The Association Between Heavy Metals Exposure and Sex Hormones: a Systematic Review on Current Evidence

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Abstract

The general population is voluntarily or unintentionally exposed to heavy metals through ingestion of food, polluted water, or contact with soil, dust, or polluted air. A number of metals are considered as endocrine disruptors and can alter the level of reproductive hormones. This study aims to systematically review the epidemiological studies on the association between heavy metals exposure and sex hormones level. We conducted a systematic search from available databases, including PubMed, Clarivate Web of Science, Scopus, Google Scholar, and Cochrane Collaboration, until April 2021. The relevant studies were selected, and two reviewers conducted the quality assessment. Then, data were extracted based on the inclusion criteria. We identified nine articles related to the association between heavy metals exposure and sex hormones level. We summarized the relevant information. Due to the diversity of metals and the variety of sex hormones, the effect of exposure on hormones level was not clear; however in most studies, at least for one metal, a significant association (inverse or positive) was observed between metals exposure and hormones level. Heavy metals exposure may potentially alter sex hormone levels; however, further research is needed to evaluate the impact of this association.

Keywords Heavy metal · Sex hormones · Exposure · Male · Female

Introduction

Puberty is the process by which adolescents reach sexual maturity and are able to reproduce. In fact, a period of physical growth involves increasing height velocity and weight and psychological development, including cognitive and social maturity [8, 46]. The results of several studies have shown that various factors, including dietary changes [12, 52], obesity [5, 23], and various types of stress [30], lead to premature puberty. However, there is ample evidence that

environmental factors also play a role in the onset of precocious puberty and sexual maturity [30, 31]. Earlier puberty may increase the risk of metabolic syndrome, type 2 diabetes, certain types of cancer, and cardiovascular disease [2, 18, 21, 28]. Humans' exposure to endocrine-disrupting chemicals (EDCs), including heavy metals, has a potential effect on synthesis, metabolism, and transport of hormones and results showed that the alter the time of pubertal [45]. The hypothalamic-pituitary–gonadal axis (HPG), gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone regulate sex hormones. In addition, SHBG (sex hormone-binding globulin) is a plasma glycoprotein that carries both testosterone and estradiol throughout the body. This substance is synthesized in the liver, and its plasma level plays an important role in regulating the level of free and bound albumin of sex hormones [27, 39]. Exposure to heavy metals may lead to improper regulation of any of these processes and thus affect sex hormone levels. Ingestion of food, water, dietary supplements, inhalation, and dermal adsorption are the main routes of heavy metals exposure [33, 44]. Exposure to heavy metals can affect infants, children, adolescents, and adults. Hormonal activities begin in utero development, so the effects of exposure to

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heavy metals may persist long after birth, leading to effects observed in other stages of life [16, 48]. Likewise, exposure to heavy metals during adolescence can also profoundly affect behavior, brain maturity, and reproductive development by causing dramatic hormonal changes during puberty [10, 42, 46, 47]. Exposure to heavy metals in adulthood can also affect sex hormone levels. Inorganic metals including zinc (Zn), iron (Fe), nickel (Ni), cobalt (Co), copper (Cu), molybdenum (Mo), magnesium (Mg), manganese (Mn, and selenium (Se are essential for human health; however, these metals can be toxic in high concentrations. On the other hand, some metals like as lead (Pb), arsenic (As), mercury (Hg), and cadmium (Cd) are toxic even at low concentrations [44]. Due to the adverse effects of heavy metals on reproductive, various studies have been conducted to evaluate the possible association between heavy metals exposure and sex hormones. For instance, in two studies of Telisman et al. that investigate the association between heavy metal exposure and sex hormones in men, results showed that there is a synergistic effect between cadmium and lead on serum testosterone levels in both occupational and non-occupational populations [49, 50]. Some other studies on both males and females reported a positive association between Cd exposure and testosterone level [3, 22, 36]. These findings are inconsistent with other studies that reported no association between cadmium and sex hormones [36]. Some other studies reported that Pb exposure affected pubertal development in girls [14, 15, 19]. Denham et al. observed that Hg levels were associated with earlier menarche [15], while obtained results from other studies revealed that Hg concentration was associated with increased estradiol levels in adults [1]. A few studies recently found a relationship between some metals like Cu, Mn, and Mo and adverse effects on reproduction in males [20, 34, 50].

Due to the conflicting evidence, various types of heavy metals, and the diversity of the sample population used, further research is needed on the role of heavy metals in sex hormone disruption. This current work aims to systematically review the human studies conducted to evaluate the relationship between heavy metals and sex hormones.

Material and Methods

Search Strategy

We conducted a systematic search on PubMed, Clarivate Web of Science, Scopus, Google Scholar, and Cochrane Collaboration for original research published until April 2021, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [37]. All epidemiological studies in males and females written in the English language were considered. Studies have been included in this systematic review article that has examined the association between exposure to one or more heavy metals and sex hormones in men and females. Sex hormones include sex hormone-binding globulin (SHBG), testosterone (T), free testosterone (FT), free androgen index (FAI), follicle-stimulating hormone (FSH), estradiol (E2), free estradiol, and luteinizing hormone (LH),these keywords are combined with keywords related to heavy metals.

We used the following keywords for founding relevant original articles: "Heavy metals" OR "Metals, Heavy" (MeSH) OR "Cadmium" (MeSH) OR "Lead" (MeSH) OR "Mercury" (MeSH) OR "Arsenic" (MeSH). We also used "Progesterone" (MeSH) OR "Testosterone" (MeSH) OR "Adrenal steroid" OR "steroid hormones"(MeSH) OR "Sex Hormone" OR "Estradiol" (MeSH) OR "steroid hormones" OR "androstenedione glucuronide" OR "Sex-hormone Binding Globulin (SHBG)" OR "Luteinizing hormone (LH)" These keywords are combined with the former keywords series using the Boolean operator "AND." We restricted PubMed search to human studies in English. This search line was used in other databases (Scopus, ISI,..). Two independent reviewers evaluated the final list of studies. We removed articles if they were duplicate, were animal studies, had irrelevant study design (case report, review, meta-analyses), and had irrelevant exposure, or irrelevant outcome. Same as in previous studies [25, 26], we assessed the qualification of articles using the STROBE checklist. Two independent reviewers rated each article, and the final score was reported as averaged (see Table 1). Some details include STROBE mean score, first author's name, publication year, country, study design, sample size, type of heavy metals, type of sex hormones, confounding factors, and adverse effect on sex hormones extracted from all eligible papers (see Table 1).

