Environmental Research 210 (2022) 112976

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

# Metals and risk of incident metabolic syndrome in a prospective cohort of midlife women in the United States

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ARTICLE INFO

*Keywords:*
Metals
Arsenic
Cobalt
Zinc
Metabolic syndrome
Women

ABSTRACT

Exposure to metals may contribute to the development of metabolic syndrome (MetS); however, evidence from midlife women who are at greater risk of cardiometabolic disease is limited. We assessed the associations of 15 urinary metal concentrations with incident MetS in a prospective cohort of midlife women in the United States. The study population included 947 White, Black, Chinese and Japanese women, aged 45–56 years, free of MetS at baseline (1999–2000), who participated in the Study of Women's Health Across the Nation Multi-Pollutant Study. Fifteen metals were detected in almost all participants urine samples using inductively coupled plasma mass spectrometry at the baseline. Incident MetS was identified annually through 2017 as having at least three of the following five components: high blood pressure, impaired fasting glucose, abdominal obesity, high triglycerides, and poor high-density lipoprotein cholesterol. We used the Cox proportional hazards models to investigate the associations between individual metals and MetS incidence. The adjusted hazard ratios (HR) (95% CI) for MetS in associations with each doubling of urinary metal concentration were 1.14 (1.08, 1.23) for arsenic, 1.14 (1.01, 1.29) for cobalt, and 1.20 (1.06, 1.37) for zinc. We further evaluated the associations between metal mixtures and MetS using the elastic net penalized Cox model and summarized the results into the environmental risk score (ERS). Arsenic, barium, cobalt, copper, nickel, antimony, thallium, and zinc had positive weights, and cadmium, cesium, mercury, molybdenum, lead, and tin had negative weights in the construction of the ERS. The adjusted HR of MetS comparing 75th vs. 25th percentiles of the ERS was 1.45 (1.13, 1.87). These findings support the view that arsenic, cobalt, zinc, as well as metal mixtures, might influence the risks of incident MetS in midlife women.

## 1. Introduction

Cardiometabolic disorders including cardiovascular disease and type 2 diabetes are major public health issues, accounting for around 30% of deaths in the United States (U.S.) (Heron, 2019). Metabolic syndrome (MetS), a collection of interconnected cardiometabolic risk factors that includes high blood pressure, impaired fasting glucose, abdominal obesity, and dyslipidemia, is frequently utilized in clinical practice as a predictor of diabetes, cardiovascular disease, and mortality (Alberti et al., 2009). Midlife women had a substantially higher risk of MetS than women in earlier life stages (Beltrán-Sánchez et al., 2013), contributing to more pronounced health effects, including cardiovascular disease and all-cause mortality (Lin et al., 2010). A greater knowledge of the risk factors of MetS is critical for preventing its development in midlife women and promoting health in later life. Increased caloric consumption and lack of physical activity have been recognized as major factors to the MetS (Grundy, 2016). Environmental exposures, including metals, may also have a potential role in development of cardiometabolic

*Abbreviations:* BMI, body mass index; CVD, cardiovascular disease; ENET, elastic net; ERS, environmental risk score; FFQ, food frequency questionnaire; IPW, inverse probability weighting; MetS, metabolic syndrome; SWAN, Study of Women's Health Across the Nation; SWAN-MPS, Study of Women's Health Across the Nation Multi-Pollutant Study; T2DM, type 2 diabetes mellitus.

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https://doi.org/10.1016/j.envres.2022.112976
Received 18 October 2021; Received in revised form 13 January 2022; Accepted 16 February 2022
Available online 22 February 2022

disorders, according to growing research (Planchart et al., 2018; Wang et al., 2020a).

Metals and metalloids (for convenience, referred to collectively as metals) are broadly distributed in the environment with common sources of smoking, food, drinking water, consumer goods, and air (Tchounwou et al., 2012; Wang et al., 2019a). Biological evidence suggests that some metals may impact MetS. For example, arsenic, cadmium, mercury, and lead are all oxidative stress inducers, and their accumulation in various tissues has been shown to lead to elevated blood pressure and lipid peroxidation (Han et al., 2003; Jomova and Valko, 2011; Lu et al., 2011; Perry et al., 1979; Preuss et al., 1994; Wakita, 1987; Yang et al., 2007). Certain metals may also act as endocrine disruptors. For example, arsenic has been found to disrupt insulin function through decreasing insulin-stimulated glucose absorption in adipocytes and skeletal muscle cells and modifying gene expression of a range of glucose homeostasis-related factors (Walton et al., 2004). In animal and *in vitro* studies, manganese and zinc have been shown to increase testosterone and estradiol (Denier et al., 2009; Lee et al., 2006), which in turn may increase the risk of metabolic disorders (Ding et al., 2007). In rats, exposure to copper was observed to impair hepatic and renal functions and lipid metabolism and to disrupt thyroid hormones, all of which are linked to metabolic disorders (Su et al., 2017). Toxicological evidence on other metals is scant. However, limited evidence indicates the potential metabolic toxicity of these metals: barium (ATSDR, 2007), cobalt (ATSDR, 2004), molybdenum (ATSDR, 2017a), nickel (ATSDR, 2005a), antimony (ATSDR, 2017b), tin (ATSDR, 2005b), and thallium (ATSDR, 1992) may impair liver function and lead to metabolic disorders. Findings on metals and MetS from population-based studies are relatively limited and mixed (Ayoub et al., 2021; Bulka et al., 2019; Guo et al., 2019; Liu et al., 2022a; Lo et al., 2021; Ma et al., 2020; Moon, 2014; Park and Oh, 2021; Tinkov et al., 2017), though evidence from epidemiologic studies of individual components of MetS suggests a contributing role of metals (Alissa and Ferns, 2011; Buhari et al., 2020; Wang et al., 2020b; Wang et al., 2018a). Moreover, even though people are routinely exposed to metal mixtures (Wang et al., 2019a), the majority of studies have concentrated on single metals, possibly attributed to the data unavailability and statistical challenges posed by the complex correlations between mixture components (Park et al., 2017; Wang et al., 2019b; Wang et al., 2018a). Finally, women become more susceptible to cardiometabolic disorders in midlife due to a shift in sex hormone profiles (Polotsky and Polotsky, 2010; Stuenkel, 2017). Menopause is also linked with an increased burden of oxidative stress caused by decreased estrogen levels (Sánchez-Rodríguez et al., 2012). Given this increased susceptibility, exposure to metals could be a risk factor of MetS, especially for women in midlife. Nonetheless, to our knowledge, no study has been conducted on the impact of metals on the development of MetS in midlife women.

Given the inconsistent findings and the paucity of studies on some metals and their metabolic toxicity, we conducted exploratory analysis examining the associations of 15 urinary metal concentrations with the MetS incidence and its components in a prospective cohort of midlife women representing multiple racial/ethnic groups, using the data from the Study of Women's Health Across the Nation (SWAN). Additionally, we developed an environmental risk score (ERS) (Park et al., 2017, 2014; Wang et al., 2020b, 2019b; Wang et al., 2018a) to assess the relationship between metal mixtures and MetS.

