HHS Public Access

Author manuscript

Environ Pollut. Author manuscript; available in PMC 2024 January 15.

Published in final edited form as:

Environ Pollut. 2023 January 15; 317: 120740. doi:10.1016/j.envpol.2022.120740.

Exposure to Heavy Metals and Hormone Levels in Midlife Women: the Study of Women's Health Across the Nation (SWAN)

Xin Wang[1], **Ning Ding**[1], **Siobán D. Harlow**[1], **John F. Randolph Jr.**[2], **Bhramar Mukherjee**[3], **Ellen B. Gold**[4], **Sung Kyun Park**[1,5]

[1]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, United States

[2]Department of Obstetrics and Gynecology, School of Medicine, University of Michigan, Ann Arbor, MI, United States

[3]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, United States

[4]Department of Public Health Sciences, University of California, Davis, School of Medicine, Davis, CA, United States

[5]Department of Environmental Health Sciences, School of Public Health, University of Michigan, Ann Arbor, MI, United States

Abstract

Exposure to heavy metals may alter the circulating levels of sex hormones. However, epidemiologic studies on heavy metals and sex hormones have been limited, and results have been inconsistent. We assessed the associations of heavy metals assayed in urine, including arsenic, cadmium, lead, and mercury, with repeated measures of serum estradiol (E_2), follicle-stimulating hormone (FSH), testosterone, and sex hormone-binding globulin (SHBG) levels in the Study of Women's Health Across the Nation Multi-Pollutant Study. The sample included 1,355 White, Black, Chinese, and Japanese women, aged 45-56 years at baseline (1999-2000), whose serum hormone levels were repeatedly measured through 2017. Urinary metal concentrations were measured at baseline. Linear mixed effect models were used to calculate percent changes in serum hormone levels per doubling of urinary metal concentrations, adjusting for demographics, socioeconomic status, lifestyle, health-related factors, and urinary creatinine. After multivariable adjustment, a doubling of urinary metal concentration was associated with lower E_2 levels by 2.2%

Corresponding author: Sung Kyun Park, Department of Epidemiology, University of Michigan, M5541 SPH II, 1415 Washington Heights, Ann Arbor, MI 48109-2029. Phone: (734) 936-1719. Fax: (734)936-2084. sungkyun@umich.edu.

Author Contributions

Xin Wang: Conceptualization, Formal analysis, Methodology, Validation, Visualization, Writing - original draft. **Ning Ding**: Writing - Review & Editing. **Siobán D. Harlow**: Writing - Review & Editing. **John F. Randolph Jr.**: Writing - Review & Editing. **Bhramar Mukherjee**: Methodology, Writing - Review & Editing. **Ellen B. Gold**: Writing - Review & Editing. **Sung Kyun Park**: Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

Conflict of interest

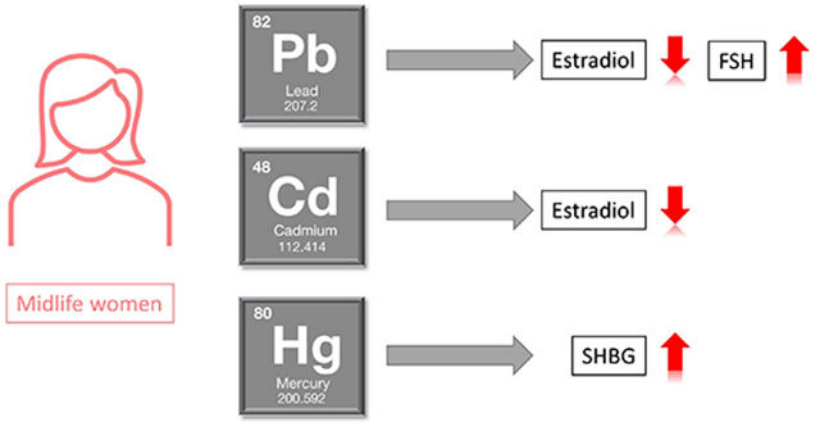
The authors declare they have no actual or potential competing interest.

Declaration of interests

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.

(95% CI: −4.0%, −0.3%) for mercury and 3.6% (95% CI: −5.7%, −1.6%) for lead; higher FSH levels by 3.4% (95% CI: 0.9%, 5.9%) for lead; and higher SHBG levels by 3.6% (95% CI: 1.3%, 5.9%) for cadmium. The overall joint effect using the Bayesian kernel machine regression showed that metal mixtures were inversely associated with E_2 and positively associated with FSH levels. No association was found between metals and testosterone levels. Results from this prospective cohort study demonstrate that environmental heavy metal exposures, including cadmium, mercury, and lead, may disturb circulating levels of E_2, FSH, and SHBG in midlife women.

Graphical Abstract



Keywords

Heavy metals; arsenic; cadmium; lead; mercury; sex hormones

1. Introduction

The menopausal transition is a significant health milestone for women, encompassing a time period during which physiologic changes mark progression toward the cessation of ovarian function. It is characterized by a shift in women's sex hormone profiles, including a relatively sharp decline in estradiol (E_2) and a gradual rise in follicle-stimulating hormone (FSH) levels toward the final menstrual period, owing to permanent changes in ovarian function (Randolph et al., 2011). By contrast, testosterone levels remained relatively stable (Randolph et al., 2003). Levels of E_2 or FSH over the menopausal transition may affect women's health in the midlife and as they age, as they influence risk of obesity (Sutton-Tyrrell et al., 2005; Wildman et al., 2012), type 2 diabetes mellitus (Park et al., 2017), cardiovascular disease (El Khoudary and Thurston, 2018), and osteoporosis (Neer, 2010). A comprehensive understanding of the factors associated with sex hormone profiles is of great importance for understanding and ultimately preventing health risks associated with ovarian aging. Evidence from epidemiologic studies indicates that genetic (Sowers et al., 2011), sociodemographic, and lifestyle factors (Randolph et al., 2011) may alter sex hormone profiles during this critical time window. However, the potential impacts of exposure to environmental chemicals are less well understood.

Heavy metals, including arsenic, cadmium, mercury, and lead, are widely dispersed in the environment, with drinking water, ambient air, food, and consumer products as possible exposure sources (Wang et al., 2019b). Arsenic, cadmium, mercury, and lead have been evaluated for their endocrine-disrupting properties (Dyer, 2007; Iavicoli et al., 2009; Sun et al., 2016). It is biologically plausible that exposure to these metals may affect hormone profiles through alteration in production and secretion of sex hormones, interaction with hormone receptors, interference with steroidogenesis, regulation of gonadal receptor expression, and/or direct alteration of gametogenesis (Iavicoli et al., 2009). Sex hormone-binding globulin (SHBG) is a glycoprotein binding globulin produced by the liver that transports sex steroids in human circulation and is therefore an important regulator of free fractions of E_2 and testosterone (Deswal et al., 2017). Dysregulation of SHBG due to heavy metal exposures may also potentially affect sex hormone profiles (Avvakumov et al., 2000; Tian et al., 2021).