Results

Study Selection and Participant Characteristics

Our systematic search returned 350 articles, 124 articles from PubMed, 90 articles from Clarivate Web of Science, and 136 articles from Scopus. All duplicate articles were excluded ($n = 110$), and the rest were screened based on title and abstract ($n = 240$). One hundred ninety-one articles were excluded in this step. We included 49 articles in this systematic review; however, 38 articles were excluded based on our inclusion/exclusion criteria (irrelevant exposure and irrelevant outcome) ($n = 11$). Evaluation of article's quality based on STROBE checklist causes to exclude of two articles due to the low quality. Finally, nine articles are included in this systematic review (Fig. 1). All included studies with cross-sectional design examined the association between heavy metals exposure and sex hormones in males and females.

Table 1 The main characteristics of selected studies in the systematic review

Hormones	Confounding factors	Heavy metals	Sample size	Study design	First author	Country	Year	Mean STROBE score
Testosterone, estradiol, free testosterone, free estradiol, androstanedione glucuronide, SHBG	Age, race, body mass index, smoking status, diabetes, alcohol intake	Lead, cadmium	869 Men >20 years	Cross-sectional	Jacob k-kresovich	USA	2015	20
Serum FSH, LH, inhibin B, testosterone, sex hormone-binding globulin levels, T/LH ratio, FAI	Age, BMI, and current smoking	Cadmium, copper, lead, arsenic, chromium, manganese, mercury, molybdenum, thallium, selenium, zinc	219 Men 18–55 years	Cross-sectional	John D. meeker	USA	2010	20
Total testosterone (TT), free testosterone (FT), estradiol (E2), sex hormone-binding globulin (SHBG), free androgen index (FAI)	Not reported	Lead, Cadmium, Mercury, Tungsten, Magnesium, Iron, Calcium, Copper, Zinc, Selenium, Chromium, Manganese, Molybdenum	313 men Aged 50–75 years	Cross-sectional	Iwona rotter	Poland	2016	13
Total testosterone (TT), estradiol (E2), sex hormone-binding globulin (SHGB)	Blood lead level, age, BMI, residence area, economic status, current smoking	Cadmium	5690 2286 men, 3404 women 18 years and older	Cross- sectional	Chi Chen	China	2016	21
Follicle-stimulating hormone (FSH)	Age, BMI, smoking status, alcohol consumption	Lead, cadmium, mercury	4689 2763 men 1926 women 50 years and over	Cross-sectional	Tae-woo lee	South Korea	2019	17
Estradiol (E2), testosterone (T), dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH), luteinizing hormone (LH)	Age, body mass index, smoking status, alcohol consumption, urinary creatinine	Cadmium	396 premenopausal women <40 207 postmenopausal women	Cross-sectional	Chisato nagata	Japan	2016	18
Luteinizing hormone (LH), free testosterone (FT), estradiol (E2), follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG)	Age, BMI, fasting, smoking status, hour of blood collection	Cadmium, copper, lead, chromium, manganese, thallium, nickel, antimony, mercury, arsenic	2671 14–15-year-old adolescents	Cross- sectional	Sam De Craemer	Belgium	2017	19
S-androstenedione, S-testosterone, S-estradiol, sex hormone-binding globulin (SHBG)	Age, education, BMI, parity, smoking, alcohol consumption	Cadmium	438 postmenopausal women 50–59 years old	Cross-sectional	Imran Ali	Sweden	2014	18

Table 1 (continued)

Hormones	Confounding factors	Heavy metals	Sample size	Study design	First author	Country	Year	Mean STROBE score
Testosterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), inhibin B, sex hormone-binding globulin (SHBG)	Child age, BMI z-score and specific gravity	Aluminum, arsenic, barium, cadmium, cobalt, copper, iron, manganese, molybdenum, nickel, antimony, selenium, zinc	132 girls 8–13 years old	Cross-sectional	Pahriya Ashrap	Mexico	2019	19

Of these, two articles were conducted on children and adolescents. In this study, we categorized the included articles by type of sex hormones as follow:

Sex Hormone-Binding Globulin (SHBG)

Based on our search, eight of nine epidemiology studies were identified related to heavy metal exposure and SHBG [3, 6, 11, 14, 27, 35, 38, 43]. These studies were conducted in six different countries in three continents of Europe, Asia, and America. Three European cross-sectional studies were as follows: one in Sweden [3], one in Belgium [14], and the other one in Poland [43]. Cross-sectional studies of Asia were conducted in China [11] and Japan [38], and finally, three American studies were conducted in the USA [6, 27, 35]. In Kresovich et al. [27], there was a significant positive association between lead and cadmium exposure and SHBG (see Table 2). Also, the evaluation of metals exposure effect on hormones and sexual maturation in Flemish adolescents revealed a significant positive association between blood copper level and SHBG [14]. Meeker et al. [35] investigated the association between metals (cadmium, copper, lead, arsenic, chromium, manganese, mercury, molybdenum, thallium, selenium, zinc) and serum FSH, LH, inhibin B, T, and sex hormone-binding globulin levels. They reported that Manganese exposure had an inverse relationship with SHBG (Table 2). The cross-sectional study of Rotter et al. [43] reported that W, Zn, and Cr had a significant negative relationship with SHBG. However, this study showed a significant positive association between manganese exposure and sex hormone-binding globulin. The cross-sectional study in China reported a significant negative association trend between blood cadmium level (BLC) and SHBG [11]. Two other cross-sectional studies conducted on premenopausal and postmenopausal women reported no associations of blood cadmium level or urinary cadmium level with serum concentration of SHBG [3, 38] (see Table 2). These results were consistent with the results of a study conducted on pregnant women in their third trimester of pregnancy and their children in 8–13 years. This study reported that there is no association between peripubertal metal levels and SHBG [6].

