complex correlations underlying multiple metals and confounding due to co-pollutants. Furthermore, the ethnically diverse population, as well as comparable metals concentrations in the SWAN cohort compared to women of the same age in the U.S. general population also increases the generalizability of our findings (Wang et al., 2019b).

Several limitations should be considered as well. First, we measured all metal concentrations in urine and urinary concentrations may not unanimously reflect exposure levels because they are influenced by renal clearance. We acknowledge that information on renal function is not available in SWAN although renal clearance is considered relatively stable in this age group (Murphy et al., 2016). Second, urinary metal concentrations were measured at a single time point at baseline. Metals included in the current analysis have very different half-lives in the

human body. Urinary concentrations of metals with short half-lives such as arsenic mainly reflect recent exposures (Navas-Acien et al., 2008). In contrast, other metals such as cadmium are not rapidly excreted and have half-lives of years to decades. As adipokine levels related to metals are likely affected by exposures over time-periods longer than a few days, information on the temporal variability of urinary metals concentrations, especially for those with short half-lives, is needed to characterize average metals exposures over time in the future study. Third, only total arsenic was measured in urine samples but information on arsenic metabolism was not available. Accumulating evidence supports the role of arsenic metabolism in cardio-metabolic diseases including type 2 diabetes and cardiovascular disease (Grau-Perez et al., 2017; Huang et al., 2009). Additional measurements of arsenic metabolism will improve our understanding of arsenic exposures and associated health risks in future studies. Fourth, although adipokines were measured prospectively in this study, they were measured at a single time point. Future studies would benefit from multiple measures of adipokines to capture longitudinal changes in their levels in relation to metals exposure. Finally, we cannot eliminate residual confounding due to the observational nature of the study, although we have controlled for many potential confounders. Other chemical stressors such as persistent organic pollutants, phthalates, and phenols that share common sources that may also affect adipokine levels (Ben-Jonathan et al., 2009; Kim et al., 2015; Lee et al., 2019; Minatoya et al., 2017; Wang et al., 2017). Future studies encompassing a broader range of these environmental exposures would provide additional information to better understand their impacts on adipokine profiles.

5. Conclusions

This study demonstrated that metals including cadmium, cesium, and lead measured in urine samples were associated with adverse levels of HMW-adiponectin and sOB-R. In contrast, molybdenum was associated with favorable profiles of HMW-adiponectin, leptin, and sOB-R. The associations we observed provide the impetus to further understand how metals may influence adipokines metabolism. Moreover, our most recent studies reported that metal exposures may impact glucose homeostasis and further influence risk of type 2 diabetes in SWAN (Wang et al., 2020a, 2020b). Future studies are also needed to determine whether these adipokine differences may partially explain the elevated risk of metabolic diseases attributed to metal exposures.

Credit author statement

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Declaration of competing interest

The authors declare they have no actual or potential competing interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.110426.

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