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Review article

The impact of endocrine disrupting chemicals on adrenal corticosteroids – A systematic review of epidemiological studies

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ABSTRACT

Background: The role of endocrine disrupting chemicals (EDCs) in the development of metabolic syndrome has gained increasing recognition in recent years. The underlying mechanisms are largely unresolved. Disruption of corticosteroid action and hypothalamic-pituitary-adrenal (HPA) axis are considered possible mechanisms.
Objective: To summarise epidemiological studies investigating an association between EDC concentration and altered levels of corticosteroids and the adrenocorticotropic hormone (ACTH).
Methods: Following the PRISMA guidelines, we searched PubMed and the Cochrane Library for epidemiological studies published from database inception until April 1st, 2024. Various groups of EDCs were evaluated with the prerequisite of direct measurement of the chemical, a metabolite, or biomarker.
Results: We identified 2094 articles. After removing duplicates and screening, 27 studies were included. Studies focused predominantly on glucocorticoids (n = 26) compared to mineralocorticoids (n = 5) and ACTH (n = 2). The most studied EDCs were pesticides (n = 9) and phthalates (n = 8). Significant associations between the concentrations of specific EDCs and hormone levels were found in all but three studies. Only one study described an association between EDCs, and hormone concentration and metabolic features.
Conclusion: There is clear evidence for the impact of specific EDCs on plasma corticosteroid concentrations in different age groups worldwide, however, results varied according to EDC class, study population and study methodology. Further research combining EDC and hormone concentrations, and clinical features, complemented by experimental investigations to study cell mechanisms, is needed to gain holistic knowledge of EDCs' influence on glucocorticoid- and mineralocorticoid-related disorders.

1. Introduction

Endocrine-disrupting chemicals (EDCs) have gained increasing recognition in the past years as important bioactive substances with major impact on public health. EDCs form a group of different chemical substances that interfere with hormone synthesis, metabolism and activity, and significantly affect endocrine homeostasis. The resulting health effects include reduced fertility, neoplastic lesions, neurobehavioral and immunological malfunction as well as metabolic disorders (Macedo et al., 2023; Haverinen et al., 2021).

EDCs can be classified into several groups. In addition to plasticizers and pesticides, they also include pharmaceuticals and cosmetics as well as a large group of organic pollutants and heavy metals. Due to their use in industrial and commercial products they occur in biosphere and living organisms including those being part of the human food chain (Bonato et al., 2020). EDCs enter organisms through food, drinking water, the skin or breathing. Due to their sometimes very long half-life, e.g. several years, current exposure includes substances that are meanwhile banned (Gore et al., 2015).

EDCs are a proven health threat in several ways. First, the effects of EDCs - especially after exposure in vulnerable developmental phases (e.g. in utero and in childhood) – may occur with a certain time delay and sometimes even only appear in subsequent generations (Egalini et al., 2022). In addition, very low concentrations of known EDCs, e.g. a few μg/L, are often sufficient to exhibit adverse health effects (Vandenberg, 2014). Furthermore, there is evidence that the simultaneous exposure to

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different EDCs can have synergistic and even superadditive effects in terms of their toxicity (Hamid et al., 2021). Due to the lipophilic features of many EDCs the adrenal gland is particularly vulnerable to EDC exposure and action (Egalini et al., 2022).

Many studies have shown that the increasing number of patients suffering from metabolic syndrome is associated with higher exposure to several types of EDCs (Haverinen et al., 2021). Childhood exposure to certain EDCs contributes to the development of adiposity (Haverinen et al., 2021) and insulin-glucose disruption while increased exposure of EDCs during pregnancy is associated with a range of adverse effects regarding birth weight and size, macrosomia and congenital anomalies (Padmanabhan et al., 2021).