Testosterone (T) and Free Testosterone (FT)

Eight of the selected studies assessed the relationship between metal exposure and testosterone levels [3, 6, 11, 14, 27, 35, 38, 43], and also four reported the association between metal exposure and free testosterone [14, 27, 38, 43]. Two American studies on males reported a positive association between lead and cadmium exposure and testosterone level [27, 35]. Also, the authors of a study in Michigan reported a positive association between blood

Fig. 1 Diagram for illustrating the process of screening and selecting eligible studies
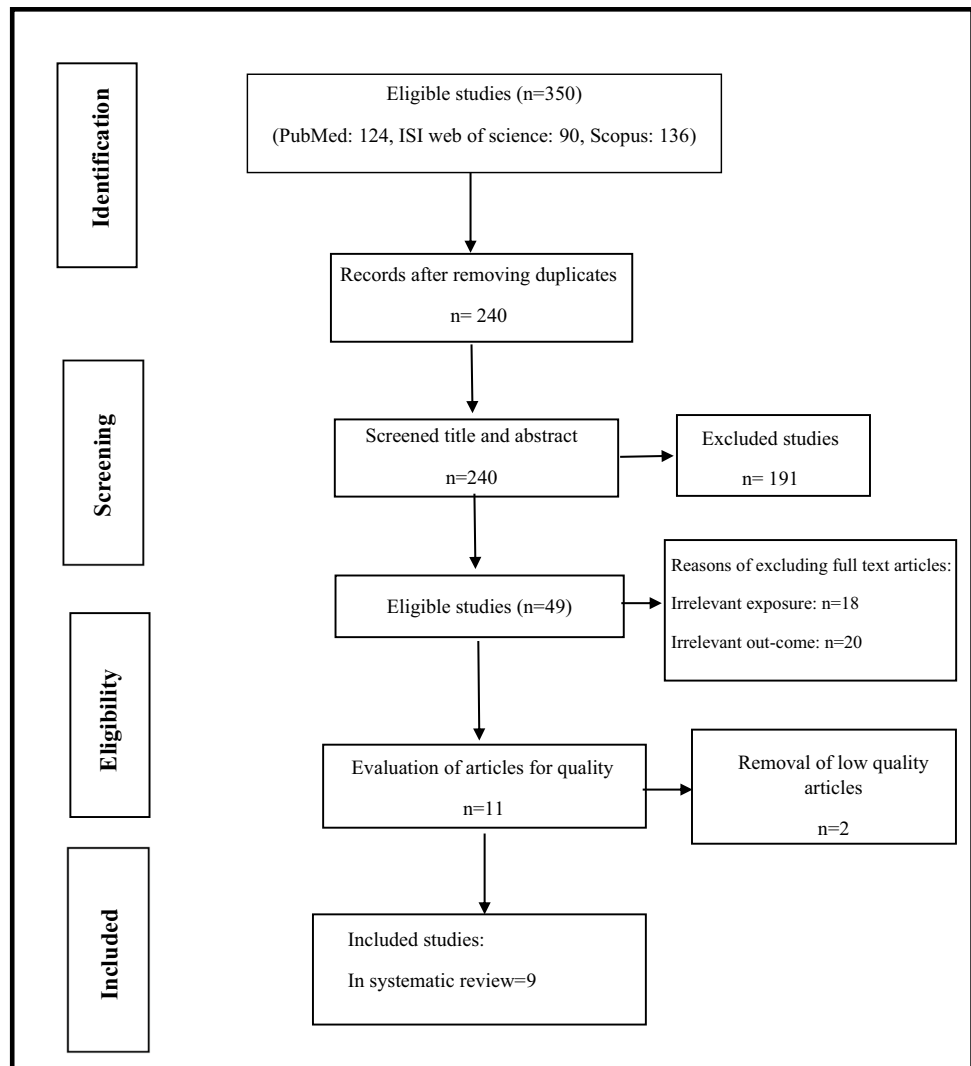
copper level and testosterone, while a significant inverse correlation was observed for molybdenum levels with testosterone [35]. The cross-sectional study of Rotter et al., which examined the associations between concentrations of metals in whole blood, microelements, and macroelements in serum and hormonal change, reported that in the blood, there is a significant positive association between Mg, Fe, Mo, and total testosterone ($r_s = 0.19$, $P = 0.00074$, $r_s = 0.12$, $P = 0.034$, $r_s = 0.11$, $P = 0.043$). However, they observed a negative correlation between Mn and total testosterone ($r_s = -0.17$, $P = 0.027$). The results found for whole blood metals showed no significant relationship between serum testosterone levels and metals (Pb, Cd, As, Hg, W). In addition, results related to the free testosterone revealed that there is a positive correlation between Fe ($r_s = 0.13$, $P = 0.025$), Cr ($r_s = 0.19$, $P = 0.00066$) and free testosterone and there is a negative correlation for Cd ($r_s = -0.14$, $P = 0.011$) and W ($r_s = -0.16$, $P = 0.004$) [43]. In a Chinese study of 5690 participants, including 2286 men and

3404 women aged 18 years and older, blood cadmium level (BLC) was negatively associated with total testosterone (TT) in men (P for trend $= 0.001$), while linear regression results in full adjustment model showed that there is no association between BLC and TT in postmenopausal women (P for trend $= 0.685$) [11], while a Sweden study ($n = 438$) on postmenopausal women reported a significant positive association between blood cadmium level and serum testosterone level after adjusted for age, education, BMI, parity, smoking, and alcohol consumption ($P = 0.036$) [3]. Another cross-sectional study on premenopausal and postmenopausal Japanese women reported that an increasing cadmium level in premenopausal women was significantly associated with a decrease in testosterone and free testosterone levels. However, in postmenopausal women, an increasing T level trend was associated with an increasing cadmium level [38]. A Belgium study using data from three cross-sectional studies ($n = 2671$) on 14–15-year-old adolescents in 2002–2015 revealed a significant negative association between blood

Table 2 Heavy metals exposure and sex hormones study table

First author name	Sample	Aim of study		Results of serum concentration of SHBG	Results of serum concentration of testosterone
Iwona Rotter	313 men 50–75 years	Assessing the relationship between heavy metals (Pb, Cd, Hg, As, W), trace elements (Zn, Cu, Mn, Mo, Se, Cr) and macro elements (Mg, Fe, Ca), and the occurrence of age-related testosterone deficiency and hormonal changes associated with testosterone deficiency in aging men	Pb	Spearman correlation coefficient −0.08	Spearman correlation coefficient −0.09
			Cd	Spearman correlation coefficient −0.06	Spearman correlation coefficient −0.02
			Hg	Spearman correlation coefficient −0.0002	Spearman correlation coefficient −0.04
			As	Spearman correlation coefficient 0.08	Spearman correlation coefficient 0.05
			w	Spearman correlation coefficient −0.25*	Spearman correlation coefficient 0.1
			Mg	Spearman correlation coefficient 0.09	Spearman correlation coefficient 0.19*
			Ca	Spearman correlation coefficient −0.04	Spearman correlation coefficient 0.09
			Fe	Spearman correlation coefficient 0.08	Spearman correlation coefficient 0.12*
			Zn	Spearman correlation coefficient −0.16*	Spearman correlation coefficient 0.03
			Cu	Spearman correlation coefficient 0.01	Spearman correlation coefficient −0.09
			Mo	Spearman correlation coefficient −0.01	Spearman correlation coefficient 0.11*
			Mn	Spearman correlation coefficient 0.18*	Spearman correlation coefficient −0.17*
			Se	Spearman correlation coefficient 0.04	Spearman correlation coefficient −0.01
			Cr	Spearman correlation coefficient −0.14* *p ≤ 0.05	Spearman correlation coefficient −0.06 *p ≤ 0.05