Information on associations between heavy metals and sex hormones in human populations, however, is limited, and results have been inconsistent (Gallagher et al., 2010; Jackson et al., 2011; Kresovich et al., 2015; Krieg and Feng, 2011; Lei et al., 2015; Nagata et al., 2005; Pollack et al., 2011; Zheng et al., 2015). Most studies have been cross-sectional, with metal exposures and hormone levels measured at a single time-point, so that causal relationships were hard to be established. Additionally, studies of the associations between heavy metals and sex hormone levels during the critical window of midlife in women have been particularly limited.

Thus, to test the hypothesis that exposure to heavy metals may adversely affect sex hormone profiles, we investigated the associations of urinary concentrations of heavy metals, including arsenic, cadmium, mercury, and lead measured at baseline with serial serum levels of E_2, FSH, testosterone, and SHBG in the Study of Women's Health Across the Nation (SWAN), a multi-site, multi-racial/ethnic prospective cohort study of midlife women.

2. Material and methods

2.1 Study population

SWAN is a prospective cohort study of midlife women designed to investigate physiological and psychosocial changes during the menopausal transition and other related health outcomes from mid-to-late life (Sowers et al., 2000). 3,302 women were recruited from seven study sites between 1996 and 1997, and each site included White women and one minority group (Black women at Boston, MA, Pittsburgh, PA, southeast Michigan, MI, and Chicago, IL sites; Hispanic women at the Newark, NJ site; Chinese women at the Oakland, CA site; and Japanese women at the Los Angeles, CA site). Inclusion criteria included between age 42 and 52, having an intact uterus and at least one ovary, without use of hormone therapy in the past three months, and having at least one menstrual period in the past three months. Institutional Review Board approval was obtained at each study site, and all participants provided signed informed consent at each study visit.

Women in this analysis were 1,400 participants in the SWAN Multi-Pollutant Study (SWAN-MPS) who had stored urine samples from the SWAN Repository between 1999

and 2000 (Ding et al., 2020a; Wang et al., 2019). For these analyses, we excluded 18 with missing information on serum hormone levels, 23 with missing information on key covariates, and 4 participants using hormone therapy at the SWAN-MPS baseline, yielding a final analytic sample of 1,355 participants. In SWAN, FSH and SHBG were measured through the 15th follow-up visit (2015-2017), E_2 through the 13th follow-up visit (2011-2012), and testosterone through the 10th follow-up visit (2006-2007). The timeframe of sex hormone measurements was shown in Figure S1. We censored observations (n=2,244) in follow-up visits when a participant was taking hormone therapy because the true untreated levels of the outcome parameters were unknown. A final sample of 1,355 women representing 10,645 observations was used for FSH and SHBG analyses, 9,754 for E_2 analyses, and 7,745 for testosterone analyses.

2.2 Serum sex hormones

E_2, FSH, testosterone, and SHBG were assayed from fasting serum samples at each visit. Optimally, serum samples were collected for each participant before 10:00 A.M. on one day during days 2-5 of a spontaneous menstrual cycle occurring within 60 days of recruitment at the baseline visit and approximately annually thereafter. If a follicular phase sample could not be obtained, a random fasting sample was taken within 90 days of the anniversary of the baseline visit. FSH was assayed in singlicate and measured with a two-site chemiluminometric immunoassay using the automated Ciba Corning Diagnostics ACS-180 analyzer (Bayer Diagnostics Corp., Norwood, MA); the inter- and intra-assay coefficients of variation (CVs) were 12% and 6%, respectively. E_2 was assayed in duplicate and measured with a modified, off-line ACS-180 (E2–6) immunoassay, with inter- and intra-assay CVs of 11% and 6%, respectively. Testosterone was assayed using the modified rabbit polyclonal anti-T ACS-180 immunoassay, with the average inter- and intra-assay CVs of 10% and 8%, respectively. SHBG was assayed using rabbit anti-SHBG antibodies, with inter- and intra-assay CVs of 10% and 6%, respectively.

2.3 Urinary metals

High-resolution inductively coupled plasma-mass spectrometry (ICP-MS) (Thermo Scientific iCAP RQ, Waltham, MA) was used to determine arsenic, cadmium, mercury, and lead concentrations in morning urine samples collected at SWAN-MPS baseline at the Applied Research Center of NSF International (Ann Arbor, Michigan), a part of the Michigan Children's Health Exposure Analysis Resource (M-CHEAR) Laboratory Hub. Details of analytic methods and quality control procedures have been described previously (Wang et al., 2019b). Limits of detection (LODs) and detection rates are presented in Table S1. Participants with metal concentrations below the LOD were assigned a value equal to the LOD divided by the square root of 2. Spearmen correlations between metal concentrations were calculated.

2.4 Covariates

Age, race/ethnicity (White, Black, Chinese, or Japanese), and education level (as high school or less, some college, or college degree or higher) were collected using a self-administered questionnaire at the SWAN baseline. Considering the possibility that metal exposures may affect BMI, we did not use time-varying BMI in the analysis in order to prevent potential

overadjustment bias (Wang et al., 2018). Urinary creatinine was measured using the Cobas Mira analyzer (Horiba ABX, Montpellier, France) at the SWAN-MPS baseline as a marker of urine dilution. At each study visit, smoking status (never smoked, former smoked only, or current smoking), menopause transition stage (pre-menopausal, early perimenopausal, late perimenopausal, postmenopausal, and unknown due to hormone therapy use), and parity (nulliparous, parous) were self-reported. Pre-menopausal was defined as having menstruation in past 3 months with no change in bleeding regularity; early perimenopausal was having menstruation in past 3 months but decreasing regularity between menses; late perimenopausal was no menstruation in past 3-11 months; and postmenopausal was no menstruation in past 12 or more months.

2.5 Statistical analysis

We used linear mixed effects models with random intercepts to evaluate the associations between baseline urinary metal concentrations and longitudinally measured serum hormone levels. Given the highly skewed distributions of hormone levels and metal concentrations, logarithmic transformations were applied so that shapes of exposure-outcome relationships were more closely log-linear. All regression coefficients and associated 95% confidence intervals (95% CIs) were back-transformed and expressed as percent change in hormone levels for a doubling increase in metal concentrations. Potential confounders were adjusted progressively. The base model included non-time-varying variables age (baseline), race/ethnicity, study site, and urinary creatinine (log-transformed). The fully adjusted model further adjusted for non-time-varying variables education, BMI (baseline), and parity; and time-varying variables included follow-up time, smoking and menopause status. Multiple comparison for each hormone was addressed at a false discovery rate (FDR) of 0.05 using the Benjamini–Hochberg Method (Benjamini and Hochberg, 1995).