One mechanism that may be fundamental to the link between the metabolic syndrome and EDCs is an interaction with the hypothalamic-pituitary-adrenal (HPA) axis and steroid hormones, particularly glucocorticoids and mineralocorticoids. Activation of the HPA axis, which is the main mediator of the central stress response system and tightly connected to the circadian clock, leads to hormone secretion of the hypothalamus stimulating the pituitary to release the adrenocorticotropic hormone (ACTH), which consequently stimulates the adrenal gland to produce and release glucocorticoids, mineralocorticoids and androgens (Joseph and Whirledge, 2017; Russell and Lightman, 2019).

Therefore, endogenous secretion of glucocorticoids physiologically underlies a circadian rhythm, affecting immune function, reproduction, behaviour and the cardiovascular and metabolic system including blood pressure, as well as glucose and lipid metabolism (Reincke and Fleseriu, 2023). Overproduction of mineralocorticoids leads to sodium and fluid retention and thus to arterial hypertension and other cardiovascular comorbidities and may therefore underlie the association of EDCs with arterial hypertension (Caroccia et al., 2023). Several mechanistic animal studies suggest altered secretion of corticosteroids in adult, pubertal or newborn mammals upon exposure of either bisphenols, phthalates or different classes of persistent organic pollutants (Pecori Giraldi et al., 2024). However, previous reviews focused either on the impact of environmental chemicals on metabolic diseases (Haverinen et al., 2021; Pan et al., 2023; Yang et al., 2023) or on *in vitro* or *in vivo* studies investigating ligand-receptor interaction as well as altered steroid hormone biosynthesis and secretion upon EDC exposure (Zhang et al., 2019; Pecori Giraldi et al., 2024).

The aim of this review was to summarise current evidence from epidemiological studies investigating the influence of various EDCs on gluco- and mineralocorticoids. We hypothesized that we would find relevant evidence for a positive association between exposure to EDCs and concentrations of glucocorticoids and mineralocorticoids. Furthermore, we speculated that these associations may be linked to steroid-sensitive metabolic phenotypes.

2. Methods

The systematic review protocol is described below following the Preferred Reporting Items for Systematic Reviews (PRISMA-P) guidelines (Page et al., 2021).

2.1. Eligibility criteria

Inclusion criteria were based on the population, exposure, comparison, outcome and study design (PECOS) approach as follows: 1) Population: humans, including mother–child pairs. All ages and both female and male sexes assigned at birth were included. Studies of cells or animals were excluded. A measured concentration of the specific EDC, its metabolites or a characterised biomarker in the mother or participant must have been examined in relation to the concentration of glucocorticoids, mineralocorticoids or adrenocorticotropic hormone (ACTH) in the participant. There was no specification on specific hormone parameters or specific EDC metabolites and no limitation for the analysed matrices for either the hormone or the EDC assessment. 2) Exposure: Concentration of one of the following EDC groups: phthalates, bisphenols, per- and polyfluoroalkyl substances (PFAS), pesticides, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (BDEs), Dioxins. The measure of exposure must have been obtained from a biological specimen. 3) Comparison: Exposed versus non-exposed individuals, individuals with exposure to higher versus lower EDC concentration. 4) Outcome: estimated concentration differences of mineralocorticoids, glucocorticoids and ACTH; association between EDC and hormone concentration. 5) Study design: The study design had to be longitudinal, cross-sectional or case-control. Full reports about original epidemiologic research had to be published online or in print.

Non-original reports, reviews, conference abstracts, editorials, commentaries, experimental (*in vitro*/animal studies) or pilot studies, and case reports were excluded. Studies that investigated solely other endocrine disruptors, e.g. heavy metals, or other hormones as androgens were also excluded. The search was restricted to studies that were published in English or German. A full list of inclusion and exclusion criteria is available in the Supplement (Table S1).

2.2. Information sources

A comprehensive literature search was conducted in PubMed and the Cochrane library to identify relevant articles published from database inception to April 1st, 2024.