Table 2 (continued)

First author name	Sample	Aim of study		Results of serum concentration of SHBG	Results of serum concentration of testosterone
Chi Chen	5690 (2286 men, 3404 women) > 18 years	To explore relationship between blood cadmium level (BCL) and reproductive hormones	Cd	Spearman correlation coefficient $rs = -0.098$ for men, $p < 0.01$ Linear regression test: Model 1(SE):Q1: Ref., Q2: −0.013 (0.014), Q3: −0.042 (0.014)**, Q4: −0.085 (0.014)**, Model 2(SE): Q1: Ref., Q2: −0.009 (0.011), Q3: −0.040 (0.011)**, Q4: −0.057(0.011)** Model 3(SE):Q1: Ref, Q2: −0.008 (0.011), Q3: −0.037 (0.011)**, Q4: −0.055(0.012)** (P for trend < 0.001) *P < 0.05 **P < 0.01	Spearman correlation coefficient: $rs = -0.057$** for men, $rs = 0.036$ for postmenopausal women **P < 0.01 Linear regression test: Model 1(SE):Q1: Ref., Q2: −0.006 (0.010), Q3: −0.015 (0.011), Q4: −0.035 (0.011)** Model 2(SE): Q1: Ref., Q2: −0.001 (0.010), Q3: −0.020 (0.010)*, Q4: −0.028 (0.010)** Model 3(SE):Q1: Ref, Q2: −0.002 (0.010), Q3: −0.022 (0.010)*, Q4: −0.030 (0.010)** (P for trend < 0.001) *P < 0.05 **P < 0.01
Imran Ali	438 postmenopausal women 50–59 years	To evaluate the associations between Cd exposure (B-Cd, U-Cd) and serum concentrations of testosterone, androstenedione, estradiol, sex hormone-binding globulin (SHBG), testosterone index, estradiol index and estradiol/testosterone ratio in a population of postmenopausal women	Cd	Spearman's rank correlation coefficient B-Cd: (rs = 0.16, p = 0.001), U-Cd: (rs = 0.06, p = 0.25) Regression coefficient (95% CI):B-Cd: (+0.012 (−0.005, +0.028), P value = 0.165 U-Cd: (−0.065 (−0.248, +0.117), P value = 0.481)	Spearman's rank correlation coefficient B-Cd: (rs = 0.09, p = 0.06) U-Cd: (rs = 0.02, p = 0.73) Spearman's rank correlation coefficient between biomarker of Cd and testosterone index: B-Cd: (rs = −0.06, p = 0.21) U-Cd: (rs = −0.05, p = 0.28) Regression coefficient (95% CI) for S-testosterone: B-Cd: (+0.021 (+0.001; +0.041) P value = 0.036) U-Cd: (−0.107 (−0.322; +0.108) P value = 0.329) For testosterone index: B-Cd: (+0.009 (−0.018; +0.036), P value = 0.511) U-Cd: (−0.046 (−0.341; +0.249) P value = 0.758)

Table 2 (continued)

First author name	Sample	Aim of study		Results of serum concentration of SHBG	Results of serum concentration of testosterone
Sam De Craemer	2671 old adolescents 14–15 years	A) To explore significant association between exposure and effect markersB) to determine a reliable urine density correction factor for urinary concentrations	Cu	Regression results for FLEHS I: B-Cu: (1.034 (1.004, 1.065), P=0.024) For FLEHS II: B-Cu: (1.047 (0.999,1.098), P=0.049) *P<0.05	Regression results for FLEHS I: B-Cu: (0.878 (0.837,0.921), P<0.001) For FLEHS II: B-Cu: (0.845 (0.785,0.909), P<0.001) *P<0.05
			Pb		
Chisato Nagata	396 premenopausal (mean age: 39.9 (5.6))207 postmenopausal(mean age: 56.4 (6.0))	To explore the association between urinary cadmium level and circulating sex hormone level that related to the breast cancer risk in healthy women	Cd	Adjusted geometric means (95% confidence intervals): Urinary cadmium (µg/g creatinine): <1.2:65.5 (56.5–73.7) 1.12–1.62: 58.3 (51.3–66.3) 1.63–2.23: 59.0 (51.9–67.0) 2.24+: 65.3 (57.3–74.4) P trend: 0.82 Urinary cadmium (µg/L): <1.2: 64.2 (55.0–75.0) 1.12–1.62: 61.9 (54.6–70.1) 1.63–2.23: 60.7 (53.1–69.5) 2.24+: 60.2 (52.1–69.4) P trend: 0.83	Adjusted geometric means (95% confidence intervals): Urinary cadmium (µg/g creatinine): <1.2:27.4 (24.6–30.4) 1.12–1.62: 27.9 (25.2–30.9) 1.63–2.23: 23.7 (21.4–26.2) 2.24+: 23.4 (21.1–26.0) P trend: 0.01 Urinary cadmium (µg/L): <1.2: 28.9 (25.5–32.7) 1.12–1.62: 25.6 (23.2–28.3) 1.63–2.23: 24.7 (22.2–27.5) 2.24+: 23.3 (20.8–26.2) P trend: 0.02
Tae-Woo Lee	2,763 men1,926 postmenopausal women ≥50 years	To investigate the association between heavy metal exposure and FSH level in Korean men and postmenopausal women	Pb		
			Cd		
			Hg		
Pahriya Ashrap	250 child participants132 girls118 boysAged 8–13 years	To examine the association between metals exposure and hormone levels	Ni		Peripubertal Ni concentrations were associated with higher testosterone levels (%Δ/IQR: 40.8, 95% CI: 18.0, 68.0)
			Cu		Peripubertal exposure to Cu was associated with lower testosterone levels (%Δ/IQR: 28.0, 95% CI:45.5, -4.8)

Table 2 (continued)