## 2. Material and methods

### 2.1. Study population

We utilized data from SWAN, which is a longitudinal, multi-site, multi-racial/ethnic, community-based cohort of midlife women designed to investigate physiological and psychosocial changes during the menopausal transition. During 1996 and 1997, 3302 women were recruited from seven study sites across the United States. This study included White women from all study sites and women from one of the following racial/ethnic groups, including, Black women from Boston, MA, Pittsburgh, PA, southeast Michigan, MI, and Chicago, IL; Hispanic women from Newark, NJ; Chinese women from Oakland, CA; and Japanese women from Los Angeles, CA (Sowers et al., 2000). Eligibility criteria were being aged 42–52 years, having an intact uterus and at least one ovary, having had at least one menstrual period in the past three months, having not taken hormone therapy in the past three months, and not being pregnant or lactating. SWAN has approximately annual or biannual follow-up visits. The institutional review board at each participating site approved the study protocol, and all participants provided written, signed informed consent.

Beginning in 2016, the SWAN Multi-Pollutant Study (MPS) was initiated to undergo measurements of environmental pollutants among 1400 women with available SWAN repository samples from the five SWAN sites including Michigan, MI, Boston, MA, Oakland, CA, Los Angeles, CA, and Pittsburgh, PA (Ding et al., 2020; Park et al., 2019; Wang et al., 2019a). Metal concentrations were assessed in repository urine samples collected at SWAN visit 03 (1999–2000, the MPS baseline). Of these 1400 participants, we excluded 366 women with prevalent MetS at the MPS baseline, and 87 women who had missing information on key covariates, yielding a final analytic sample of 947 women with 8283 observations followed from 1999 to 2017. A flow chart of the current study is shown in Fig. 1.

### 2.2. Metabolic syndrome

Blood pressure and waist circumference were measured using standardized protocols by trained and certified personnel. Serum samples were collected to measure fasting glucose and lipid levels. Incident MetS and its components were determined at SWAN visit 04, 05, 06, 07, 09, 12, 13, and 15 using the National Cholesterol Education Program Adult Treatment Panel III criteria for MetS for women (Grundy et al., 2005). Women who had at least 3 of the following 5 components were identified as having MetS: (1) high blood pressure defined as systolic blood pressure $\geq$130 mmHg, or diastolic blood pressure $\geq$85 mmHg, or current use of antihypertensive medication; (2) impaired fasting glucose ascertained by fasting glucose $\geq$100 mg/dL or current use of antidiabetic medication; (3) abdominal obesity defined as waist circumference $\geq$88 cm for White and Black women and $\geq$80 cm for Chinese and Japanese women; (4) high triglyceride defined as serum triglyceride $\geq$150 mg/dL; and (5) low high-density lipoprotein cholesterol (HDL) defined as serum HDL $<$50 mg/dL.

### 2.3. Urinary metals

Concentrations of a panel of 15 metals, including arsenic, barium, cadmium, cobalt, cesium, copper, mercury, manganese, molybdenum, nickel, lead, antimony, tin, thallium, and zinc, were measured in morning spontaneously voided urine samples using high-resolution inductively-coupled plasma mass spectrometry (Thermo Scientific iCAP RQ, Waltham, MA) at the SWAN-MPS baseline. The measurements followed the CDC method 3018.3 (CDC, 2012), with modifications for the expanded metals panel, performed at the Applied Research Center of NSF International (Ann Arbor, Michigan) (Wang et al., 2019a). Concentrations below the limits of detection (LODs) were substituted with the LODs divided by the square root of 2 (Lubin et al., 2004). Urinary creatinine was measured using the Cobas Mira analyzer (Horiba ABX, Montpellier, France) as a marker of urine dilution.

### 2.4. Other covariates

Adjustment covariates included were race/ethnicity, study site, education, smoking status, alcohol drinking, physical activity score, total energy intake, menopausal status, body mass index (BMI), and urinary creatinine (log-transformed). Self-reported race/ethnicity (defined as