2.3. Search strategy

The search strategy used terms describing the hormone system and EDCs of interest to capture all pertinent information on the effects of the chemicals on glucocorticoids, mineralocorticoids and ACTH. EDCs of interest are listed and characterized in the supplementary material S1. No search filters were applied.

Our strategy included a combination of the following key terms:

(cortisol) OR (aldosterone) OR (renin-angiotensin-aldosterone system) OR (renin) OR (hypothalamic-pituitary-adrenal axis) OR (glucocorticoid receptor) OR (mineralocorticoid receptor) OR (glucocorticoid hormone) OR (mineralocorticoid hormone) AND

(pesticides) OR (persistent organic pollution) OR (POP) OR (endocrine disrupting chemical) OR (phthalate) OR (bisphenol) OR (polybrominated diphenyl ether) OR (BDE) OR (polychlorinated biphenyls) OR (PCB) OR (polyfluorinated alkyl substances) OR (perfluorinated alkyl substances) OR (PFAS).

A manual search of the included article's reference lists was subsequently performed. The detailed search string is listed as supplementary material S2.

2.4. Study selection process

Title and abstracts were screened from database inception to April 1, 2024 by two independent reviewers (IS, JS). Articles were first graded as eligible/not eligible/might be eligible. A study was considered potentially relevant, and the methods were reviewed when it could not be clearly excluded based on its title and abstract following discussion between the two reviewers. Discrepancies were resolved by discussion or consultation with a third reviewer (MR). When the same participants were included in more than one eligible report and the age at outcome and exposure measurement was the same, the report with the largest number of participants was included.

2.5. Data extraction and data items

Full texts were retrieved for all articles for data extraction. Data collection and extraction was performed by means of a predefined data extraction sheet and conducted by IS.

Variables included the year, country of origin, study type, sample size, sex and age of study population, level of EDC exposure (high/

occupational vs low), biological specimen collected for EDC and hormone measurement, analysed chemical and metabolites, hormone parameters (e.g. glucocorticoids comprising cortisol, cortisone, etc.), as well as analytical and statistical methods including covariates and whether an association was found for each analysed metabolite. Associations between EDCs and hormone concentrations were reported along with their corresponding effect measures and p-values, where available.

2.6. Quality and risk of bias assessment

To assess the quality and risk of bias of the included studies we used an adapted version of the checklist for Analytical Cross-Sectional Studies developed in the Joanna Briggs Institute (JBI) (available from https://reviewersmanual.joannabriggs.org/) (Moola et al., 2015). The tool comprises eight items which can be answered with 'yes', 'no' or 'unclear'. Key criteria included selection bias, detection bias and confounding bias. Appraisal using this tool allowed authors to either 'include' or 'exclude' studies based on overall quality. If a study had >75 % 'no' or 'unclear' quality categories, then it was excluded from the review.

Low risk of bias was only stated when all items were answered with 'yes'. If one item was answered with 'no' or two items with 'unclear' the risk of bias was considered 'moderate', otherwise as 'high'.

Two authors independently conducted the assessment (IS, FV). Any inconsistencies were resolved through discussion. Discrepancies were resolved by discussion or consultation with a third reviewer (MR).

2.7. Data synthesis and certainty assessment

As cortisol concentrations can change with aging (Martocchia et al., 2022) and during pregnancy (Chai et al., 2024), and to provide a clinical perspective on the topic, studies were grouped by study populations. Due to major heterogeneity between the methodology of the included studies meta-analysis and certainty assessment was not feasible. It was rare for two studies to investigate an association between the same EDC (e.g. PFOA) and the same hormone parameter (e.g. cortisol), with both being measured in the same biological matrix (e.g. maternal serum, cord blood), using the same analytical (e.g. LC-MS) and statistical method (e.g. multiple linear regression analysis). We therefore provided a narrative synthesis of studies by study population.