In secondary analyses, we quantified differences in hormone levels associated with exposure to metal mixtures using a two-stage modeling strategy (Wang et al., 2020), addressing correlations for both exposures and repeatedly measured outcomes. In stage 1, linear mixed effects models with random intercepts were fitted to estimate participant-specific hormone levels while accounting for correlations in hormone levels within each participant over time. In stage 2, the Bayesian kernel machine regression (BKMR) was used to examine the associations between metal mixtures and participant-specific hormone levels estimated from stage 1, while handling the correlations between metal exposures and potential non-linear relationships (Bobb et al., 2015). It should be noted that we used the two-stage modeling approach instead of specifying a random intercept within BKMR because of the computational limits. The R package ‘bkmr’ was used to implement BKMR (Bobb et al., 2015).

In other secondary analyses, we repeated analyses stratified by menopausal status and race/ethnicity to evaluate potential effect modifications. Additionally, we evaluated the associations between metal concentrations and log-transformed testosterone-to-E_2 ratio. Finally, we further adjusted for stress, dietary intake of fat, alcohol drinking, and physical activity. All data analyses were performed using SAS version 9.4 (SAS Institute Inc.) and R version 4.2.1 (www.R-project.org).

3. Results

3.1 Descriptive statistics

The mean (SD) age was 49.3 (2.6) years (Table 1). The proportions of each racial/ethnic group were 50.0% for white, 21.8% for Black American, 13.1% for Chinese, and 15.2% for Japanese. Most women had at least some college education and had never smoked. The geometric mean (GM) (geometric standard deviation, GSD) at baseline was 34.5 (2.7) pg/mL for E_2, 34.5 (2.8) mIU/mL for FSH, 32.3 (1.7) ng/dL for testosterone, and 35.0 (2.0) nM for SHBG. The detection rate and distributions of urinary metal concentrations is presented in Table S1. All four metals were positively correlated, with the strongest correlation between cadmium and lead (r=0.57, Figure S2).

3.2 Associations between sex hormones and metals

Significant inverse associations of serum E_2 levels with cadmium, mercury, and lead were observed in the base models, whereas the associations were attenuated and only significant for mercury and lead in the full model after adjusting for multiple comparison with FDRs < 0.05 (Table 2). After adjustments for age, race/ethnicity, study site, education, BMI at baseline, smoking, parity, menopausal status, and urinary creatinine (log-transformed), a doubling increase in urinary metal concentration was associated with 2.2% (95% CI: −4.0%, −0.3%) lower E_2 level for mercury, and 3.6% (95% CI: −5.7%, −1.6%) for lead.

In the base models, significant positive associations with FSH levels were found for cadmium, mercury, and lead (Table 3). Adjustment for additional covariates in the full model attenuated these associations, and significant association was only observed for lead after controlling for multiple comparison. After full adjustment for covariates, a doubling increase in urinary lead concentration was associated with 3.4% (95% CI: 0.9%, 5.9%) higher FSH level.

Significant positive associations of serum SHBG levels with arsenic, cadmium, and mercury were found in the base model, whereas results were significant only for cadmium in the full model after controlling for multiple comparison (Table 4). A doubling increase in urinary cadmium concentration was associated with 3.6% (95% CI: 1.3%, 5.9%) higher serum SHBG levels after fully adjusting for covariates. No association was observed between urinary metal concentrations and serum testosterone levels (Table S2).

3.3 Secondary analyses

In the secondary analysis evaluating the associations between metal mixtures and hormone levels, we found that lead was inversely associated with E_2 levels, as observed in the primary analyses (Figure S3). Similarly, a positive association was observed between lead and FSH (Figure S4) and between cadmium and SHBG (Figure S5). No associations between metals and testosterone were observed (Figure S6). Figure 1 shows the overall effects of metal mixtures as the estimated changes in log-transformed hormone levels, comparing concentrations of all metals simultaneously at different percentiles of their distributions to all metals at their 10th percentiles. Metal mixtures were inversely associated with E_2 and positively associated with FSH levels.

In the secondary analysis stratifying the associations by menopausal status (pre-menopausal, early and late perimenopausal, and postmenopausal) (Table S3), we found stronger inverse associations of E_2 with mercury and lead and a stronger positive association between FSH and lead in the early and late perimenopausal stages. Additionally, arsenic was inversely associated with E_2 and positively associated with SHBG in the early and late perimenopausal stages. Mercury was positively associated with FSH in the early and late perimenopausal stages. In stratified analysis by race/ethnicity, we found stronger positive associations between lead and FSH in Japanese women (Table S4). We also observed an inverse association between cadmium and testosterone in Black women.

In other secondary analyses, positive associations of testosterone-to-E_2 ratio (log-transformed) with mercury and lead were observed (Table S5). Similar associations were observed after additional adjustment for stress, dietary intake of fat, alcohol drinking, and physical activity (Table S6).

4. Discussion

This study examined associations between heavy metal exposures and longitudinal measures of sex hormone levels in midlife women as they aged through the menopausal transition. Higher urinary mercury and lead concentrations were associated with lower serum E_2 levels. Higher lead concentrations were associated with higher serum FSH levels. A positive association between cadmium concentration and serum SHBG levels was also observed. Stratification by menopausal status revealed stronger associations in early and late perimenopausal women.

Several hormones in the hypothalamic-pituitary-ovarian axis are markers of ovarian aging, including FSH and E_2 (Strauss and Barbieri, 2013). The progressive depletion of follicles and cessation of ovarian function during the menopausal transition lead to altered ovarian feedback in the hypothalamic-pituitary-ovarian axis, resulting in a reduction in E_2 and subsequent elevation in FSH (Strauss and Barbieri, 2013). The observed associations of heavy metals with FSH and E_2 in the present study, particularly in the early and late perimenopausal stages, suggested that heavy metals may influence ovarian aging. Previous studies have shown that lower E_2 in postmenopausal is associated with cardiovascular disease (Zhao et al., 2018), lower bone mineral density and osteoporosis (Ettinger et al., 1998), depression (Bromberger et al., 2010), and other conditions (Notelovitz et al., 2000). This finding is also in agreement with our recent report on the association between heavy metal exposures and earlier age at natural menopause in SWAN (Wang et al., 2021). Our findings are of public health importance, given the fact that the alterations in hormone profiles accelerate ovarian aging and may lead to reproductive, physiologic, psychological, and behavioral changes that shape women's midlife and future health (El Khoudary et al., 2019).