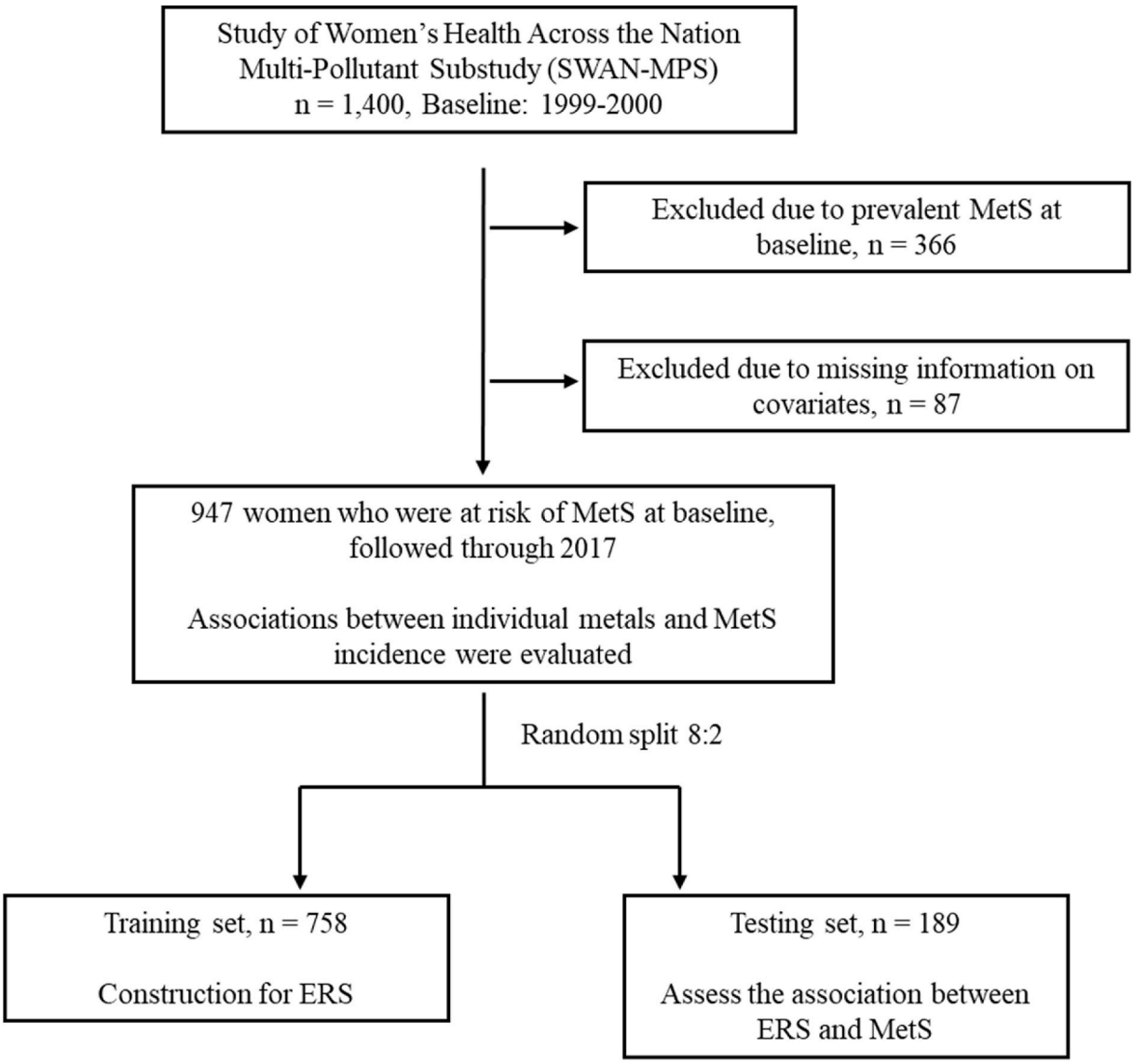


**Fig. 1.** Flow chart of the study design. MetS: metabolic syndrome; ERS: Environment Risk Score.

White, Black, Chinese, or Japanese), and education (categorized as high school or less, some college, or college degree or higher) were assessed through a self-administered questionnaire at the MPS baseline. At each study visit, smoking status (never smoked, former smokers, or current smoking), alcohol drinking (<1 drink/month, >1 drink/month and ≤1/week, and >1 drink/week), physical activity, and menopausal status (pre-menopausal, post-menopausal, and unknown due to hormone therapy use) were obtained from standardized interviews. Physical activity was measured using a modified version of the Kaiser Physical Activity Survey (Sternfeld et al., 2000). The total score ranged from 3 to 15 was calculated, indicating the activity levels during the previous 12 months in 3 distinct domains: active living (1–5), household/caregiving (1–5), and sports/exercise (1–5). A total score of 3 indicated least, and 15 indicated most physically active. Total energy intake, and zinc and Vitamin $B_{12}$ intake from diet and supplements were assessed using a detailed semi-quantitative food frequency questionnaire (FFQ) adopted from the Block FFQ (Block et al., 1986). BMI was calculated as weight in kilograms divided by the square of height in meters. We used a Directed Acyclic Graph to show the hypothesized relations between metals, confounders, and MetS (Fig. S1) (Baik and Shin, 2008; Cena et al., 2011; He et al., 2014; Scuteri et al., 2008; Wang et al., 2019a).

### 2.5. Statistical analysis

We used Cox proportional hazards models to estimate the hazard ratio (HR) and 95% confidence interval (CI) for incident MetS associated with each metal. We used age as the time scale, and participants contributed survival time from the SWAN-MPS baseline to the date of the first MetS event for incident cases and participants without incident MetS were right-censored at the date of the last study visit. Metal concentrations were modeled as continuous variables in the Cox models. Given the right-skewed distributions of metal concentrations, logarithmic transformations with base two were applied to all metal concentrations. Effect estimates were thus interpreted as HR of MetS per doubling of each urinary metal concentration. To capture the potential non-linear associations, metal concentrations were also categorized into quartiles and HRs were calculated comparing the second, third, and fourth quartiles to the first quartile (the reference group). A linear trend of the association across the quartiles was tested by including metal quartiles as a continuous variable. All the models were adjusted for race/ethnicity, study site, and urinary creatinine (log-transformed), smoking (time-varying), alcohol drinking (time-varying), physical activity score (time-varying), total energy intake (time-varying), and menopausal status (time-varying), and BMI at baseline. Time-varying BMI was not

included in the analysis because of its possible role as an intermediate variable (Wang et al., 2018a). For the association between urinary zinc and MetS, we adjusted for total zinc intake from food and supplements in all three models. Dietary zinc intake has been associated with lower risk of diabetes and MetS (Sun et al., 2009; Wang et al., 2018b). Therefore, urinary zinc adjusted for dietary zinc intake and zinc supplements could better capture the excessive renal clearance and excretion of zinc independent of beneficial zinc intake from diet. For the association between urinary cobalt and MetS, we also adjusted for dietary and supplemental Vitamin $B_{12}$ intake since the cobalt is an important metal constitute of vitamin $B_{12}$ and vitamin $B_{12}$ intake has been associated with a lower risk of MetS (Li et al., 2018). For other essential elements, such as copper, we did not adjust for dietary intake due to a lack of data. We also examined associations of metals with the incidence of each of the five MetS components. Given the relatively large number of associations examined for MetS components, we addressed multiple comparisons at a false discovery rate (FDR) of 0.05 using the Benjamini–Hochberg Method (Benjamini and Hochberg, 1995).

We developed an ERS an integrative score of health risk associated with multiple environmental exposures to summarize the associations between metal mixtures and MetS (Park et al., 2017; Wang et al., 2019b; Wang et al., 2018a). We randomly split the study population into the training set to construct the MetS-related ERS of metal mixtures and the testing set to evaluate its association with MetS while avoid overfitting. We tried multiple split ratios and found that a ratio of 8:2 (N = 758 for training set and N = 189 for testing set) was the most accurate split with the least prediction errors in the testing set. In the training set, we first used the elastic net (ENET) penalized Cox regression (Yang and Zou, 2013), a machine learning algorithm designed for analyzing high-dimensional data in survival analyses, to identify metals associated with incident MetS while accounting for the potential multicollinearity due to the complex correlations between metals. This ENET penalized Cox model included all 15 metals ($log_2$-transformed) as independent variables and coefficients of "unimportant" metals were shrunk to zero in the model fitting process. The covariates from the Cox model in the individual metal analyses were adjusted in the ENET model. The regularization parameters (λ and α) were ascertained through a grid search based on minimal 10-fold cross-validation errors. The R package 'glmnet' was used to implement the ENET penalized Cox model (Friedman et al., 2010). ERS was then computed as a weighted sum of non-zero metal predictors estimated from ENET penalized Cox model by

$$\mathrm{ERS_i} = \sum_{j=1}^{P} \widehat{\beta}_j E_i^j$$

where $E_i^j$ ($j = 1, \ldots, p$) is the log-transformed concentration of the $j$-th metal and $\widehat{\beta}_j$ is the beta coefficient (weight) of the $j$-th metal. In the testing set, we fitted the ERS in the Cox model and report the adjusted HR of MetS comparing the 75th vs. the 25th percentile of the ERS. All metals were fitted as continuous variables. It is not statistically efficient to incorporate quartiles of all metal concentrations in the ENET model if all the metals are treated as categorical variables, and it is possible that the ENET only select one but not all quartiles of specific metals that the ERS cannot be calculated.

We recognized that the associations between metals and MetS might be influenced by the selective participation into the SWAN-MPS. To account for this potential bias, we calculated weights to participation into the SWAN-MPS using probability weighting (IPW) to create a pseudo population representing the women who were at risk of developing incident MetS at the time of metal measurements in the original SWAN cohort. Details illustrating the construction of IPW are presented in our previous study (Wang et al., 2020a).

To test the robustness of our results, we performed following sensitivity analyses. First, we used covariate-adjusted creatinine standardization instead of adjusting for urinary creatinine concentration as a covariate in regression models for adjusting urine dilution (O'Brien et al., 2016). Briefly, we first fitted the linear regression with log-transformed urinary creatinine as dependent variables and all covariates included in the primary analysis as independent variables and predicted each participant's creatinine concentration based on the regression results. The predicted creatinine concentrations (after back transformed) are therefore independent of the covariates and capture only variations due to urine dilution. We then calculated the covariates-adjusted creatinine standardized metal concentrations by dividing the urinary metal concentrations by the ratio of the measured to the predicted urinary creatinine concentration. Second, we additionally adjusted for seafood and rice intake in analyses for arsenic, cadmium, and mercury as we have identified these dietary components as important determinants in a previous study (Wang et al., 2019a). Finally, we examined the effect modification by race/ethnicity and menopausal status at baseline by incorporating the interaction terms between metals and modifiers in the Cox models. All analyses were conducted using R, version 4.0.3 (www.R-project.org).