3. Results

A total of 2094 articles was identified by our search terms in PubMed (n = 2039) and the Cochrane library database (n = 55). After removing one duplicate, 2052 studies were removed because they did not meet our inclusion criteria. The remaining 41 articles were assessed for eligibility. Of these, one study was not in English/German (Hu et al., 2014), two were reviews (Farnbach et al., 2019; Jenkins, 2023), two (Manh et al., 2013, NHU DD et al., 2010) analysed the same study population as a third study (Kido et al., 2014), which was included, three measured EDC and glucocorticoid concentrations but performed no correlation or regression analysis (Suarez-Lopez et al., 2021; Chronister et al., 2023; Yu et al., 2022), four studies did not measure the chemical or a

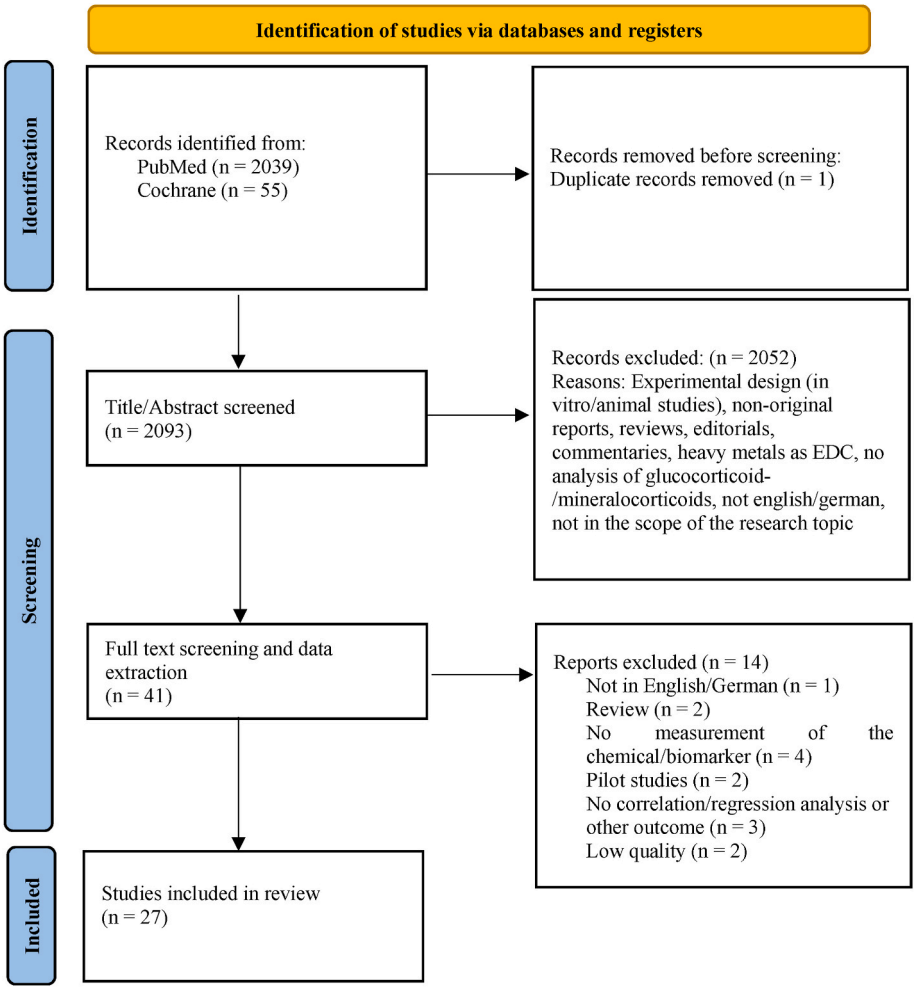

Fig. 1. Flow diagram of article selection according to the PRISMA guidelines.

biomarker directly and assessed exposure upon questionnaire/surveys or geographical data (Jumes et al., 2024; Kongtip et al., 2021; Erkudov et al., 2023; Verplanke et al., 2000), and two studies did not fulfil quality criteria according to JBI (level of quality <75 %) (C., 1973, J, 1972). Therefore, 27 studies were included for further analysis (Fig. 1). The outcomes of the quality and risk of bias assessment of included studies are shown in the Supplement (Table S2). In summary, besides six studies with moderate and four studies with high risk of bias all included studies fulfilled criteria of high quality and low risk of bias.