First author name	Sample	Aim of study	Results of serum concentration of	Results of serum concentration of SHBG	Results of serum concentration of testosterone
Jacob K. Kresovich	869 men > 20 years	Investigation of the associations between lead and cadmium exposures in relation to various sex hormones (i.e., testosterone, free testosterone, estradiol, free estradiol, androstanedione glucuronide and SHBG) in an adult men in the USA	**Pb**	Beta coefficients (standard errors) Crude: Q1: Ref., Q2: 0.08 (0.02)*, Q3: 0.16 (0.02)*, Q4: 0.19 (0.02)*, P for trend < 0.0001 Full adjusted model: Q1: Ref., Q2: 0.01 (0.02), Q3: 0.05 (0.02)*, Q4: 0.05 (0.02), P for trend = 0.0187	Beta coefficients (standard errors) Crude: Q1: Ref., Q2: 0.21 (0.25), Q3: 0.62 (0.22)*, Q4: 0.84 (0.20)*, P for trend < 0.0001 Full adjusted model: Q1: Ref., Q2: 0.39 (0.21), Q3: 0.56 (0.22)*, Q4: 0.81 (0.20)*, P for trend = 0.0008
			Cd	Beta coefficients (standard errors): Crude: Q1: Ref., Q2: 0.08 (0.02)*, Q3: 0.11 (0.03)*, Q4: 0.16 (0.03)*, P for trend < 0.0001 Full adjusted model: Q1: Ref., Q2: 0.03 (0.02), Q3: 0.05 (0.02)*, Q4: 0.09 (0.03)*, P for trend = 0.0021	Beta coefficients (standard errors): Crude: Q1: Ref., Q2: − 0.12 (0.21), Q3: 0.04 (0.19), Q4: 1.14 (0.24)*, P for trend < 0.0001 Full adjusted model: Q1: Ref., Q2: 0.11 (0.17), Q3: 0.03 (0.19), Q4: 0.46 (0.33), P for trend = 0.2178
John D. Meeker	219 men 18–55 years	To explore the relationship between metal exposure and levels of male reproductive hormones	**Mg**	Adjusted a regression coefficients < 25th: 0 25–50th: − 0.03 (− 0.18–0.11) 50th–75th: − 0.06 (− 0.23–0.12) > 75th: − 0.17 (− 0.33–0.003) P for trend = 0.06	
			Cu		Adjusted a regression coefficients < 25th: 0 25–50th: − 11.9 (− 47.9, 24.2) 50th–75th: 6.23 (− 30.5, 43.0 > 75th: 41.9 (3.52, 80.3) P for trend = 0.03

Table 2 (continued)

First author name	Sample	Aim of study	Results of serum concentration of SHBG	Results of serum concentration of testosterone
			Pb	Adjusted a regression coefficients <25th: 0 25–50th: 28.6 (−6.82, 64.1) 50th–75th: 15.8 (−21.8, 53.3) >75th: 39.9 (3.32, 76.4) P for trend = 0.07
			Mo	Adjusted a regression coefficients <70th: 0 70th–85th: −23.0 (−58.3, 12.3) >85th: −60.0 (−97.2, −22.8) P for trend = 0.001
			Cr	
			As	
			Se	
			Tl	

First author name	-Results of serum concentration of free testosterone	-Results of concentration of free androgen index (FAI)	-Results of concentration of Follicle-stimulating hormone (FSH)	-Results of concentration of estradiol (E2)	-Results of concentration of luteinizing hormone (LH)
Iwona Rotter	Spearman correlation coefficient −0.1	Spearman correlation coefficient −0.18*		Spearman correlation coefficient −0.07	
	Spearman correlation coefficient −0.14*	Spearman correlation coefficient −0.06		Spearman correlation coefficient −0.06	
	Spearman correlation coefficient −0.12*	Spearman correlation coefficient −0.02		Spearman correlation coefficient −0.12*	
	Spearman correlation coefficient 0.05	Spearman correlation coefficient 0.11*		Spearman correlation coefficient 0.14*	
	Spearman correlation coefficient −0.16*	Spearman correlation coefficient 0.34*		Spearman correlation coefficient 0.05	
	Spearman correlation coefficient 0.07	Spearman correlation coefficient 0.09		Spearman correlation coefficient 0.07	
	Spearman correlation coefficient 0.07	Spearman correlation coefficient 0.15*		Spearman correlation coefficient 0.09	
	Spearman correlation coefficient 0.13*	Spearman correlation coefficient 0.02		Spearman correlation coefficient 0.04	
	Spearman correlation coefficient 0.06	Spearman correlation coefficient 0.20*		Spearman correlation coefficient 0.02	
	Spearman correlation coefficient −0.01	Spearman correlation coefficient −0.07		Spearman correlation coefficient 0.05	

Table 2 (continued)

First author name	Results of serum concentration of free testosterone	Results of concentration of free androgen index (FAI)	Results of concentration of Follicle-stimulating hormone (FSH)	Results of concentration of estradiol (E2)	Results of concentration of luteinizing hormone (LH)
	Spearman correlation coefficient-0.05	Spearman correlation coefficient0.09		Spearman correlation coefficient −0.01	
	Spearman correlation coefficient 0.02	Spearman correlation coefficient −0.35*		Spearman correlation coefficient −0.06	
	Spearman correlation coefficient 0.06	Spearman correlation coefficient 0.04		Spearman correlation coefficient0.1	
	Spearman correlation coefficient -0.19* *p≤0.05	Spearman correlation coefficient −0.14* *p≤0.05		Spearman correlation coefficient −0.12* *p≤0.05	
Chi Chen			Spearman correlation coefficient rs = −0.034 for men, rs=0.009 for postmenopausal women**P<0.01	Spearman correlation coefficient rs=−0.019 for men, rs=0.013 for postmenopausal women **P<0.01 Linear regression test: Model 1(SE):Q1: Ref., Q2: −0.023 (0.016), Q3: −0.031 (0.016), Q4: −0.018 (0.017) Model 2(SE): Q1: Ref., Q2: −0.010 (0.016), Q3: −0.020 (0.016), Q4: 0.004 (0.017) Model3(SE):Q1: Ref, Q2: −0.012 (0.016), Q3: −0.023 (0.017), Q4: −0.002 (0.017) (P for trend <0.001) *P<0.05 **P<0.01	Spearman correlation coefficient rs = −0.041 for men, rs=0.030 for postmenopausal women**P<0.01
Imran Ali				Spearman's rank correlation coefficient B-Cd: (rs = −0.14, p=0.003) U-Cd: (rs = −0.07, p=0.15) Regression coefficient (95% CI):B-Cd:−0.052 (−0.085, −0.019),P value=0.002), U-Cd: (−0.364 (−0.733,+0.005), P value = 0.053)	

Table 2 (continued)