## 3. Results

Among 947 women free of MetS at the SWAN-MPS baseline, 173 developed incident cases with the median follow-up of 15.7 years. Participants who developed MetS tended to be Black and from Michigan. They tended to have a higher BMI but less education and poorer individual components of MetS (Table 1).

Table 2 presents the distribution of urinary metal concentrations. The percentage of participants with detectable metal concentrations ranged from 78.1% to 100%, while most metals had detection rates greater than 90%. Participants who developed incident MetS were more likely to have higher arsenic and zinc concentrations.

Table 3 summarizes the associations between urinary metal concentrations and the incidence of MetS. After adjustment for race/ethnicity, study site, and urinary creatinine (log-transformed), education, smoking status, alcohol drinking, physical activity score, total energy intake, menopausal status, BMI at baseline, and dietary intake of zinc or Vitamin $B_{12}$, comparing the highest to the lowest quartiles, the HR for MetS was 1.72 (95% CI: 1.20, 2.46) for arsenic (P for trend = 0.002), 1.85 (95% CI: 1.25, 2.74) for cobalt (P for trend = 0.02), and 1.66 (95% CI: 1.08, 2.58) for zinc. The associations of arsenic, cobalt, and zinc with MetS were log linear. The HR for MetS associated with each doubling of urinary metal concentration was 1.14 (95% CI: 1.08, 1.23) for arsenic, 1.14 (95% CI: 1.01, 1.29) for cobalt, and 1.20 (95% CI: 1.06, 1.37) for zinc, when they were fit as continuous variables ($log_2$-transformed).

Associations between metals and the incidence of MetS components are presented in Table 4. After full adjustment for confounders, arsenic was associated with higher incidences of high blood pressure and impaired fasting glucose but a lower incidence of high triglyceride. Cobalt was associated with higher incidences of high blood pressure, impaired fasting glucose, and abdominal obesity. Zinc was associated with higher incidences of high blood pressure, impaired fasting glucose, abdominal obesity, and high triglyceride. For other metals where the association with MetS were not observed, we found that barium was associated with higher incidences of impaired fasting glucose and abdominal obesity, cadmium was associated with high blood pressure, copper and lead were associated with a higher incidence of abdominal obesity, molybdenum was associated with a lower incidence of abdominal obesity, and nickel was associated with higher incidences of high blood pressure and impaired fasting glucose, after adjusting for multiple comparison with FDRs <5%.

We further examined the associations between metal mixtures and MetS using the ERS approach. In the training set, 14 metals were selected in the ENET penalized Cox model associated with MetS incidence, with eight (arsenic, barium, cobalt, copper, nickel, antimony, thallium, and zinc) showing positive and six (cadmium, cesium,

**Table 1**
Characteristics of participants in the Study of Women's Health Across the Nation Multi-Pollutant Study at baseline.

| | Non-MetS (n = 774) | Incident MetS (n = 173) |
|---|---|---|
| Age (years)[a] | 49.4 (47.3, 51.3) | 49.5 (47.4, 51.7) |
| Race/ethnicity | | |
| White | 415 (53.6) | 75 (43.4) |
| Black | 123 (15.9) | 41 (23.7) |
| Chinese | 108 (14.0) | 23 (13.3) |
| Japanese | 128 (16.5) | 34 (20.0) |
| Study site | | |
| Michigan | 100 (12.9) | 39 (22.5) |
| Boston | 136 (17.6) | 18 (10.4) |
| Oakland | 181 (23.4) | 37 (21.4) |
| Los Angeles | 235 (30.4) | 50 (28.9) |
| Pittsburgh | 122 (15.8) | 29 (16.8) |
| Body mass index (kg/m$^2$) | 23.5 (21.2, 26.6) | 27.6 (25.0, 32.2) |
| Education | | |
| High school or less | 113 (14.6) | 43 (24.9) |
| Some college | 228 (29.5) | 64 (37.0) |
| College or higher | 433 (55.9) | 66 (38.1) |
| Smoking status | | |
| Never | 509 (65.8) | 103 (59.5) |
| Former | 197 (25.5) | 52 (30.1) |
| Current | 68 (8.8) | 18 (10.4) |
| Alcohol drinking | | |
| ≤1 drink/month | 361 (46.6) | 96 (55.5) |
| >1 drink/month and ≤1/week | 186 (24.0) | 43 (24.9) |
| >1 drink/week | 227 (29.3) | 34 (19.7) |
| Physical activity score | 8.2 (7.0, 9.3) | 7.5 (6.2, 8.6) |
| Menopausal status | | |
| Pre-menopausal | 549 (70.9) | 126 (72.8) |
| Post-menopausal | 113 (14.6) | 15 (8.7) |
| Unknown[b] | 112 (14.5) | 32 (18.5) |
| Systolic blood pressure (mmHg) | 107 (99, 116) | 117 (105, 124) |
| Diastolic blood pressure (mmHg) | 70 (65, 77) | 75 (69, 80) |
| Fasting glucose (mg/dL) | 84.0 (79.4, 88.5) | 87.6 (83.0, 93.1) |
| Waist circumference (cm) | 75.8 (70.4, 83.3) | 86.2 (79.6, 93.9) |
| HDL cholesterol (mg/dL) | 66 (57, 76) | 56 (50, 64) |
| Triglyceride (mg/dL) | 84 (65, 109) | 111 (79, 142) |
| Total energy intake (kCal) | 1657 (1332, 2070) | 1604 (1236, 2318) |
| Total zinc intake (mg/day) | 10.6 (7.4, 19.9) | 11.6 (7.5, 20.4) |
| Total Vitamin B12 intake (μg/day) | 2.4 (1.7, 3.4) | 2.4 (1.5, 3.6) |
| Dietary seafood intake (times/week) | 1.5 (0.8, 2.5) | 1.6 (0.8, 2.8) |
| Dietary rice intake (times/week) | 2.0 (1.0, 5.5) | 2.0 (1.0, 5.5) |

Note: MetS, metabolic syndrome.
[a] Data are median (interquartile range) or n (%).
[b] Menopausal status unknown due to hormone therapy or hysterectomy.