The studies were conducted in 15 countries. The majority were conducted in China, the remaining in countries in Europe, Asia, and America. Of the 27 studies, 26 analysed glucocorticoid, five mineralocorticoid and two ACTH concentrations either in serum and plasma, urine, hair, follicular fluid, cord blood or saliva. Seven studies (Mustieles et al., 2023; Jenkins et al., 2019; Peng et al., 2023; Sun et al., 2018; Goudarzi et al., 2017; Araki et al., 2017; Dreyer et al., 2020) analysed the cortisol/cortisone ratio which could give information about a potential mechanism via disruption of hydroxysteroid dehydrogenase 11 (11β-HSD) 1 or 2 activity. 11β-HSD1 converts cortisone to cortisol, 11β-HSD2 catalyses the reverse-reaction. One study analysed 6β-hydroxycortisol/cortisol ratio investigating Cytochrom P450 (CYP) 3A4 activity (Petersen et al., 2007). The most frequently analysed EDCs were pesticides (9 studies) and phthalates (8 studies), followed by PFAS (6 studies), persistent organic pollutants (POPs) (6 studies) and bisphenols (5 studies). Pesticides and PFAS were listed as own groups while PCBs, BDEs and dioxins were grouped as POPs. Pesticides and respective groups are listed in the Supplement (Table S3). The study populations were primarily infants/children (15 studies), nine of which investigated an association between maternal EDC exposure and hormone concentrations in their offspring. Five studies examined pregnant women. Study characteristics are summarised in the Supplement (Table S4). EDC concentrations were measured either by liquid or gas chromatography-mass spectrometry (LC-MS, GC-MS). Two studies measured acetylcholinesterase and butyrylcholinesterase as biomarker of pesticide exposure (Cecchi et al., 2012; Silvia et al., 2020). Almost every analysis was adjusted for the typical covariates for the respective study population (e.g. sex, body mass index (BMI), smoking status, gestational age). Covariates are listed in the Supplement. Different statistical methods were applied to study an association, mostly linear or multivariate regression analysis but also Pearson/Spearman correlation, quantile-based g computation, linear mixed models and generalized estimating equations (GEE) analysis. A detailed summary of metabolites, level of exposure, covariates and statistical methods is listed in the Supplement (Tables S5–S8).

Of all included studies investigating an association between EDC and hormone concentration only one study further investigated their impact on metabolic features (Jenkins et al., 2019).

To provide a clinical perspective on the topic data were sorted by study population (pregnant woman, mother/child association, children, adults) and summarised in Tables 1–4.

3.1. Association of EDCs with glucocorticoids and mineralocorticoids in pregnant woman

Five studies investigated EDCs association with glucocorticoids and mineralocorticoids in pregnant women, with focus on pesticides (n = 2),

Table 1
Association of EDC concentration and hormone levels in pregnant woman.