One major finding of this study was that urinary lead was associated with higher FSH and lower E_2 levels, suggesting its potential effect on accelerated ovarian aging. Evidence from epidemiologic studies supports that lead exposures may disrupt sex hormones in women. For example, three large population-based, cross-sectional studies found that blood lead

concentration was associated with elevated serum FSH levels among premenopausal women (Chen et al., 2016; Krieg and Feng, 2011; Lee et al., 2019); however, in other studies with smaller samples, associations between lead and FSH were not observed (Jackson et al., 2011; Pollack et al., 2011). No previous studies have reported a significant association between lead and E_2 (Chen et al., 2016; Jackson et al., 2011; Pollack et al., 2011). Although the biological pathways that may underlie the association of lead with FSH and E_2 are still largely unknown; findings from mechanistic studies suggest that lead may affect hormone profiles in several ways. For example, in an *in vitro* study of human ovarian granulosa cells, lead treatment led to reduced production of p450 aromatase messenger RNA and cytochrome p450 aromatase, which is required for the transformation of androgen to E_2 (Taupeau et al., 2003). Lead can also directly disrupt the hypothalamic-pituitary axis. A study of lead exposure in rats reported that long-term, low-dose treatment of lead significantly upregulated the production of gonadotropin-releasing hormone, which further triggers the secretion of FSH (Sokol et al., 2002). Additionally, lead has been suggested to increase concentrations of homocysteine, which play a role in the stimulation of FSH release (Schafer et al., 2005).

Our finding of a positive association between cadmium and SHBG levels is in line with the positive associations between blood cadmium and serum SHBG reported in 869 adult men in NHANES (Kresovich et al., 2015) and in a U.S. prospective cohort of 251 healthy premenopausal women (Kim et al., 2021). SHBG is a transporter of both E_2 and testosterone in human circulation, and its levels are important in the regulation of free and albumin bound levels of these hormones (Deswal et al., 2017). The observed positive association between cadmium and SHBG might indicate reduced bioavailable free and albumin-bound E_2 levels due to cadmium exposure. Alternatively, the observed association could be the result of competitive binding of cadmium to SHBG, which in turn stimulates SHBG production (Avvakumov et al., 2000). SHBG is produced primarily in liver. Cadmium can induce hepatic necroinflammation and lead to non-alcoholic fatty liver disease (NAFLD) and metabolic disorders (Souza-Arroyo et al., 2022). SHBG is considered a hepatokine and is involved in the development of NAFLD and metabolic impairments (Qu and Donnelly, 2020). The observed associations may also be due to the potential liver toxicity of cadmium among midlife women. We also observed urinary cadmium was positively associated with FSH in the early and late perimenopausal stages. In the National Health and Nutrition Examination Survey (NHANES) III, urinary cadmium was associated with higher serum FSH levels in premenopausal women (Gallagher et al., 2010). In contrast, a prospective study of 252 premenopausal women in the U.S. found a positive association between blood cadmium and serum FSH (Pollack et al., 2011). However, in a large cross-sectional study of postmenopausal women in South Korea, no significant association between urinary cadmium and serum FSH was found (Lee et al., 2019). Cadmium has been identified as an endocrine disruptor linked with alteration in ovarian cell morphology in human ovarian granulosa cell cultures (Paksy et al., 1997) and has been found to suppress the secretion of progesterone in animal models (Zhang et al., 2008), which in turn upregulates FSH levels (Ding et al., 2020).

Urinary mercury was inversely associated with E_2 levels in our study. The general population can be exposed to methylmercury (organic form) primarily through consumption

of seafood and to inorganic mercury through occlusal surfaces of teeth that are filled with mercury-containing amalgams (Mutter, 2011) or through skin lightening products (Park and Zheng, 2012). In humans, urinary mercury mainly reflects inorganic mercury (ATSDR, 1999). Epidemiologic studies examining the relationship between mercury and E_2 have been few, and none has reported a significant association (Jackson et al., 2011; Lee et al., 2019; Pollack et al., 2011). Our findings add a reference for an association of mercury, particularly the inorganic form, with reduced E_2 in midlife women. The potential impact of mercury exposure on E_2 is supported by several experimental animal studies, although the underlying mechanism is still unclear. In a study in rats, exposure to inorganic mercury vapor has been shown to reduce serum E_2 levels (Davis et al., 2001). Inorganic mercury has also been detected within ovarian follicles and in the corpora lutea of rats and golden hamsters after chronic exposure accompanied by decreased ovulation (Lamperti and Printz, 1974; Stadnicka, 1980).

Urinary arsenic was inversely associated with E_2 and positively associated with SHBG levels in early and late perimenopausal women. In a case-control study of women with primary ovarian insufficiency and healthy controls, urinary arsenic was positively associated with the odds of primary ovarian insufficiency and inversely associated with E_2 levels (Pan et al., 2020). Urinary arsenic was also associated with higher odds of infertility in another case-control study of infertile and pregnant women (Lei et al., 2015). In studies of rats, exposure to inorganic arsenic has been found to inhibit ovarian activities of 3β- and 17β-hydroxysteroid dehydrogenase, induce degeneration of luminal epithelial, stromal and myometrial cells of the rat uterus, and downregulate the estrogen receptor and estrogen-responsive genes in the estrogen signaling pathway, leading to reduced serum E_2 levels (Chatterjee and Chatterji, 2010; Chattopadhyay and Ghosh, 2010).

The primary strength of our study is its use of a large, prospective cohort with prospective and reliable measures of serum hormones, menopausal status, and covariates over 17 years of follow-up as women transitioned through menopause. To our knowledge, this is the first large prospective cohort study investigating the associations of heavy metal exposures with repeated measures of sex hormones in midlife women. Standard annualized measures also provided reliable estimates of hormone levels and ensure temporality between exposure and outcome.

Several limitations should be considered as well. First, all metal concentrations were determined in urine samples, and urinary concentrations may not reflect the total body burden from all forms of these metals or their exposure sources. Second, we relied on baseline measures of all metals to examine their associations with longitudinal measures of hormones. Existing evidence demonstrates long-term consistency in arsenic exposure, and urinary arsenic provides the most accurate exposure assessment (Navas-Acien et al., 2009). Urinary cadmium has been proposed as a biomarker for long-term exposure because cadmium is not rapidly excreted and has a half-life that ranges from years to decades (Vacchi-Suzzi et al., 2016). Urinary lead adjusted for urine dilution has been used as a biomarker of lead from bone resorption; bone lead is a biomarker of long-term exposure and has been suggested as an endogenous and primary source of lead in mid-and late life (Wang et al., 2019a). Nevertheless, reliance on one-time measurement of metal concentrations

might underestimate the associations between metals and hormones. Third, in SWAN, E_2 levels were assessed in the early follicular phase, which does not represent the peak E_2 levels in premenopausal women. Thus, the impact of metal exposures on E_2 could still be underestimated.