**Table 2**
Detection rates and concentrations of urinary metals by incident metabolic syndrome.

| Metals | LOD | Percent > LOD | Median concentration (IQR), μg/L | |
|---|---|---|---|---|
| | | | Non-MetS (n = 774) | Incident MetS (n = 173) |
| Arsenic | 0.3 | 100 | 13.85 (6.59, 38.66) | 14.41 (7.02, 41.53) |
| Barium | 0.1 | 99.6 | 1.76 (0.98, 2.95) | 1.73 (0.92, 3.06) |
| Cadmium | 0.06 | 94.0 | 0.46 (0.23, 0.79) | 0.47 (0.23, 0.82) |
| Cobalt | 0.05 | 99.2 | 0.63 (0.37, 0.91) | 0.61 (0.42, 1.20) |
| Cesium | 0.01 | 100 | 4.69 (3.13, 7.27) | 4.92 (2.98, 7.23) |
| Copper | 2.5 | 96.8 | 9.29 (6.14, 13.28) | 10.14 (6.40, 12.80) |
| Mercury | 0.05 | 100 | 1.31 (0.71, 2.52) | 1.12 (0.61, 2.18) |
| Manganese | 0.08 | 99.7 | 0.90 (0.61, 1.45) | 0.89 (0.59, 1.34) |
| Molybdenum | 0.3 | 100 | 45.13 (24.35, 73.68) | 45.79 (24.86, 70.58) |
| Nickel | 0.8 | 96.2 | 3.77 (2.30, 5.92) | 3.76 (2.22, 6.21) |
| Lead | 0.1 | 97.5 | 0.80 (0.50, 1.28) | 0.85 (0.46, 1.29) |
| Antimony | 0.04 | 78.1 | 0.07 (0.04, 0.13) | 0.09 (0.05, 0.14) |
| Tin | 0.1 | 96.6 | 0.95 (0.49, 1.79) | 0.87 (0.52, 1.80) |
| Thallium | 0.02 | 92.0 | 0.14 (0.08, 0.22) | 0.14 (0.08, 0.24) |
| Zinc | 2 | 100 | 292 (159, 479) | 332 (188, 541) |

Note: LOD: limit of detection; IQR: interquartile range; MetS: metabolic syndrome.

mercury, molybdenum, lead, and tin) showing negative beta coefficients, representing log-transformed hazard ratio of MetS for a two-fold increase in metal concentrations (Table 5). The beta coefficient of manganese was shrunk to zero. The ERS was then constructed using these beta coefficients as weights, with higher ERS indicating a combination of higher concentrations of metals with positive weights and lower concentrations of metals with negative weights. Meanwhile, individuals with a greater ERS had a higher risk of MetS than those with a lower ERS in the training set. The distributions of the ERS are similar in the training and testing sets (Fig. S2). In the testing set, an increase in the ERS from 25th percentile (0.25) to 75th percentile (0.44) was associated with a higher incidence of MetS with an adjusted HR of 1.45 (95% CI: 1.13, 1.87).

Similar findings were found in sensitivity analyses when covariate-adjusted creatinine standardization was used (Table S1). Additional adjustment for seafood and rice intake did not alter the results for arsenic, cadmium, and mercury (Table S2). When examining effect modifications by race/ethnicity, we found a stronger positive association between manganese and MetS in Asian (Chinese and Japanese) women than White and Black women (Table S3). A stronger association between nickel and MetS was observed in White and Asian women compared to Black women. We also found significant effect modification of the association between manganese and MetS that a stronger association was observed in post-menopausal women (Table S4). Stronger associations between most other metals and MetS incidence were also observed in post-menopausal women than pre-menopausal women, though the interactions were not statistically significant, possibly due to reduced statistical power in accordance with the smaller number of post-menopausal women at baseline.

## 4. Discussion

In this 18-year multi-site, prospective cohort study of 947 midlife women with diverse racial/ethnic groups, higher urinary arsenic, cobalt, and zinc concentrations were significantly associated with elevated MetS incidence. These associations persisted after controlling for demographic, socioeconomic, lifestyle factors, menopausal status, BMI, and dietary factors. Using the ENET penalized Cox model and integrating the associations into the ERS, we again found a significant association between the ERS and the risk of MetS after controlling for overfitting. These findings suggest that metals, including arsenic, cobalt, and zinc, as well as metal mixtures, may play a role in the development of MetS in a cohort of midlife women with similar metal concentrations as women of the same age range in the U.S. general population (Wang et al., 2019a).

More than one-third of women in the U.S. have MetS (Hirode and Wong, 2020). The risk of developing MetS increases substantially across the menopausal transition (Beltrán-Sánchez et al., 2013), and MetS becomes a more pronounced predictor of cardiovascular disease in post-menopausal women (Lin et al., 2010). A better knowledge of the risk factors for the MetS is of substantial public health importance as effective preventive efforts can be undertaken. This is the first prospective study, to the best of our knowledge, that assessed the associations of a panel of 15 metals with the incidence of MetS in midlife women. The mixture analysis in our study (ENET penalized Cox model) was conducted to account for potential confounding from co-exposure to other metals in the mixture. For example, copper was not associated with incident MetS in the single metal Cox model; however, it showed one of the strongest associations in the ENET penalized Cox model, suggesting that there may be confounding by co-exposure to other metals in either direction. Finally, we summarized the joint effects of metal mixtures into the ERS, and our findings indicate that people with higher ERS as a

**Table 3**
Hazard ratios (HR) (95% confidence intervals, 95% CI) for incident metabolic syndrome in relation to urinary metal concentrations.