First author name	-Results of serum concentration of free testosterone	-Results of concentration of free androgen index (FAI)	-Results of concentration of Follicle-stimulating hormone (FSH)	-Results of concentration of estradiol (E2)	-Results of concentration of luteinizing hormone (LH)
Sam De Craemer	Regression results for FLEHS I: B-Cu: 0.853 (0.804,0.906), P<0.001) For FLEHS II: B-Cu: 0.886 (0.793,0.989), P=0.029) *P<0.05 B-Pb: 0.909 (0.828,0.997), P=0.041) *P<0.05			Regression results for FLEHS I: B-Cu: (0.967 (0.948,0.986), P=0.001) For FLEHS II: B-Cu: (0.88 (0.833,0.93), P<0.001) *P<0.05	Regression results for FLEHS I: B-Cu: (0.941 (0.908,0.975), P=0.001) For FLEHS II: B-Cu: (0.868 (0.813,0.926), P<0.001
Chisato Nagata	Adjusted geometric means (95% confidence intervals): Urinary cadmium (µg/g creatinine): <1.2:0.4 (0.36–0.46) 1.12–1.62: 0.42 (0.37–0.48) 1.63–2.23: 0.35 (0.31–0.40) 2.24+: 0.34 (0.30–0.38)P trend: 0.02 Urinary cadmium (µg/L): <1.2: 0.43 (0.37–0.49) 1.12–1.62: 0.38 (0.33–0.42) 1.63–2.23: 0.37 (0.33–0.42) 2.24+: 0.34 (0.30–0.39)P trend: 0.03		Adjusted geometric means (95% confidence intervals):Urinary cadmium (µg/g creatinine): <1.2: 4.52 (4.03–5.07) 1.12–1.62: 4.89 (4.37–5.47) 1.63–2.23: 4.63 (4.14–5.19) 2.24+: 5.01 (4.47–5.61) P trend: 0.28 Urinary cadmium (µg/L): <1.2: 4.59 (4.01–5.26) 1.12–1.62: 4.74 (4.24–5.31) 1.63–2.23: 4.69 (4.17–5.28) 2.24+: 5.00 (4.41–5.66) P trend: 0.29	Adjusted geometric means (95% confidence intervals): Urinary cadmium (µg/g creatinine): <1.2:106.2 (91.2–123.8) 1.12–1.62: 120.8 (104.2–140.0) 1.63–2.23: 103.4 (89.3–119.7) 2.24+: 98.2 (84.5–114.1) P trend: 0.37 Urinary cadmium (µg/L): <1.2: 116.3 (97.2–139.2) 1.2–1.9: 104.5(90.4–120.7) 2.0–2.9: 108.7(93.1–126.9) +3.0: 99.9 (84.6–117.8) P trend: 0.40	Adjusted geometric means (95% confidence intervals): Urinary cadmium (µg/g creatinine): <1.2:3.92 (3.38–4.55) 1.12–1.62: 4.44 (3.84–5.14) 1.63–2.23: 3.96 (3.42–4.58) 2.24+: 3.85 (3.32–4.46) P trend: 0.29 Urinary cadmium (µg/L): <1.2:4.83 (3.68–5.23) 1.2–1.9:3.89 (3.37–4.49) 2.0–2.9:3.76 (3.23–4.37) +3.0:4.13 (3.52–4.85) P trend: 0.30

Table 2 (continued)

First author name	-Results of serum concentration of free testosterone	-Results of concentration of free androgen index (FAI)	-Results of concentration of Follicle-stimulating hormone (FSH)	-Results of concentration of estradiol (E2)	-Results of concentration of luteinizing hormone (LH)
Tae-Woo Lee			Linear regression coefficients in men Blood lead: Unadjusted β (95% CI): 0.166 (0.107,0.224), p value < 0.001 Adjusted β (95% CI): 0.005 (−0.043,0.052), p value = 0.851 Linear regression coefficients in postmenopausal women: Blood lead: Unadjusted β (95% CI): 2.415 (−0.098,4.928), p value = 0.06 Adjusted β (95% CI): 2.929 (0.480,5.377), p value = 0.019 Linear regression coefficients in men Urine cadmium: Unadjusted β (95% CI): 0.269 (0.230,0.308), p value < 0.001 Adjusted β (95% CI): −0.016 (0.052,0.019), p value = 0.228 Linear regression coefficients in postmenopausal women: Urine cadmium: Unadjusted β (95% CI): 1.976 (−0.118, 4.069), p value = 0.064 Adjusted β (95% CI): 1.355 (−0.700, 3.410), p value = 0.196		

Table 2 (continued)

First author name	-Results of serum concentration of free testosterone	-Results of concentration of free androgen index (FAI)	-Results of concentration of Follicle-stimulating hormone (FSH)	-Results of concentration of estradiol (E2)	-Results of concentration of luteinizing hormone (LH)
			Linear regression coefficients in men Blood mercury: Unadjusted β (95% CI): 0.000 (− 0.040, 0.039), p value = 0.986 Adjusted β (95% CI): 0.030 (− 0.002, 0.061), p value = 0.064 Linear regression coefficients in postmenopausal women: Blood mercury: Unadjusted β (95% CI): − 2.507 (− 4.227, − 0.736), p-value = 0.006 Adjusted β (95% CI): − 1.000 (− 2.755, 0.755), p value = 0.264		
Pahriya Ashrap					
Jacob K. Kresovich	Beta coefficients (standard errors) Crude: Q1: Ref., Q2: − 0.43 (0.59), Q3: − 0.55 (0.47), Q4: − 0.64 (0.48), P for trend = 0.1513 Full adjusted model: Q1: Ref., Q2: 0.83 (0.47), Q3: 0.55 (0.48), Q4: 0.81 (0.48), P for trend = 0.2374			Beta coefficients (standard errors): Crude: Q1: Ref., Q2: − 0.03(0.03), Q3: − 0.01(0.03), Q4: − 0.02(0.04), P for trend = 0.7547 Full adjusted model: Q1: Ref., Q2: − 0.01 (0.03), Q3: − 0.01 (0.04), Q4: − 0.01 (0.04), P for trend = 0.7849	

Table 2 (continued)