5. Conclusions

The results from this prospective cohort study demonstrate that environmental heavy metal exposures, including cadmium, mercury, and lead, may disturb circulating levels of E_2, FSH, and SHBG in midlife women. Given the known link between sex hormones and health endpoints, our findings provide important information about potential factors of environmental origins that may affect women's midlife health and healthy aging. Our findings also highlight the need to avoid exposure to heavy metals by reducing possible environmental sources and modifying lifestyle exposure to improve midlife and older women's health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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 also supported by the SWAN Repository (U01AG017719). This publication was supported in part by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 RR024131.

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.

Clinical Centers: University of Michigan, Ann Arbor – Carrie Karvonen-Gutierrez, PI 2021 – present, Siobán Harlow, PI 2011 – 2021, MaryFran Sowers, PI 1994-2011; Massachusetts General Hospital, Boston, MA – Joel Finkelstein, PI 1999 – present; Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Howard Kravitz, PI 2009 – present; Lynda Powell, PI 1994 – 2009; University of California, Davis/ Kaiser – Ellen Gold, PI; University of California, Los Angeles – Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004; and the University of Pittsburgh, Pittsburgh, PA – Karen Matthews, PI.

NIH Program Office: National Institute on Aging, Bethesda, MD – Rosaly Correa-de-Araujo 2020 – present; Chhanda Dutta 2016- 2020; Winifred Rossi 2012–2016; Sherry Sherman 1994 – 2012; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers.

Central Laboratory: *University of Michigan, Ann Arbor – Daniel McConnell* (Central Ligand Assay Satellite Services).

NIA Biorepository: *Rosaly Correa-de-Araujo 2019 – Present;* SWAN Repository: *University of Michigan, Ann Arbor – Siobán Harlow 2013 - 2018; Dan McConnell 2011 - 2013; MaryFran Sowers 2000 – 2011.*

Coordinating Center: University of Pittsburgh, Pittsburgh, PA – Maria Mori Brooks, PI 2012 - present; Kim Sutton-Tyrrell, PI 2001 – 2012; New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001.

Steering Committee: Susan Johnson, Current Chair

Chris Gallagher, Former Chair

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

Abbreviations:

BMI	body mass index
CV	coefficients of variation
E_2	estradiol
FSH	follicle-stimulating hormone
GM	geometric mean
GSD	geometric standard deviation
LOD	limit of detection
SHBG	sex hormone-binding globulin
SWAN	Study of Women's Health Across the Nation
SWAN-MPS	Study of Women's Health Across the Nation Multi-Pollutant Study

Reference

ATSDR, 1999. Toxicological profile for Mercury.

Avvakumov GV, Muller YA, Hammond GL, 2000. Steroid-binding Specificity of Human Sex Hormone-binding Globulin Is Influenced by Occupancy of a Zinc-binding Site. J. Biol. Chem 275, 25920–25925. 10.1074/JBC.M004484200 [PubMed: 10859323]

Benjamini Y, Hochberg Y, 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J. R. Stat. Soc. Ser. B 57, 289–300. 10.2307/2346101

Bobb JF, Valeri L, Claus Henn B, Christiani DC, Wright RO, Mazumdar M, Godleski JJ, Coull BA, 2015. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics 16, 493–508. 10.1093/biostatistics/kxu058 [PubMed: 25532525]

Bromberger JT, Schott LL, Kravitz HM, Sowers MF, Avis NE, Gold EB, Randolph JF, Matthews KA, 2010. Longitudinal Change in Reproductive Hormones and Depressive Symptoms Across the Menopausal Transition: Results From the Study of Women's Health Across the Nation (SWAN). Arch. Gen. Psychiatry 67, 598–607. 10.1001/ARCHGENPSYCHIATRY.2010.55 [PubMed: 20530009]

Chatterjee A, Chatterji U, 2010. Arsenic abrogates the estrogen-signaling pathway in the rat uterus. Reprod. Biol. Endocrinol 8, 1–11. 10.1186/1477-7827-8-80/FIGURES/7 [PubMed: 20051099]

Chattopadhyay S, Ghosh D, 2010. The involvement of hypophyseal-gonadal and hypophyseal-adrenal axes in arsenic-mediated ovarian and uterine toxicity: Modulation by hCG. J. Biochem. Mol. Toxicol 24, 29–41. 10.1002/JBT.20309 [PubMed: 20146381]

Chen C, Wang N, Zhai H, Nie X, Sun H, Han B, Li Q, Chen Y, Cheng J, Xia F, Zhao L, Zheng Y, Shen Z, Lu Y, 2016. Associations of blood lead levels with reproductive hormone levels in men and

postmenopausal women: Results from the SPECT-China Study. Sci. Rep 6, 1–9. 10.1038/srep37809 [PubMed: 28442746]

Davis BJ, Price HC, O'Connor RW, Fernando R, Rowland AS, Morgan DL, 2001. Mercury vapor and female reproductive toxicity. Toxicol. Sci 59, 291–296. 10.1093/toxsci/59.2.291 [PubMed: 11158722]

Deswal R, Yadav A, Dang AS, 2017. Sex hormone binding globulin - an important biomarker for predicting PCOS risk: A systematic review and meta-analysis. 10.1080/19396368.2017.1410591 64, 12–24. 10.1080/19396368.2017.1410591

Ding N, Harlow SD, Randolph JF, Loch-Caruso R, Park SK, 2020. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and their effects on the ovary. Hum. Reprod. Update 26, 724–752. 10.1093/humupd/dmaa018 [PubMed: 32476019]

El Khoudary SR, Greendale G, Crawford SL, Avis NE, Brooks MM, Thurston RC, Karvonen-Gutierrez C, Waetjen LE, Matthews K, 2019. The menopause transition and women's health at midlife: A progress report from the Study of Women's Health across the Nation (SWAN). Menopause 26, 1213–1227. 10.1097/GME.0000000000001424 [PubMed: 31568098]

El Khoudary SR, Thurston RC, 2018. Cardiovascular Implications of the Menopause Transition: Endogenous Sex Hormones and Vasomotor Symptoms. Obstet. Gynecol. Clin. North Am 45, 641–661. 10.1016/j.ogc.2018.07.006 [PubMed: 30401548]

Ettinger B, Pressman A, Sklarin P, Bauer DC, Cauley JA, Cummings Steven R, Cummings SR, Browner WS, Bauer D, Stone K, Ensrud K, Jamal S, 1998. Associations between Low Levels of Serum Estradiol, Bone Density, and Fractures among Elderly Women: The Study of Osteoporotic Fractures. J. Clin. Endocrinol. Metab 83, 2239–2243. 10.1210/JCEM.83.7.4708 [PubMed: 9661589]