| Metals | Quartile of metal concentrations | | | | P for trend | Per doubling[a] | P |
|---|---|---|---|---|---|---|---|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | | | |
| **Arsenic** | | | | | | | |
| Range, μg/L | 0.73, 7.37 | 7.40, 15.55 | 15.65, 44.94 | 45.02, 2983.79 | | | |
| HR (95% CI)[b] | Ref | 1.32 (0.96, 1.82) | 1.78 (1.23, 2.58) | 1.72 (1.20, 2.46) | 0.002 | 1.14 (1.07, 1.23) | 0.0001 |
| **Barium** | | | | | | | |
| Range, μg/L | <LOD, 0.98 | 0.98, 1.75 | 1.76, 2.93 | 2.94, 51.03 | | | |
| HR (95% CI) | Ref | 0.66 (0.48, 0.91) | 0.71 (0.51, 0.99) | 0.82 (0.59, 1.15) | 0.96 | 1.04 (0.94, 1.14) | 0.45 |
| **Cadmium** | | | | | | | |
| Range, μg/L | <LOD, 0.22 | 0.23, 0.44 | 0.44, 0.77 | 0.77, 23.97 | | | |
| HR (95% CI) | Ref | 0.95 (0.67, 1.35) | 0.93 (0.63, 1.38) | 0.98 (0.65, 1.49) | 0.99 | 0.95 (0.85, 1.06) | 0.35 |
| **Cobalt** | | | | | | | |
| Range, μg/L | <LOD, 0.38 | 0.38, 0.63 | 0.63, 0.95 | 0.95, 8.32 | | | |
| HR (95% CI) | Ref | 1.47 (1.02, 2.11) | 0.89 (0.59, 1.34) | 1.85 (1.25, 2.74) | 0.02 | 1.14 (1.01, 1.29) | 0.03 |
| **Cesium** | | | | | | | |
| Range, μg/L | 0.37, 3.12 | 3.13, 4.78 | 4.81, 7.35 | 7.36, 104.43 | | | |
| HR (95% CI) | Ref | 0.75 (0.53, 1.06) | 1.04 (0.71, 1.52) | 1.03 (0.65, 1.63) | 0.58 | 1.04 (0.86, 1.25) | 0.22 |
| **Copper** | | | | | | | |
| Range, μg/L | <LOD, 5.96 | 5.97, 9.17 | 9.18, 13.22 | 13.22, 1889.40 | | | |
| HR (95% CI) | Ref | 1.03 (0.71, 1.50) | 1.13 (0.76, 1.69) | 0.75 (0.47, 1.20) | 0.22 | 1.00 (0.87, 1.15) | 0.99 |
| **Mercury** | | | | | | | |
| Range, μg/L | 0.07, 0.70 | 0.70, 1.30 | 1.30, 2.47 | 2.48, 32.37 | | | |
| HR (95% CI) | Ref | 1.01 (0.74, 1.37) | 1.06 (0.77, 1.47) | 0.65 (0.44, 0.94) | 0.06 | 0.91 (0.82, 1.01) | 0.06 |
| **Manganese** | | | | | | | |
| Range, μg/L | <LOD, 0.58 | 0.59, 0.87 | 0.87, 1.43 | 1.43, 41.97 | | | |
| HR (95% CI) | Ref | 0.93 (0.66, 1.30) | 0.76 (0.54, 1.09) | 0.77 (0.53, 1.13) | 0.11 | 1.01 (0.89, 1.15) | 0.87 |
| **Molybdenum** | | | | | | | |
| Range, μg/L | 2.48, 24.60 | 24.65, 45.95 | 46.00, 74.80 | 74.82, 694.53 | | | |
| HR (95% CI) | Ref | 1.30 (0.92, 1.82) | 1.35 (0.95, 1.91) | 1.13 (0.76, 1.68) | 0.55 | 1.10 (0.97, 1.24) | 0.14 |
| **Nickel** | | | | | | | |
| Range, μg/L | <LOD, 2.35 | 2.35, 3.79 | 3.80, 5.94 | 5.94, 73.60 | | | |
| HR (95% CI) | Ref | 1.02 (0.72, 1.44) | 0.77 (0.53, 1.12) | 1.01 (0.69, 1.48) | 0.77 | 1.01 (0.89, 1.16) | 0.84 |
| **Lead** | | | | | | | |
| Range, μg/L | <LOD, 0.47 | 0.47, 0.78 | 0.78, 1.25 | 1.25, 43.59 | | | |
| HR (95% CI) | Ref | 0.57 (0.40, 0.81) | 0.78 (0.55, 1.12) | 0.75 (0.51, 1.12) | 0.57 | 0.90 (0.79, 1.02) | 0.09 |
| **Antimony** | | | | | | | |
| Range, μg/L | <LOD, 0.04 | 0.04, 0.07 | 0.07, 0.12 | 0.12, 1.38 | | | |
| HR (95% CI) | Ref | 1.35 (0.94, 1.94) | 1.58 (1.09, 2.31) | 1.24 (0.84, 1.84) | 0.32 | 1.04 (0.92, 1.17) | 0.55 |
| **Tin** | | | | | | | |
| Range, μg/L | <LOD, 0.48 | 0.48, 0.90 | 0.90, 1.73 | 1.74, 106.82 | | | |
| HR (95% CI) | Ref | 1.53 (1.10, 2.21) | 1.01 (0.70, 1.46) | 1.03 (0.71, 1.48) | 0.44 | 0.96 (0.88, 1.04) | 0.28 |
| **Thallium** | | | | | | | |
| Range, μg/L | <LOD, 0.08 | 0.08, 0.14 | 0.14, 0.22 | 0.22, 15.73 | | | |
| HR (95% CI) | Ref | 1.41 (1.01, 1.95) | 0.96 (0.66, 1.39) | 1.52 (1.05, 2.21) | 0.12 | 1.03 (0.93, 1.14) | 0.55 |
| **Zinc** | | | | | | | |
| Range, μg/L | 7.01, 157.38 | 157.44, 277.26 | 277.71, 464.33 | 466.99, 2295.46 | | | |
| HR (95% CI) | Ref | 1.37 (0.94, 1.98) | 1.04 (0.69, 1.56) | 1.66 (1.08, 2.58) | 0.05 | 1.20 (1.06, 1.37) | 0.006 |

Note: LOD: limit of detection.

[a] Results based on when $\log_2$-transformed metal concentrations were fitted.

[b] All models were adjusted for race/ethnicity, study sites, urinary creatinine (log-transformed), education, smoking status, alcohol drinking, physical activity score, total energy intake, menopausal status, and body mass index at baseline. Zinc intake from diet and supplements was additionally adjusted for zinc model. Vitamin $B_{12}$ intake from diet and supplements was additionally adjusted for cobalt model.

weighted combination of multiple metal concentrations may be at higher risk of MetS.

We observed that urinary arsenic was positively associated with an elevated incidence of MetS, high blood pressure, and impaired fasting glucose. Arsenic is pervasive in the environment, and inorganic arsenic is a toxicant that people can be exposed through drinking water and foods such as cereal and rice (Wang et al., 2019a). Urinary arsenic was associated with higher MetS prevalence in two highly exposed Taiwanese populations and the U.S. general population (Bulka et al., 2019; Chen et al., 2012; Wang et al., 2007). Epidemiologic studies have also found associations of arsenic with high blood pressure (Abhyankar et al., 2012; Jiang et al., 2015), impaired fasting glucose (Spratlen et al., 2018), and type 2 diabetes (Grau-Perez et al., 2017; Navas-Acien et al., 2008; Wang et al., 2014, 2020a), which are consistent with the results observed in the current study. Arsenic induces the generation of reactive oxygen species, leading to oxidative stress and related inflammation, endothelial dysfunction, and renal dysfunction, and the development of cardiovascular disorders such as hypertension (Abhyankar et al., 2012; Chen et al., 2011). Arsenic is also related to a higher risk of insulin resistance through disrupting insulin-stimulated glucose uptake in peripheral tissues (Mohammed Abdul et al., 2015; Walton et al., 2004). In this study, we also observed an inverse association between arsenic and the incidence of high triglyceride levels. In contrast to our finding, a positive association between arsenic exposure and triglyceride was shown in Mexican Adults (Mendez et al., 2016), while a null association was reported in American Indian adults and adults in the U.S. general population (Bulka et al., 2019; Spratlen et al., 2018).

Cobalt is a metal component of Vitamin $B_{12}$ (cyanocobalamin), a vital nutrient for human health. Despite the beneficial role of cyanocobalamin, other cobalt compounds have been described as environmental toxicants, and people can be exposed to cobalt through ambient air and drinking water (Leyssens et al., 2017). In the current study, cobalt was associated with higher incidence of MetS, high blood pressure, impaired fasting glucose, and abdominal obesity, and these associations persisted after adjusting for dietary and supplement intake of Vitamin $B_{12}$. Existing evidence on the impact of cobalt exposure on MetS is extremely

**Table 4**
Hazard ratios (HR) (95% confidence intervals, 95% CI) for incident metabolic syndrome components for a doubling increase in urinary metal concentrations.