Study	Study population and samples size	Mean/median age in years (SD/range)	Assessment of exposure (biological matrix)	Assessment of outcome (biological matrix)	Key findings
Mustieles et al. (2023)	382 pregnant women in France	32.6 (3.9)	Phthalates using high-performance LC-MS (3 urine samples per day for 7 consecutive days)	Cortisol, cortisone, cortisol/cortisone ratio, 11-dehydro-corticosterone in hair samples	Association of 2-fold increase in: • MBzP with increased cortisol (PC = 13.3 %; 95 % CI 2.65 %, 24.9 %), cortisone (PC = 10.0 %; 95 % CI 0.26 %, 20.7 %), 11-dehydrocorticosterone in third trimester (PC = 17.3 %; 95 % CI 1.67 %, 35.4 %; $p < 0.05$) • MEP with decreased cortisol/cortisone ratio in second and third trimester (PC = −4.98 %; 95 % CI -9.05 %, −0.72 %; PC = −4.18 %; 95 % CI -8.12 %, −0.07 %; $p < 0.05$) • MnBP with increased 11-dehydrocorticosterone (women carrying male fetuses) (PC = 40.4 %; 95 % CI 3.53 %, 91.9 %%; $p < 0.05$) • MnBP with decreased 11-dehydrocorticosterone (women carrying female fetuses) (PC = −22.6 %; 95 % CI -40.5 %, 0.00 %; $p < 0.05$)
Dreyer et al. (2020)	1592 pregnant women in Denmark	30.2 (4.5)	PFAS using LC-MS (serum)	Cortisone, cortisol/ cortisone ratio in diurnal urine	Association of 2-fold increase in: • PFOS with decreased cortisone (PC = −9.1 %; 95 % CI -14.7 %; −3.0 %; $p < 0.05$) • PFOS with increased cortisol/cortisone ratio (PC = 9.3 % (95 % CI 3.3 %, 15.6 %); $p < 0.05$)
Silvia et al. (2020)	53 pregnant women (3rd trimester) in Argentina	24.33 (6.29) (non-spraying period) 23.26 (5.10) (spraying period)	Pesticides by measurement of Acetylcholin-/ Butyrylcholinesterase (blood)	Cortisol in serum (after overnight fasting, before physical activity, 6–8AM)	Decrease in cortisol by 12 % in spraying period compared to non-spraying period ($p = 0.052$)
Cecchi et al. (2012)	97 pregnant women (1st, 2nd trimester) in Argentina	24 (15–36)	Pesticides by measurement of Acetylcholin-/ Butyrylcholinesterase (blood)	Cortisol in serum (after overnight fasting, before physical activity)	Increase in cortisol by 55 % in the spraying period compared to non-spraying period ($p \leq 0.01$)
Giesbrecht et al. (2016)	174 pregnant women in Kanada	31.5 (22.4–42.8)	BPA using high performance MC/ Orbitrap Elite hybrid MS (spot urine)	Cortisol in saliva (upon waking, 30 min after waking, at 11.30 a.m., and at 8.30 p.m.)	Association of 10-fold higher BPA with flattened diurnal cortisol pattern (β = 0.01; 95 % CI 0.001 %, 0.19 %)

LC-MS, liquid-chromatography mass spectrometry; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; MnBP, mono-n-butyl phthalate; PFAS, per- and polyfluoroalkyl substances; PFOS, perfluorooctanesulfonic acid; PFOA, perfluorooctanoic acid; BPA, Bisphenol A; PC, percentage change; CI, confidence interval.

phthalates (n = 1), bisphenols (n = 1) and PFAS (n = 1). Studies suggest that EDC exposure during pregnancy was mostly associated with higher glucocorticoid concentrations in pregnant women while association with mineralocorticoids depended on the sex of the fetus. All studies measured cortisol with time standardized specimen collection and all have considered relevant, but not always the same covariates. Data are summarised in Table 1. Further information are presented in the Supplement (Table S5).

A recent study from 2023 demonstrated a significant association between the concentration of urinary phthalate metabolites and glucocorticoid and mineralocorticoid levels in hair samples of 382 pregnant women. Regression estimates were expressed as percent change (PC) for each twofold increase in standardized urinary phthalate biomarkers. Each doubling in urinary monobenzyl phthalate (MBzP) concentration was associated with an average increase of 13.3 % for cortisol, 10.0 % for cortisone, and 17.3 % for 11-dehydrocorticosterone in hair samples ($p = < 0.05$), while monoethyl phthalate (MEP) was associated with a decreased cortisol/cortisone ratio (percentage change (PC) = −4.98 %, $p < 0.05$). Interestingly, the association between mono-n-butyl phthalate (MnBP) and 11-dehydrocorticosterone differed according to the gender of the fetus (PC in woman carrying male fetuses = 40.4 %, $p < 0.05$; PC in women carrying female fetuses = −22.6 %, $p < 0.05$) (Mustieles et al., 2023).