Gallagher CM, Moonga BS, Kovach JS, 2010. Cadmium, follicle-stimulating hormone, and effects on bone in women age 42-60 years, NHANES III. Environ. Res 110, 105–111. 10.1016/j.envres.2009.09.012 [PubMed: 19875111]

Iavicoli I, Fontana L, Bergamaschi A, 2009. The Effects of Metals as Endocrine Disruptors. J. Toxicol. Environ. Heal. Part B 12, 206–223. 10.1080/10937400902902062

Jackson LW, Howards PP, Wactawski-Wende J, Schisterman EF, 2011. The association between cadmium, lead and mercury blood levels and reproductive hormones among healthy, premenopausal women. Hum. Reprod 26, 2887–2895. 10.1093/humrep/der250 [PubMed: 21778284]

Kim K, Pollack AZ, Nobles CJ, Sjaarda LA, Zolton JR, Radoc JG, Schisterman EF, Mumford SL, 2021. Associations between blood cadmium and endocrine features related to PCOS-phenotypes in healthy women of reproductive age: a prospective cohort study. Environ. Heal 2021 201 20, 1–8. 10.1186/S12940-021-00749-4

Kresovich JK, Argos M, Turyk ME, 2015. Associations of lead and cadmium with sex hormones in adult males. Environ. Res 142, 25–33. 10.1016/J.ENVRES.2015.05.026 [PubMed: 26093239]

Krieg EF, Feng HA, 2011. The relationships between blood lead levels and serum follicle stimulating hormone and luteinizing hormone in the National Health and Nutrition Examination Survey 1999-2002. Reprod. Toxicol 32, 277–285. 10.1016/j.reprotox.2011.05.012 [PubMed: 21669282]

Lamperti AA, Printz RH, 1974. Localization, Accumulation, and Toxic Effects of Mercuric Chloride on the Reproductive Axis of the Female Hamster12. Biol. Reprod 11, 180–186. 10.1095/biolreprod11.2.180 [PubMed: 4477028]

Lee TW, Kim DH, Ryu JY, 2019. The effects of exposure to lead, cadmium and mercury on follicle-stimulating hormone levels in men and postmenopausal women: Data from the Second Korean National Environmental Health Survey (2012-2014). Ann. Occup. Environ. Med 31. 10.35371/AOEM.2019.31.E21

Lei HL, Wei HJ, Ho HY, Liao KW, Chien LC, 2015. Relationship between risk factors for infertility in women and lead, cadmium, and arsenic blood levels: A cross-sectional study from Taiwan. BMC Public Health 15, 1220. 10.1186/s12889-015-2564-x [PubMed: 26653029]

Mutter J, 2011. Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission. J. Occup. Med. Toxicol 6, 2. 10.1186/1745-6673-6-2 [PubMed: 21232090]

Nagata C, Nagao Y, Shibuya C, Kashiki Y, Shimizu H, 2005. Urinary cadmium and serum levels of estrogens and androgens in postmenopausal Japanese women. Cancer Epidemiol. Biomarkers Prev 14, 705–708. 10.1158/1055-9965.EPI-04-0619 [PubMed: 15767353]

Navas-Acien A, Umans JG, Howard BV, Goessler W, Francesconi KA, Crainiceanu CM, Silbergeld EK, Guallar E, 2009. Urine Arsenic Concentrations and Species Excretion Patterns in American Indian Communities Over a 10-year Period: The Strong Heart Study. Environ. Health Perspect 117, 1428–1433. 10.1289/ehp.0800509 [PubMed: 19750109]

Neer RM, 2010. Bone loss across the menopausal transition. Ann. N. Y. Acad. Sci 1192, 66–71. 10.1111/j.1749-6632.2009.05233.x [PubMed: 20392219]

Notelovitz M, Lenihan JP, McDermott M, Kerber IJ, Nanavati N, Arce JC, 2000. Initial 17β-Estradiol dose for treating vasomotor symptoms. Obstet. Gynecol 95, 726–731. 10.1016/S0029-7844(99)00643-2 [PubMed: 10775738]

Paksy K, Rajczy K, Forgács Z, Lázár P, Bernard A, Gáti I, Kaáli GS, 1997. Effect of cadmium on morphology and steroidogenesis of cultured human ovarian granulosa cells. J. Appl. Toxicol 17, 321–327. 10.1002/(SICI)1099-1263(199709)17:5<321::AID-JAT443>3.0.CO;2-E [PubMed: 9339745]

Pan W, Ye X, Zhu Z, Li C, Zhou J, Liu J, 2020. A case-control study of arsenic exposure with the risk of primary ovarian insufficiency in women. Environ. Sci. Pollut. Res 27, 25220–25229. 10.1007/S11356-020-08806-0/TABLES/4

Park J-D, Zheng W, 2012. Human exposure and health effects of inorganic and elemental mercury. J. Prev. Med. Public Health 45, 344–52. 10.3961/jpmph.2012.45.6.344 [PubMed: 23230464]

Park SK, Harlow SD, Zheng H, Karvonen-Gutierrez C, Thurston RC, Ruppert K, Janssen I, Randolph JF, 2017. Association between changes in oestradiol and follicle-stimulating hormone levels during the menopausal transition and risk of diabetes. Diabet. Med 34, 531–538. 10.1111/dme.13301 [PubMed: 27973745]

Pollack AZ, Schisterman EF, Goldman LR, Mumford SL, Albert PS, Jones RL, Wactawski-Wende J, 2011. Cadmium, Lead, and Mercury in Relation to Reproductive Hormones and Anovulation in Premenopausal Women. Environ. Health Perspect 119, 1156–1161. 10.1289/ehp.1003284 [PubMed: 21543284]

Qu X, Donnelly R, 2020. Sex Hormone-Binding Globulin (SHBG) as an Early Biomarker and Therapeutic Target in Polycystic Ovary Syndrome. Int. J. Mol. Sci 2020, Vol. 21, Page 8191 21, 8191. 10.3390/IJMS21218191 [PubMed: 33139661]

Randolph JF, Sowers M, Gold EB, Mohr BA, Luborsky J, Santoro N, McConnell DS, Finkelstein JS, Korenman SG, Matthews KA, Sternfeld B, Lasley BL, 2003. Reproductive Hormones in the Early Menopausal Transition: Relationship to Ethnicity, Body Size, and Menopausal Status. J. Clin. Endocrinol. Metab 88, 1516–1522. 10.1210/JC.2002-020777 [PubMed: 12679432]

Randolph JF, Zheng H, Sowers MR, Crandall C, Crawford S, Gold EB, Vuga M, 2011. Change in Follicle-Stimulating Hormone and Estradiol Across the Menopausal Transition: Effect of Age at the Final Menstrual Period. J. Clin. Endocrinol. Metab 96, 746–754. 10.1210/jc.2010-1746 [PubMed: 21159842]

