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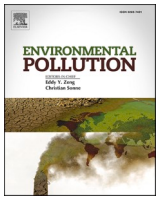

Exposure to heavy metals and hormone levels in midlife women: The Study of Women's Health Across the Nation (SWAN)☆

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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 1355 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% (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.

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

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 Substudy.

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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). 3302 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 1400 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 1355 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 Fig. S1. We censored observations ($n = 2244$) 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 1355 women representing 10,645 observations was used for FSH and SHBG analyses, 9754 for E_2 analyses, and 7745 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, post-menopausal, and unknown due to hysterectomy or hormone therapy), 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 post-menopausal 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, 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, Fig. 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

Table 1
Descriptive characteristics at the SWAN-MPS baseline (n = 1355).

Characteristics	Mean (SD), GM (GSD), or n (%)
Age, mean (SD), years	49.3 (2.6)
Race/ethnicity, n (%)	
White	677 (50.0)
Black	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.

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 (Fig. S3). Similarly, a positive association was observed between lead and FSH (Fig. S4) and between cadmium and SHBG (Fig. S5). No associations between metals and testosterone were observed (Fig. S6). Fig. 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 post-menopausal) (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).

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.

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

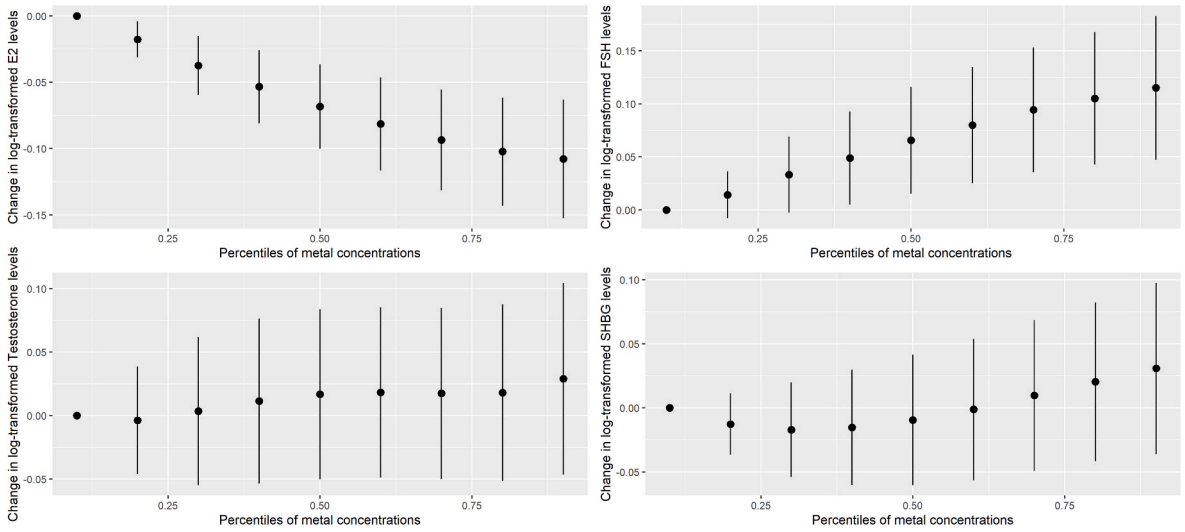

Fig. 1. Associations between heavy metal concentrations and sex hormone levels, estimated by Bayesian kernel machine regression. The plots show the estimated changes and 95% confidence intervals (95% CIs) in log-transformed hormone levels, comparing concentrations of all metals simultaneously at different 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.

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 lightning 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.

Author contributions

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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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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References

ATSDR, 1999. Toxicological Profile for Mercury.

Avvakumov, G.V., Muller, Y.A., Hammond, G.L., 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. https://doi.org/10.1074/JBC.M004484200.

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. https://doi.org/10.2307/2346101.

Bobb, J.F., Valeri, L., Claus Henn, B., Christiani, D.C., Wright, R.O., Mazumdar, M., Godleski, J.J., Coull, B.A., 2015. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics 16, 493–508. https://doi.org/10.1093/biostatistics/kxu058.