| Metals | High blood pressure | FDR | Impaired fasting glucose | FDR | Abdominal obesity | FDR | High triglyceride | FDR | Low HDL | FDR |
|---|---|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | | HR (95% CI) | | HR (95% CI) | | HR (95% CI) | | HR (95% CI) | |
| Arsenic | 1.06 (1.01, 1.12) | 0.03 | 1.16 (1.07, 1.26) | 0.01 | 0.96 (0.92, 1.01) | 0.23 | 0.90 (0.83, 0.96) | 0.02 | 0.93 (0.86, 1.00) | 0.15 |
| Barium | 1.07 (1.00, 1.13) | 0.08 | 1.19 (1.06, 1.33) | 0.02 | 1.10 (1.04, 1.17) | 0.01 | 0.93 (0.86, 1.01) | 0.33 | 0.99 (0.91, 1.07) | 0.92 |
| Cadmium | 1.09 (1.02, 1.16) | 0.03 | 1.16 (1.02, 1.31) | 0.05 | 1.05 (0.99, 1.12) | 0.22 | 0.96 (0.88, 1.05) | 0.59 | 1.02 (0.94, 1.12) | 0.92 |
| Cobalt | 1.12 (1.03, 1.21) | 0.02 | 1.25 (1.07, 1.46) | 0.02 | 1.12 (1.04, 1.22) | 0.008 | 0.94 (0.85, 1.05) | 0.58 | 0.88 (0.79, 0.97) | 0.08 |
| Cesium | 1.11 (0.98, 1.25) | 0.12 | 1.16 (0.94, 1.43) | 0.21 | 1.02 (0.90, 1.15) | 0.81 | 0.92 (0.79, 1.08) | 0.58 | 0.87 (0.74, 1.03) | 0.33 |
| Copper | 1.08 (0.98, 1.19) | 0.12 | 1.16 (0.99, 1.36) | 0.11 | 1.24 (1.14, 1.34) | 0.001 | 0.95 (0.81, 1.10) | 0.59 | 0.82 (0.70, 0.96) | 0.08 |
| Mercury | 0.95 (0.89, 1.01) | 0.13 | 1.09 (0.96, 1.24) | 0.20 | 0.88 (0.83, 0.94) | 0.001 | 1.01 (0.93, 1.11) | 0.88 | 0.97 (0.89, 1.06) | 0.92 |
| Manganese | 0.96 (0.89, 1.04) | 0.29 | 1.14 (1.00, 1.30) | 0.08 | 1.03 (0.95, 1.10) | 0.57 | 0.85 (0.76, 0.94) | 0.02 | 0.97 (0.87, 1.07) | 0.92 |
| Molybdenum | 0.96 (0.88, 1.04) | 0.29 | 1.17 (1.01, 1.36) | 0.08 | 0.90 (0.83, 0.98) | 0.03 | 1.05 (0.94, 1.17) | 0.59 | 1.01 (0.90, 1.13) | 0.92 |
| Nickel | 1.14 (1.04, 1.24) | 0.02 | 1.26 (1.07, 1.49) | 0.02 | 1.07 (0.98, 1.16) | 0.22 | 0.99 (0.87, 1.12) | 0.88 | 0.99 (0.88, 1.12) | 0.92 |
| Lead | 1.08 (1.00, 1.17) | 0.09 | 1.15 (1.00, 1.33) | 0.08 | 1.14 (1.06, 1.24) | 0.004 | 0.94 (0.84, 1.04) | 0.55 | 1.12 (1.00, 1.24) | 0.15 |
| Antimony | 0.93 (0.86, 1.01) | 0.11 | 1.08 (0.93, 1.25) | 0.32 | 1.06 (0.99, 1.14) | 0.19 | 1.04 (0.94, 1.16) | 0.59 | 1.02 (0.92, 1.13) | 0.92 |
| Tin | 1.03 (0.98, 1.08) | 0.29 | 1.08 (0.98, 1.19) | 0.15 | 0.97 (0.93, 1.02) | 0.33 | 1.00 (0.93, 1.07) | 0.93 | 1.00 (0.94, 1.07) | 0.92 |
| Thallium | 1.05 (0.99, 1.12) | 0.12 | 1.00 (0.88, 1.14) | 0.99 | 1.01 (0.95, 1.07) | 0.81 | 0.93 (0.85, 1.01) | 0.30 | 0.99 (0.92, 1.08) | 0.92 |
| Zinc | 1.15 (1.05, 1.25) | 0.02 | 1.58 (1.34, 1.87) | 0.002 | 1.15 (1.06, 1.25) | 0.004 | 1.28 (1.14, 1.44) | 0.002 | 1.08 (0.96, 1.21) | 0.55 |

Note: all models were constructed by Cox proportional hazards model. FDR: false discovery rate. All models were adjusted for race/ethnicity, study sites, urinary creatinine (log-transformed), education, smoking status, alcohol drinking, physical activity score, total energy intake, menopausal status, and body mass index at baseline. Zinc intake from diet and supplements was additionally adjusted for zinc model. Vitamin $B_{12}$ intake from diet and supplements was additionally adjusted for cobalt model.

**Table 5**
Selected non-zero beta coefficients of metals for incidence of metabolic syndrome in elastic-net (ENET) penalized Cox model[a].

| Selected non-zero metal predictors[b] | β for $\log_2$-transformed metal concentrations[c] |
|---|---|
| Arsenic | 0.038 |
| Barium | 0.006 |
| Cadmium | −0.037 |
| Cesium | −0.024 |
| Cobalt | 0.033 |
| Copper | 0.053 |
| Mercury | −0.091 |
| Manganese | 0[d] |
| Molybdenum | −0.028 |
| Nickel | 0.008 |
| Lead | −0.026 |
| Antimony | 0.032 |
| Tin | −0.017 |
| Thallium | 0.028 |
| Zinc | 0.051 |

[a] Model was adjusted for race/ethnicity, study sites, and urinary creatinine (log-transformed), education, smoking status, alcohol drinking, physical activity score, total energy intake, menopausal status, body mass index (baseline), and dietary intake of zinc and Vitamin $B_{12}$.

[b] Logarithmic transformations with base 2 were applied to all urinary metal concentrations.

[c] Beta coefficients of selected predictors were used as weights in the following construction of the environmental risk score.

[d] Beta coefficient was shrunk to zeros.

limited: a null association between urinary cobalt and MetS prevalence was recently reported in a large community-based cross-sectional study in China (Ma et al., 2020). The cardiovascular effects of cobalt, in contrast, have been more extensively examined in occupational settings. Epidemiologic studies in highly occupationally exposed populations have found associations of cobalt exposure with cardiovascular endpoints, including altered diastole, reduced left ventricular systolic function, left ventricular and atrial hypertrophy, reversible electrocardiographic changes, arrhythmias, and hypertension (D'Adda et al., 1994; Horowitz et al., 1988; Leyssens et al., 2017; Linna et al., 2004; Machado et al., 2012; Oldenburg et al., 2009). Cobalt appears to exert toxic effects through the inhibition of cellular respiration due to interruption of the mitochondrial function (Leyssens et al., 2017). Our findings, leveraging a community-based prospective cohort design, suggest cobalt exposure may also increase the risk of MetS among midlife women from the U.S. general population (Wang et al., 2019a). Finally, we observed a positive association between cobalt and abdominal obesity in the fully adjusted model. In contrast, two cross-sectional studies in the U.S. found an inverse association of cobalt with waist circumference and BMI (Niehoff et al., 2020; Wang et al., 2018a). We found a null association in models without BMI adjustment in the current analysis. Given the positive correlation between BMI at baseline and waist circumference at follow-up (β = 1.93, 95% CI: 1.87, 1.99 for BMI at baseline in the linear mixed regression with time-varying waist circumference as the outcome), it is possible that the association observed could be positively biased due to the overadjustment.