Schafer JH, Glass TA, Bressler J, Todd AC, Schwartz BS, 2005. Blood Lead Is a Predictor of Homocysteine Levels in a Population-Based Study of Older Adults. Environ. Health Perspect 113, 31–35. 10.1289/ehp.7369 [PubMed: 15626644]

Sokol RZ, Wang S, Wan Y-JY, Stanczyk FZ, Gentzschein E, Chapin RE, 2002. Long-term, low-dose lead exposure alters the gonadotropin-releasing hormone system in the male rat. Environ. Health Perspect 110, 871–874. 10.1289/ehp.02110871

Souza-Arroyo V, Fabián JJ, Bucio-Ortiz L, Miranda-Labra RU, Gomez-Quiroz LE, Gutiérrez-Ruiz MC, 2022. The mechanism of the cadmium-induced toxicity and cellular response in the liver. Toxicology 480, 153339. 10.1016/J.TOX.2022.153339 [PubMed: 36167199]

Sowers MF, Crawford SL, Sternfeld B, Morganstein D, Gold EB, Greendale GA, Evans D, Neer R, Matthews K, Sherman S, Lo A, Weiss G, Kelsey J, 2000. SWAN: a multi-center, multi-ethnic, community-based cohort study of women and the menopausal transition, in: Lobo RA, Kelsey J, Marcus R (Eds.), Menopause : Biology and Pathobiology. Academic Press, pp. 175–188.

Sowers MR, Randolph JF, Zheng H, Jannausch M, McConnell D, Kardia SR, Crandall CJ, Nan B, 2011. Genetic polymorphisms and obesity influence estradiol decline during the menopause. Clin. Endocrinol. (Oxf) 74, 618–623. 10.1111/j.1365-2265.2010.03968.x [PubMed: 21198743]

Stadnicka A, 1980. Localization of mercury in the rat ovary after oral administration of mercuric chloride. Acta Histochem. 67, 227–233. 10.1016/S0065-1281(80)80026-2 [PubMed: 6452017]

Strauss JF, Barbieri RL, 2013. Yen and Jaffe's Reproductive Endocrinology: Seventh Edition, Yen and Jaffe's Reproductive Endocrinology: Seventh Edition. Elsevier Inc. 10.1016/C2011-0-04643-4

Sutton-Tyrrell K, Wildman RP, Matthews KA, Chae C, Lasley BL, Brockwell S, Pasternak RC, Lloyd-Jones D, Sowers MF, Torréns JI, 2005. Sex hormone-binding globulin and the free androgen index are related to cardiovascular risk factors in multiethnic premenopausal and perimenopausal women enrolled in the study of women across the nation (SWAN). Circulation 111, 1242–1249. 10.1161/01.CIR.0000157697.54255.CE [PubMed: 15769764]

Taupeau C, Poupon J, Treton D, Brosse A, Richard Y, Machelon V, 2003. Lead Reduces Messenger RNA and Protein Levels of Cytochrome P450 Aromatase and Estrogen Receptor β in Human Ovarian Granulosa Cells1. Biol. Reprod 68, 1982–1988. 10.1095/biolreprod.102.009894 [PubMed: 12606482]

Tian M, Wang YX, Wang X, Wang H, Liu L, Zhang J, Nan B, Shen H, Huang Q, 2021. Environmental doses of arsenic exposure are associated with increased reproductive-age male urinary hormone excretion and in vitro Leydig cell steroidogenesis. J. Hazard. Mater 408, 124904. 10.1016/J.JHAZMAT.2020.124904 [PubMed: 33385727]

Vacchi-Suzzi C, Kruse D, Harrington J, Levine K, Meliker JR, 2016. Is Urinary Cadmium a Biomarker of Long-term Exposure in Humans? A Review. Curr. Environ. Heal. reports 3, 450–458. 10.1007/s40572-016-0107-y

Wang X, Ding N, Harlow SD, Randolph JF, Mukherjee B, Gold EB, Park SK, 2021. Urinary metals and metal mixtures and timing of natural menopause in midlife women: The Study of Women's Health Across the Nation. Environ. Int 157, 106781. 10.1016/J.ENVINT.2021.106781 [PubMed: 34311223]

Wang X, Kim D, Tucker KL, Weisskopf MG, Sparrow D, Hu H, Park SK, 2019a. Effect of Dietary Sodium and Potassium Intake on the Mobilization of Bone Lead among Middle-Aged and Older Men: The Veterans Affairs Normative Aging Study. Nutrients 11, 2750. 10.3390/nu11112750 [PubMed: 31766133]

Wang X, Mukherjee B, Batterman S, Harlow SD, Park SK, 2019b. Urinary metals and metal mixtures in midlife women: The Study of Women's Health Across the Nation (SWAN). Int. J. Hyg. Environ. Health 222, 778–789. 10.1016/J.IJHEH.2019.05.002 [PubMed: 31103473]

Wang X, Mukherjee B, Karvonen-Gutierrez CA, Herman WH, Batterman S, Harlow SD, Park SK, 2020. Urinary metal mixtures and longitudinal changes in glucose homeostasis: The Study of Women's Health Across the Nation (SWAN). Environ. Int 145, 106109. 10.1016/j.envint.2020.106109 [PubMed: 32927284]

Wang X, Mukherjee B, Park SK, 2018. Associations of cumulative exposure to heavy metal mixtures with obesity and its comorbidities among U.S. adults in NHANES 2003–2014. Environ. Int 121, 683–694. 10.1016/j.envint.2018.09.035 [PubMed: 30316184]

Wildman RP, Tepper PG, Crawford S, Finkelstein JS, Sutton-Tyrrell K, Thurston RC, Santoro N, Sternfeld B, Greendale GA, 2012. Do Changes in Sex Steroid Hormones Precede or Follow Increases in Body Weight during the Menopause Transition? Results from The Study of Women's Health Across the Nation. J. Clin. Endocrinol. Metab 97, E1695–E1704. 10.1210/jc.2012-1614 [PubMed: 22723312]

Zhang W, Pang F, Huang Y, Yan P, Lin W, 2008. Cadmium exerts toxic effects on ovarian steroid hormone release in rats. Toxicol. Lett 182, 18–23. 10.1016/j.toxlet.2008.07.016 [PubMed: 18708132]

Zhao D, Guallar E, Ouyang P, Subramanya V, Vaidya D, Ndumele CE, Lima JA, Allison MA, Shah SJ, Bertoni AG, Budoff MJ, Post WS, Michos ED, 2018. Endogenous Sex Hormones and Incident Cardiovascular Disease in Post-Menopausal Women. J. Am. Coll. Cardiol 71, 2555–2566. 10.1016/J.JACC.2018.01.083 [PubMed: 29852978]

Zheng G, Wang Lijun, Guo Z, Sun L, Wang Lingling, Wang C, Zuo Z, Qiu H, 2015. Association of Serum Heavy Metals and Trace Element Concentrations with Reproductive Hormone Levels and

Polycystic Ovary Syndrome in a Chinese Population. Biol. Trace Elem. Res 167, 1–10. 10.1007/s12011-015-0294-7 [PubMed: 25758722]

Highlights

- Heavy metal exposures disrupted sex hormone levels in midlife women.
- Lead was associated with lower E_2 and higher FSH levels.
- Mercury was associated with lower E_2 levels.
- Cadmium was associated with higher SHBG levels.