Bromberger, J.T., Schott, L.L., Kravitz, H.M., Sowers, M.F., Avis, N.E., Gold, E.B., Randolph, J.F., Matthews, K.A., 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. Psychiatr. 67, 598–607. https://doi.org/10.1001/ARCHGENPSYCHIATRY.2010.55.

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

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. https://doi.org/10.1002/JBT.20309.

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. https://doi.org/10.1038/srep37809.

Davis, B.J., Price, H.C., O'Connor, R.W., Fernando, R., Rowland, A.S., Morgan, D.L., 2001. Mercury vapor and female reproductive toxicity. Toxicol. Sci. 59, 291–296. https://doi.org/10.1093/toxsci/59.2.291.

Deswal, R., Yadav, A., Dang, A.S., 2017. Sex Hormone Binding Globulin - an Important Biomarker for Predicting PCOS Risk: A Systematic Review and Meta-Analysis. https://doi.org/10.1080/19396368.2017.1410591, 10.1080/19396368.2017.1410591 64, 12–24.

Ding, N., Harlow, S.D., Randolph, J.F., Loch-Caruso, R., Park, S.K., 2020. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and their effects on the ovary. Hum. Reprod. Update 26, 724–752. https://doi.org/10.1093/humupd/dmaa018.

Dyer, C.A., 2007. Heavy metals as endocrine-disrupting chemicals. In: Endocrine-Disrupting Chemicals. Humana Press, pp. 111–133. https://doi.org/10.1007/1-59745-107-x_5.

El Khoudary, S.R., Greendale, G., Crawford, S.L., Avis, N.E., Brooks, M.M., Thurston, R. C., Karvonen-Gutierrez, C., Waetjen, L.E., 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. https://doi.org/10.1097/GME.0000000000001424.

El Khoudary, S.R., Thurston, R.C., 2018. Cardiovascular implications of the menopause transition: endogenous sex hormones and vasomotor symptoms. Obstet. Gynecol. Clin. N. Am. 45, 641–661. https://doi.org/10.1016/j.ogc.2018.07.006.

Ettinger, B., Pressman, A., Sklarin, P., Bauer, D.C., Cauley, J.A., Cummings, Steven R., Cummings, S.R., Browner, W.S., 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. https://doi.org/10.1210/JCEM.83.7.4708.

Gallagher, C.M., Moonga, B.S., Kovach, J.S., 2010. Cadmium, follicle-stimulating hormone, and effects on bone in women age 42-60 years, NHANES III. Environ. Res. 110, 105–111. https://doi.org/10.1016/j.envres.2009.09.012.

Iavicoli, I., Fontana, L., Bergamaschi, A., 2009. The effects of metals as endocrine disruptors. J. Toxicol. Environ. Health Part B 12, 206–223. https://doi.org/10.1080/10937400902902062.

Jackson, L.W., Howards, P.P., Wactawski-Wende, J., Schisterman, E.F., 2011. The association between cadmium, lead and mercury blood levels and reproductive hormones among healthy, premenopausal women. Hum. Reprod. 26, 2887–2895. https://doi.org/10.1093/humrep/der250.

Kim, K., Pollack, A.Z., Nobles, C.J., Sjaarda, L.A., Zolton, J.R., Radoc, J.G., Schisterman, E.F., Mumford, S.L., 2021. Associations between blood cadmium and endocrine features related to PCOS-phenotypes in healthy women of reproductive age: a prospective cohort study. Environ. Health 20, 1–8. https://doi.org/10.1186/S12940-021-00749-4, 2021 201.

Kresovich, J.K., Argos, M., Turyk, M.E., 2015. Associations of lead and cadmium with sex hormones in adult males. Environ. Res. 142, 25–33. https://doi.org/10.1016/J.ENVRES.2015.05.026.

Krieg, E.F., Feng, H.A., 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. https://doi.org/10.1016/j.reprotox.2011.05.012.

Lamperti, A.A., Printz, R.H., 1974. Localization, accumulation, and toxic effects of mercuric chloride on the reproductive Axis of the female Hamster12. Biol. Reprod. 11, 180–186. https://doi.org/10.1095/biolreprod11.2.180.