First author name	-Results of serum concentration of free testosterone	-Results of concentration of free androgen index (FAI)	-Results of concentration of Follicle-stimulating hormone (FSH)	-Results of concentration of estradiol (E2)	-Results of concentration of luteinizing hormone (LH)
	Beta coefficients (standard errors) between Testosterone for blood Cadmium: Crude: Q1: Ref., Q2: −0.96 (0.44)*, Q3: −1.03 (0.53), Q4: 0.54 (0.53), P for trend = 0.4216 Full adjusted model: Q1: Ref., Q2: 0.14 (0.40), Q3: −0.36 (0.38), Q4: −0.31 (0.58), P for trend = 0.4482			Beta coefficients (standard errors)Crude: Q1: Ref., Q2: −0.03(0.02), Q3: −0.04 (0.03), Q4: 0.07 (0.02)*, P for trend = 0.0345* Full adjusted model: Q1: Ref., Q2: −0.01 (0.02), Q3: −0.05 (0.03), Q4: −0.02 (0.04), P for trend = 0.3834	
John D. Meeker		Adjusted a regression coefficients: <70th: 0 70th–85th: −0.07 (−0.20, 0.05) >85th: −0.19 (−0.32, −0.06) P for trend = 0.004 Adjusted a regression coefficients: 70th: 0 70th–85th: 0.11 (−0.01, 0.23) >85th: 0.09 (−0.04, 0.21) P for trend = 0.08	Adjusted a regression coefficients: 70th: 0 70th–85th: 0.30 (0.07, 0.54) >85th: 0.12 (−0.11, 0.36) P for trend = 0.09		Adjusted a regression coefficients: <25th: 0 25–50th: 0.01 (−0.18, 0.24) 50th–75th: 0.01 (−0.19, 0.23) >75th: −0.23 (−0.44, −0.02) P for trend = 0.04

Table 2 (continued)

First author name	Results of serum concentration of free testosterone	Results of concentration of free androgen index (FAI)	Results of concentration of Follicle-stimulating hormone (FSH)	Results of concentration of estradiol (E2)	Results of concentration of luteinizing hormone (LH)
					Adjusted a regression coefficients: <25th: 0 25–50th: −0.11 (−0.32, 0.10) 50th–75th: −0.15 (−0.36, 0.06) >75th: −0.29 (−0.50, −0.02) P for trend = 0.008 Adjusted a regression coefficients: <50th: 0 50th–75th: −0.25 (−0.43, −0.07) >85th: −0.14 (−0.32, −0.05) P for trend = 0.06

copper (B-Cu) and T and FT in both groups of FLEHS I and FLEHS II. Also, they found B-Pb was negatively associated with FT in FLEHS II [14]. A Mexican cross-sectional study on pregnant women in the third trimester and their children reported peripubertal exposure to Ni was associated with higher testosterone level (%Δ/IQR: 40.8, 95% CI: 18.0, 68.0), while peripubertal Cu concentrations were associated with lower testosterone level (%Δ/IQR: 28.0, 95% CI: 45.5, −4.8) [6]. Extracted results of studies were shown in Table 2.

Free Androgen Index (FAI)

Among nine selected articles, only two studies reported data related to the relationship between heavy metals exposure and FAI [35, 43]. A cross-sectional Polish study of 313 men aged 50 to 75 reported positive association between FAI and the concentrations of As ($r_s = 0.11$, $P = 0.046$), W ($r_s = 0.34$, $P < 0.0001$), Zn ($r_s = 0.2$, $P = 0.0003$), and Ca ($r_s = 0.15$, $P = 0.009$). However they found a negative correlation between FAI and Pb ($r_s = -0.18$, $P = 0.001$), and Mn ($r_s = -0.35$, $P < 0.0001$) [43]. The cross-sectional study of Meeker et al. revealed that molybdenum has inverse associated with FAI (P for trend = 0.004), while in the adjusted models of FAI for other metals and covariates, results showed that FAI was also positively associated with chromium and copper [35].

Follicle-Stimulating Hormone (FSH)

Three cross-sectional studies evaluated the association between heavy metals exposure and follicle-stimulating hormone [11, 29, 35]. One Korean study ($n = 4689$) and also a Chinese study ($n = 5690$) assessed this association in men and postmenopausal women; however, their results were inconsistent. The Korean study evaluated concentrations of blood lead and mercury and the urinary level of cadmium. They reported that only Pb exposure had a positive association with FSH in postmenopausal women. However, they found no significant association between metals exposure and serum FSH concentration [29]. On the other hand, Chen et al. reported no association between exposure to cadmium and FSH in men and postmenopausal women [11]. In a study by Meeker et al., with 219 men participants in Michigan, no association was observed between metals (As, Cd, Cr, Cu, Pb, Mn, Hg, Mo, Se, Tl, Zn) exposure and serum concentrations of FSH [35] (see Table 2).

Estradiol (E₂) and Free Estradiol

Seven studies evaluated the association between heavy metals exposure and estradiol or free estradiol (Table 2) [3, 6, 11, 14, 27, 38, 43]. Despite differences in participants, sample

size, and geographical location, most of studies reported an inverse association between metals exposure and estradiol level. The cross-sectional study of Ali et al. observed an inverse association between blood cadmium concentration and serum estradiol levels ($P = 0.009$) and the estradiol index ($P = 0.002$); also, urinary cadmium level showed inversely associated with serum estradiol level ($P = 0.013$) [3], and results are consistent with the results of a study on Flemish adolescents which found blood copper concentration is significantly negatively associated with estradiol ($P = 0.001$) and free estradiol ($P < 0.001$); also, blood lead showed the same association with free estradiol ($P = 0.015$) [14]. Two other cross-sectional studies conducted on pre- and postmenopausal women [38], and pregnant women and their children [6] reported the negative trend same as previous named studies between association of metals exposure and serum estradiol levels. The Chinese study on men and postmenopausal women reported no significant association between blood cadmium level and E_2 [11], At the same time, evaluation of Pb and Cd concentration in adults male by Kresovich et al. revealed a significant positive crude trend between blood Cd and estradiol (P for trend $= 0.0345$). Also, the positive correlation between whole-blood arsenic levels and E_2 ($r_s = 0.14$, $P = 0.013$) in andropausal men was observed in the study of Rotter et al., while they found negative correlation between E_2 and Cr ($r_s = -0.12$, $P = 0.034$) and Hg ($r_s = -0.12$, $P = 0.033$) [43].

Luteinizing Hormone (LH)

Four studies assessed the relationship between metals exposure and LH (see Table 2). Two of them observed a significant negative association, while two others reported no association between metals exposure and LH (see Table 2) [11, 14, 35, 38]. A cross-sectional study on 219 men between 18 and 55 years of age reported arsenic, selenium, and copper were inversely associated with LH [35]. Consistent with the results of this study, Craemer et al. observed a significant negative association between blood copper and LH [14]. However, two cross-sectional studies on pre- and postmenopausal women and men reported no association between metals exposure and LH [11, 38].

Discussion

This systematic review summarized the current epidemiological studies related to the association between heavy metals exposure and sex hormones. Due to the high diversity of heavy metals and different types of sex hormones, we categorized the effects of exposure to heavy metals in different groups based on sex hormones. Also, according

to the differences in the selected participants and different geographical locations, inconsistent results were observed in each part.