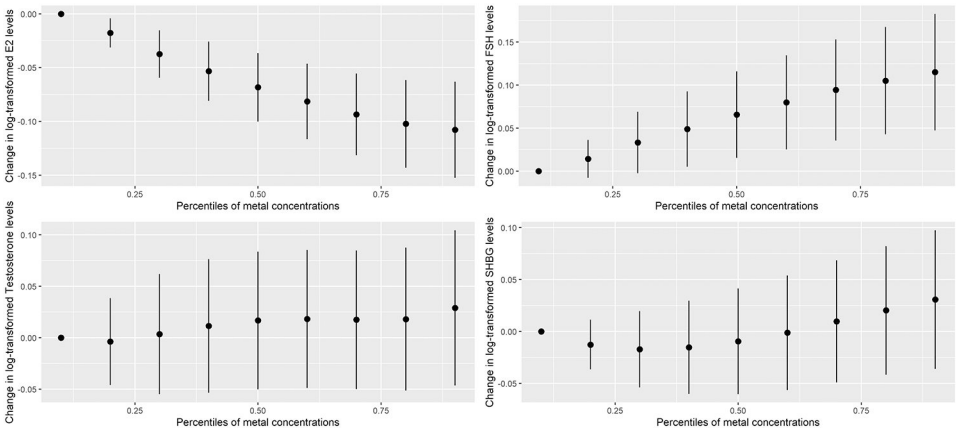


Figure 1.

Associations between heavy metal concentrations and sex hormone levels, estimated by Bayesian kernel machine regression. The plots show the estimated changes and 95% confidence intervals (95% CIs) in log-transformed hormone levels, comparing concentrations of all metals simultaneously at different percentiles of their distributions to all metals at their 10th percentiles. The models were adjusted for age, race/ethnicity, study site, urinary creatinine (log-transformed), education, baseline body mass index, smoking, parity, menopausal status, stress, dietary intake of fat, alcohol drinking, and physical activity.

Table 1.

Descriptive characteristics at the SWAN-MPS baseline (n=1,355).

Characteristics	Mean (SD), GM (GSD), or n (%)
Age, mean (SD), years	49.3 (2.6)
Race/ethnicity, n (%)	
White	677 (50.0)
African American	295 (21.8)
Chinese	177 (13.1)
Japanese	206 (15.2)
Study site, n (%)	
Southeast Michigan	248 (18.3)
Boston	226 (16.7)
Oakland	302 (22.3)
Los Angeles	354 (26.1)
Pittsburgh	225 (16.6)
Education, n (%)	
High school or less	245 (18.2)
Some College	434 (32.2)
College	333 (24.7)
Post-college	336 (24.9)
Smoking status, n (%)	
Never	854 (63.0)
Former	359 (26.5)
Current	142 (10.5)
Parity, n (%)	
Nulliparous	262 (19.3)
Parous	1093 (80.7)
Menopausal status, n (%)	
Premenopausal	166 (12.3)
Early perimenopausal	749 (55.3)
Late perimenopausal	125 (9.2)
Postmenopausal	302 (22.3)
Unknown[a]	13 (1.0)
Body mass index, mean (SD), kg/m^2	27.95 (7.3)
Estradiol, GM (GSD), pg/mL	34.5 (2.7)
Follicle-stimulating hormone, GM (GSD), mIU/mL	34.5 (2.8)
Testosterone, GM (GSD), ng/dL	32.3 (1.7)
Sex hormone-binding globulin, GM (GSD), nM	35.0 (2.0)

Note: SD: standard deviation; GM: geometric mean; GSD: geometric standard deviation.

[a]Menopausal status unknown due to hysterectomy or hormone therapy.

Table 2.

Percent changes (95% CIs) in serum levels of estradiol (E_2) per doubling increase in urinary metal concentrations.

Metals	Base model[a]	Full Model[b]
	Percent changes (95% CI)	Percent changes (95% CI)
Arsenic	1.3 (−2.8, 0.3)	−0.8 (−2.2, 0.5)
Cadmium	−3.5 (−5.5, −1.5)	−1.5 (−3.3, 0.3)
Mercury	−3.2 (−5.3, −1.1)	−2.2 (−4.0, −0.3)
Lead	−6.6 (−8.8, −4.3)	−3.6 (−5.7, −1.6)

[a]Base model: adjustment for age, race/ethnicity, study site, and urinary creatinine (log-transformed).

[b]Full model: base model with additional adjustment for education, baseline body mass index, smoking, parity, follow-up time, and time-varying menopausal status.

Table 3.

Percent changes (95% CIs) in serum levels of follicle stimulating hormone (FSH) per doubling increase in urinary metal concentrations.

Metals	Base model[a]	Full Model[b]
	Percent changes (95% CI)	Percent changes (95% CI)
Arsenic	0.1 (−1.8, 2.1)	−0.9 (−2.4, 0.6)
Cadmium	5.3 (2.7, 8.0)	1.8 (−0.3, 4.0)
Mercury	3.4 (0.7, 6.2)	0.8 (−1.3, 2.9)
Lead	7.8 (4.7, 11.1)	3.4 (0.9, 5.9)

[a]Base model: adjustment for age, race/ethnicity, study site, and urinary creatinine (log-transformed).

[b]Full model: base model with additional adjustment for education, baseline body mass index, smoking, parity, follow-up time, and time-varying menopausal status.

Table 4.

Percent changes (95% CIs) in serum levels of sex hormone-binding globulin (SHBG) per doubling increase in urinary metal concentrations.

Metals	Base model[a]	Full Model[b]
	Percent changes (95% CI)	Percent changes (95% CI)
Arsenic	2.0 (0.3, 3.8)	1.5 (−0.1, 3.2)
Cadmium	4.8 (2.4, 7.2)	3.6 (1.3, 5.9)
Mercury	3.9 (1.5, 6.4)	1.4 (−0.8, 3.7)
Lead	2.5 (−0.2, 5.3)	1.5 (−1.1, 4.1)

[a]Base model: adjustment for age, race/ethnicity, study site, and urinary creatinine (log-transformed).

[b]Full model: base model with additional adjustment for education, baseline body mass index, smoking, parity, follow-up time, and time-varying menopausal status.