Lee, T.W., Kim, D.H., Ryu, J.Y., 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 https://doi.org/10.35371/AOEM.2019.31.E21.

Lei, H.L., Wei, H.J., Ho, H.Y., Liao, K.W., Chien, L.C., 2015. Relationship between risk factors for infertility in women and lead, cadmium, and arsenic blood levels: a cross-sectional study from Taiwan. BMC Publ. Health 15, 1220. https://doi.org/10.1186/s12889-015-2564-x.

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. https://doi.org/10.1186/1745-6673-6-2.

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. https://doi.org/10.1158/1055-9965.EPI-04-0619.

Navas-Acien, A., Umans, J.G., Howard, B.V., Goessler, W., Francesconi, K.A., Crainiceanu, C.M., Silbergeld, E.K., 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. https://doi.org/10.1289/ehp.0800509.

Neer, R.M., 2010. Bone loss across the menopausal transition. Ann. N. Y. Acad. Sci. 1192, 66–71. https://doi.org/10.1111/j.1749-6632.2009.05233.x.

Notelovitz, M., Lenihan, J.P., McDermott, M., Kerber, I.J., Nanavati, N., Arce, J.C., 2000. Initial 17β-Estradiol dose for treating vasomotor symptoms. Obstet. Gynecol. 95, 726–731. https://doi.org/10.1016/S0029-7844(99)00643-2.

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

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. https://doi.org/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, 344–352. https://doi.org/10.3961/jpmph.2012.45.6.344.

Park, S.K., Harlow, S.D., Zheng, H., Karvonen-Gutierrez, C., Thurston, R.C., Ruppert, K., Janssen, I., Randolph, J.F., 2017. Association between changes in oestradiol and follicle-stimulating hormone levels during the menopausal transition and risk of diabetes. Diabet. Med. 34, 531–538. https://doi.org/10.1111/dme.13301.

Pollack, A.Z., Schisterman, E.F., Goldman, L.R., Mumford, S.L., Albert, P.S., Jones, R.L., Wactawski-Wende, J., 2011. Cadmium, lead, and mercury in relation to reproductive hormones and anovulation in premenopausal women. Environ. Health Perspect. 119, 1156–1161. https://doi.org/10.1289/ehp.1003284.

Qu, X., Donnelly, R., 2020. Sex hormone-binding globulin (SHBG) as an early biomarker and therapeutic target in polycystic ovary syndrome, 2020 Int. J. Mol. Sci. 21, 8191. https://doi.org/10.3390/IJMS21218191. Page 8191 21.

Randolph, J.F., Sowers, M., Gold, E.B., Mohr, B.A., Luborsky, J., Santoro, N., McConnell, D.S., Finkelstein, J.S., Korenman, S.G., Matthews, K.A., Sternfeld, B., Lasley, B.L., 2003. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. J. Clin. Endocrinol. Metab. 88, 1516–1522. https://doi.org/10.1210/JC.2002-020777.

Randolph, J.F., Zheng, H., Sowers, M.R., Crandall, C., Crawford, S., Gold, E.B., 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. https://doi.org/10.1210/jc.2010-1746.

Schafer, J.H., Glass, T.A., Bressler, J., Todd, A.C., Schwartz, B.S., 2005. Blood lead is a predictor of homocysteine levels in a population-based study of older adults. Environ. Health Perspect. 113, 31–35. https://doi.org/10.1289/ehp.7369.

Sokol, R.Z., Wang, S., Wan, Y.-J.Y., Stanczyk, F.Z., Gentzschein, E., Chapin, R.E., 2002. Long-term, low-dose lead exposure alters the gonadotropin-releasing hormone system in the male rat. Environ. Health Perspect. 110, 871–874. https://doi.org/10.1289/ehp.02110871.

Souza-Arroyo, V., Fabián, J.J., Bucio-Ortiz, L., Miranda-Labra, R.U., Gomez-Quiroz, L.E., Gutiérrez-Ruiz, M.C., 2022. The mechanism of the cadmium-induced toxicity and cellular response in the liver. Toxicology 480, 153339. https://doi.org/10.1016/J.TOX.2022.153339.