Sex hormone-binding globulin (SHBG) is a protein that is made primarily in the liver. SHBG can bind to sex steroids, including testosterone, estradiol, and dihydrotestosterone (DHT). SHBG carries these hormones through the bloodstream, causing them to remove from direct circulation in the body [53]. In general, a low SHBG level means more unbound sex hormones for use, whereas a high SHBG level means lower concentrations of free sex hormone in the body. Therefore, SHBG levels have a significant effect on the sex hormones regulation process. In this regard, various studies have been performed to evaluate parameters affecting the SHBG level. Heavy metal exposure is one of these parameters that we reported related results in this systematic review study. According to the results reported in Table 2, it was found that 37.5% of them showed a negative relationship [11, 35, 43], 25% showed a positive relationship [14, 27], and 37.5% reported no association between metals exposure and SHBG [3, 6, 38]. Although according to the data, studies with a higher number of participants found an inverse result between exposure to heavy metals and SHBG, this correlation is unclear due to the heterogeneity of the results. In addition, observation of a negative association may be due to some studies limitations. For instance, in the study by Meeker et al., a high percentage of blood samples had lower concentrations of metals than LOD (limit of detection, and they also used only one blood sample for their study. Because metals such as cadmium and molybdenum accumulate in the kidneys and are excreted in the urine, the use of urine samples as a biomarker can affect the study results.

Similar to what was observed for SBHG, the results of testosterone and free testosterone are inconsistent during studies. Based on the reported results in the previous section, at least one metal has a significant relationship with the level of testosterone or free testosterone (positive or negative relationship) in all studies that evaluated the association between heavy metals exposure and T or FT level. These results showed the importance of exposure to heavy metals on the level of testosterone or free testosterone in men and women. Although a cross-sectional study by Chen et al. [11] showed that blood cadmium levels were negatively correlated with testosterone levels in men, studies by Kresovich et al. [27] and Meeker et al. [35] found that cadmium concentrations were positively correlated with testosterone levels. The same heterogeneity is observed in the results for other metals such as lead, iron, and manganese. Thus, it is not possible to comment with certainty about the positive or negative relationship between exposure to heavy metals and testosterone or free testosterone levels, however, it can be said that heavy metals may have significant effects on the level of this hormone. Although these studies evaluate the

association between exposure to heavy metals and testosterone and free testosterone, all of them have a cross-sectional design. Therefore, they cannot draw a causal connection between metal exposure and hormone levels. In addition, blood samples have been used in most studies, while long-term exposure can be measured using urine samples.

Because any change in reproductive hormone levels can reduce fertility or increase the risk of endocrine-secreting cancers or other side effects, so metals exposure effecting should be more considered [35]. The results of two studies related to the relationship between heavy metal exposure and free androgen index (FAI) showed that metals could affect increasing or decreasing FAI levels. However, since these results are related to the only two studies with a relatively low number of participants ($n = 219$, $n = 313$) (32, 36), it is necessary to conduct studies with a larger sample size to determine this relationship.

Similar to FAI, few studies have examined the association between exposure to heavy metals and FSH [11, 29, 35]. However, the most obtained results reported no significant relationship between metals concentration and FSH levels for most metals during these studies. Thus more studies with a larger sample size should be conducted to evaluate the effect of heavy metals exposure on the FSH level.

Estradiol (E_2) is the most common compound in a group of steroids called estrogen. While men and women have the hormone estradiol, which plays a role in their bodies, women have higher estradiol levels, and it is known as the most important female sex hormone. In women, the main function of estradiol is to mature and maintain the reproductive system. Estradiol is made primarily in the ovaries, so its levels decline as women age and decrease significantly during menopause. In men, proper levels of estradiol help maintain bone, produce nitric oxide, and improve brain function [54]. While men need lower levels of E_2 than women, they still need this important hormone to function properly [51]. Heavy metals as endocrine disruptors may affect the function of endogenous hormones such as estradiol by interfering with their synthesis or activity [17]. In this regard, some studies assessed the association between heavy metals exposure and estradiol or free estradiol. Of the seven studies that reported estradiol levels, more than 70% of the studies for at least one metal found an inverse relationship between metals exposure and estradiol levels [3, 6, 14, 38, 43]. Estrogen deficiency has different consequences for men and women and accounts for the risk of osteoporotic fractures [7]. For instance, two case–control studies reported that lower estrogen or androgen levels in postmenopausal women are associated with vertebral fractures [4, 32]. In addition, another study observed that in women, very low levels of estradiol were associated with the prevalence and incidence of vertebral deformities [13]. Also, in the study of Barrett-Connor and co-workers, a clear association was found between vertebral fractures and estradiol levels in older men [7]. Therefore, the effect of exposure to heavy metals on estradiol levels seems to be important, especially in elderly age and should be considered.

Luteinizing hormone (LH) is a hormone produced in the anterior pituitary gland [40]. LH and FSH act together to regulate gonadal function [41]. Stimulation of puberty and testicular and ovarian function and regulation of gametogenesis and steroidogenesis are among the biological actions of these two hormones [9], so LH is essential for puberty and normal sexual function. Due to the same source of secretion, LH deficiency usually occurs with FSH deficiency, and a deficiency of these two hormones can have consequences such as delayed puberty, reproductive abnormalities, and hypoglycemia [24]. In this systematic review, the obtained results of four studies that examined the LH level are 50:50. Two reported the negative association between metals exposure, such as arsenic, selenium, and copper [14, 35], while two others found no association between metals exposure and LH levels [11]. For this, more research should be performed to determine the relationship between metals exposure and LH level.

Study Limitation

All of the selected studies in this systematic review have been observational and cross-sectional; studies with large sample sizes and long-term follow-up are necessary to obtain the association between heavy metals exposure and sex hormones. Also, due to the high diversity of heavy metals and the variety of sex hormones, the results of studies were heterogeneous.

Conclusion

The current evidence proposes that heavy metal exposure during life could potentially affect levels of some sex hormones and lead to decline reproductive health or increase the risk of endocrine-related cancers or other adverse effects. Given the current knowledge about the potential effects of metals on hormone levels and, of course, human health, exposure to these compounds should be considered as a detrimental factor, and less input these compounds should be emphasized to protect the environment.

Declarations

Ethics Approval Not applicable.

Consent to Participate I, Bahareh Shoshtari-Yeganeh, as the corresponding author of the project, agree that the research project entitled "The Association between Heavy Metals exposure and Sex Hormones: A Systematic Review on Current Evidence" has been carried out with the participation of Yasaman Rami, Karim Ebrahimpour, Mahboobeh Maghami, and Roya Kelishadi.

Consent for Publication Not applicable.

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