Our analyses also revealed that urinary zinc was associated with an elevated risk of MetS and its components, including high blood pressure, impaired fasting glucose, abdominal obesity, and high triglyceride. Zinc is an essential element that people need on a daily basis to be healthy and prevent disease (Jansen et al., 2009). Zinc is excreted in the urine and feces (Roohani et al., 2013). After adjusting for dietary and supplemental zinc intake, we observed a positive association between urinary zinc and MetS, demonstrating that women who had higher urinary zinc excretion might be at a greater risk of MetS independent of zinc intake. Mechanistic evidence suggests that zinc can protect against oxidative stress by inhibiting lipid peroxidation and inflammatory cytokines expression (Goel et al., 2005; Hennig et al., 1999, 2001; Mansour and Mossa, 2009). Increased urinary zinc excretion was also linked with zinc loss in β-cells, affecting insulin synthesis, storage, and secretion. Urinary zinc excretion has previously been associated with a higher incidence of type 2 diabetes, accelerated increase in insulin resistance, and decrease in β-cell function over time in SWAN (Wang et al., 2020a, 2020b). In contrast, some observational studies have demonstrated a positive association of serum zinc with adverse cardiometabolic outcomes, including MetS, hypertension, and dyslipidemia (Bulka et al., 2019; Ghasemi et al., 2014; Kunutsor and Laukkanen, 2016), while the underlying biological mechanisms are still unclear. Future prospective studies with the quantification of zinc in multiple biological matrices are needed to confirm these findings, and further mechanistic studies are needed to unravel the underlying biological pathways. Finally, we need to acknowledge that hyperglycemia may inhibit the active transport of zinc into renal cells, resulting in a zinc loss through urine (Chausmer, 1998). It is possible that the observed association between urinary zinc and MetS is a result of increased urinary zinc excretion among women with relatively high glucose levels at baseline. However, the prospective cohort design of our study, and the fact that women with prevalent MetS were excluded in the survival analyses, reduce the likelihood that our finding occurred as a result of reverse causation.

Our data provided evidence for associations between other metals and MetS and its components. A significant positive association between manganese and MetS was observed in Asian women. Race/ethnicity was not found as a determinant for urinary manganese concentration in SWAN (Wang et al., 2019a). In a most recent study of the U.S. general population, no association was observed between urinary manganese and MetS prevalence (Lo et al., 2021). Cadmium was positively associated with high blood pressure. Existing evidence regarding cadmium and high blood pressure is mixed. Positive associations between urinary cadmium and blood pressure have been reported in U.S. adults (Tellez-Plaza et al., 2008) and in a large cohort study of American Indian adults (Franceschini et al., 2017). By contrast, no association was found in other studies (Mordukhovich et al., 2012; Park and Oh, 2021; Staessen et al., 2000). We observed positive associations of barium with impaired fasting glucose and abdominal obesity, which is in line with findings from two large cross-sectional studies in China that barium was associated with higher prevalence of impaired fasting glucose and high waist circumference (Feng et al., 2015; Zhang et al., 2020). We found positive associations of nickel with high blood pressure and impaired fasting glucose, and MetS in White and Asian women, who showed higher concentrations compared to Black women in SWAN (Wang et al., 2019a). One cross-sectional study conducted in China showed that urinary nickel was associated with higher diabetes prevalence, higher fasting glucose, HbA1c, and elevated insulin resistance (Liu et al., 2015). By contrast, an inverse association between urinary nickel and diastolic blood pressure was reported in U.S. adults without hypertension in a most recent study (Liu et al., 2022b). Molybdenum was inversely associated with abdominal obesity in our study, which is supported by an inverse association between molybdenum and waist circumference in the U.S. adults (Wang et al., 2018a). In our latest SWAN study, favorable relationships between molybdenum and adipokine profiles were observed (Wang et al., 2021b). Copper was positively associated with abdominal obesity. Though no identified literature has examined the association between urinary copper and waist circumference, a recent meta-analysis suggested a possible link between serum copper and obesity risk (Gu et al., 2020). Given the limited and conflicting data now exist, further research is required to confirm these findings in the future. Finally, the null association between one specific metal and MetS does not necessarily mean null associations between this metal and MetS components. For example, cadmium was not associated with MetS but was significantly associated with high blood pressure.

Strengths of the present study include the large sample size, diverse racial/ethnic groups, and longitudinal design with up to 18 years of follow-up of SWAN. A list of 15 metals was also measured, enabling us to examine a reasonably large number of associations between MetS of multiple individual metals, as well as metal mixtures. We note, however, that all metal concentrations were determined in urine, which may not capture all metal forms and exposure sources. Furthermore, total arsenic concentrations in urine samples were measured, but not for arsenic metabolites. Based upon the evidence that arsenic metabolites may impact metabolic outcomes (Grau-Perez et al., 2017; Spratlen et al., 2018), further measures of arsenic metabolites will give a clearer understanding of arsenic body burden and related health problems in the future. Additionally, metals examined in this study have varying half-lives. Urinary metals having short half-lives, such as arsenic, primarily represent recent exposures. In comparison, metals such as cadmium have half-lives ranging from years to decades. Future studies should incorporate repeated measures of metal concentrations to better elucidate the associations with MetS, given that metal exposures over a more extended time span are expected to impact MetS risk. Furthermore, although we applied IPW to address the potential for selective participation into the SWAN-MPS, we cannot rule out potential selection bias due to the initial selection process of the parent SWAN design. Estimates of the metal-MetS associations may be underestimated because women who might be more susceptible to metabolic effects of metals were more likely to excluded at the enrollment. Arsenic, for example, has been associated to an earlier age at natural menopause (Wang et al., 2021a), which is a risk factor for MetS (Janssen et al., 2008). Finally, we utilized cross-validation to reduce the prediction errors of the ENET penalized Cox model, and the association between ERS and MetS was examined in the testing set. Nevertheless, these results may have limited generalizability to populations with distinct characteristics due to a lack of external validation datasets. While further prospective studies are required to confirm the results of individual metals and the ERS, our findings from a broad, multi-racial/ethnic population indicate that exposure to metals and their mixtures may influence the risk of MetS.

## 5. Conclusion

Our findings found that urinary arsenic, cobalt, and zinc concentrations were associated with the incidence of MetS in midlife women. Using the ENET penalized Cox model and integrating the associations into the ERS with positive weights of arsenic, barium, cobalt, copper, nickel, antimony, thallium, and zinc, and negative weights of cadmium, cesium, mercury, molybdenum, lead, and tin, we again found a significant association between the ERS and the risk of MetS. These findings provide evidence that metals may be an underappreciated contributing factor to MetS, especially during the sensitive period of midlife for women. More prospective studies are needed to confirm these findings, and mechanistic studies are encouraged to investigate the underlying biological mechanisms.

## Author contributions

**Xin Wang:** Conceptualization, Formal analysis, Methodology, Validation, Visualization, Writing – original draft. **Carrie A. Karvonen-Gutierrez:** Writing – review & editing. **William H. Herman:** Writing – review & editing. **Bhramar Mukherjee:** Methodology, Writing – review & editing. **Sung Kyun Park:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495, and U19AG063720). The study was supported by the SWAN Repository (U01AG017719).

This study was also supported by grants from the National Institute of Environmental Health Sciences (NIEHS) R01-ES026578, R01-ES026964 and P30-ES017885, and by the Center for Disease Control and Prevention (CDC)/National Institute for Occupational Safety and Health (NIOSH) grant T42-OH008455.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

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We thank the study staff at each site and all the women who participated in SWAN.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.112976.

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