Sowers, M.F., Crawford, S.L., Sternfeld, B., Morganstein, D., Gold, E.B., Greendale, G.A., 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, R.A., Kelsey, J., Marcus, R. (Eds.), Menopause : Biology and Pathobiology. Academic Press, pp. 175–188.

Sowers, M.R., Randolph, J.F., Zheng, H., Jannausch, M., McConnell, D., Kardia, S.R., Crandall, C.J., Nan, B., 2011. Genetic polymorphisms and obesity influence estradiol decline during the menopause. Clin. Endocrinol. 74, 618–623. https://doi.org/10.1111/j.1365-2265.2010.03968.x.

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

Strauss, J.F., Barbieri, R.L., 2013. Yen and Jaffe's Reproductive Endocrinology: Seventh Edition, seventh ed. In: Yen and Jaffe's Reproductive Endocrinology. Elsevier Inc. https://doi.org/10.1016/C2011-0-04643-4.

Sun, H.J., Xiang, P., Luo, J., Hong, H., Lin, H., Li, H.B., Ma, L.Q., 2016. Mechanisms of arsenic disruption on gonadal, adrenal and thyroid endocrine systems in humans: A review. Environ. Int. https://doi.org/10.1016/j.envint.2016.07.020.

Sutton-Tyrrell, K., Wildman, R.P., Matthews, K.A., Chae, C., Lasley, B.L., Brockwell, S., Pasternak, R.C., Lloyd-Jones, D., Sowers, M.F., Torréns, J.I., 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. https://doi.org/10.1161/01.CIR.0000157697.54255.CE.

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. https://doi.org/10.1095/biolreprod.102.009894.

Tian, M., Wang, Y.X., 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 https://doi.org/10.1016/J.JHAZMAT.2020.124904.

Vacchi-Suzzi, C., Kruse, D., Harrington, J., Levine, K., Meliker, J.R., 2016. Is urinary cadmium a biomarker of long-term exposure in humans? A review. Curr. Environ. Heal. reports 3, 450–458. https://doi.org/10.1007/s40572-016-0107-y.

Wang, X., Ding, N., Harlow, S.D., Randolph, J.F., Mukherjee, B., Gold, E.B., Park, S.K., 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 https://doi.org/10.1016/J.ENVINT.2021.106781.

Wang, X., Kim, D., Tucker, K.L., Weisskopf, M.G., Sparrow, D., Hu, H., Park, S.K., 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. https://doi.org/10.3390/nu11112750.

Wang, X., Mukherjee, B., Batterman, S., Harlow, S.D., Park, S.K., 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. https://doi.org/10.1016/J.IJHEH.2019.05.002.

Wang, X., Mukherjee, B., Karvonen-Gutierrez, C.A., Herman, W.H., Batterman, S., Harlow, S.D., Park, S.K., 2020. Urinary metal mixtures and longitudinal changes in glucose homeostasis: the Study of Women's Health across the Nation (SWAN). Environ. Int. 145, 106109 https://doi.org/10.1016/j.envint.2020.106109.

Wang, X., Mukherjee, B., Park, S.K., 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. https://doi.org/10.1016/j.envint.2018.09.035.

Wildman, R.P., Tepper, P.G., Crawford, S., Finkelstein, J.S., Sutton-Tyrrell, K., Thurston, R.C., Santoro, N., Sternfeld, B., Greendale, G.A., 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. https://doi.org/10.1210/jc.2012-1614.

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. https://doi.org/10.1016/j.toxlet.2008.07.016.

Zhao, D., Guallar, E., Ouyang, P., Subramanya, V., Vaidya, D., Ndumele, C.E., Lima, J.A., Allison, M.A., Shah, S.J., Bertoni, A.G., Budoff, M.J., Post, W.S., Michos, E.D., 2018. Endogenous sex hormones and incident cardiovascular disease in post-menopausal women. J. Am. Coll. Cardiol. 71, 2555–2566. https://doi.org/10.1016/J.JACC.2018.01.083.

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. https://doi.org/10.1007/s12011-015-0294-7.