A negative association between EDCs and glucocorticoids in pregnant women was observed for higher urinary bisphenol levels (creatinine-adjusted), as for each 10-fold increase in bisphenol A (BPA), diurnal cortisol patterns in salivary cortisol flattened by 1 % ($\beta = 0.01$; 95 % CI 0.001–0.19) (Giesbrecht et al., 2016). Another study investigated 1592 pregnant women and showed that a twofold increase in perfluorooctanesulfonic acid (PFOS) concentration was associated with a significant ($p < 0.05$) decrease by −9.1 % in urinary cortisone levels and an increase by 9.3 % in urinary cortisol/cortisone ratio with a significant ($p < 0.01$) dose-response association in the test for trend across tertiles (Dreyer et al., 2020). Two studies conducted in 2012 and 2020 compared cortisol concentrations in 97 and 52 pregnant women, respectively, in the spraying versus non-spraying period in Argentina showing the exact difference when measuring hormones in different trimester (increase of cortisol levels by 55 % in 1st/2nd trimester ($p \leq 0.01$) (Cecchi et al., 2012) vs. decrease in cortisol levels by 12 % in the 3rd trimester, $p = 0.052$) (Silvia et al., 2020). Applied pesticides were organophosphates in both studies, and furthermore neonicotinamides and carbamates in the study reporting a decrease in cortisol levels (Silvia et al., 2020).

3.2. Association of maternal EDC exposure with glucocorticoids and mineralocorticoids in offspring

Nine studies investigated an association between EDC levels in pregnant woman and glucocorticoid and mineralocorticoid hormone concentrations in offspring with focus on PFAS (n = 4), phthalates (n = 3), pesticides (n = 2) and bisphenols (n = 1). Studies suggest that most maternal PFAS exposures were associated with higher glucocorticoids in offspring, independent from the fetal sex, while phthalates, bisphenols and pesticides were associated with higher glucocorticoids in female offspring and lower glucocorticoids and mineralocorticoids in male offspring. The data are summarised in Table 2 (further information in Supplemental Table S6).

In 2017, a study of 185 mother-child pairs demonstrated that PFOS concentration in maternal serum was negatively associated with cortisol ($\beta = -0.844$, $p < 0.001$) and cortisone ($\beta = -1.15$, $p < 0.001$) in cord blood but positively associated with the cortisol/cortisone ratio ($\beta = 0.312$, $p = 0.032$) (Goudarzi et al., 2017). The opposite was shown by another group investigating 202 mother-child pairs in 2023 with higher cortisol concentration in cord blood being significantly associated with higher maternal-branched PFAS (PC of cortisol: 14.16–24.40 % upon one unit change of PFAS concentration, $p < 0.05$) with a dose–response effect (Cai et al., 2023). This is concordant with one study from 2020 showing a positive association between interquartile range changes in cord serum PFAS levels and 11-deoxycortisol, a direct precursor of cortisol, in 374 mother-child pairs (PC of 11-deoxycortisol = 6.41 %, $p = 0.02$); they further found that perfluoroalkyl ether sulfonic acid (PFESA) and serum cortisol concentration were significantly associated in female offspring (PC = 13.13 %, $p < 0.01$) indicating a sex-specific association (Liu et al., 2020). All three studies considered relevant covariates, but only the two that suggested a positive association between glucocorticoids and PFAS included pre-pregnancy BMI in their model. In 2017, Araki et al. investigated 202 mother-child-pairs and detected a significant association between an interquartile range increase in mothers' mono(2-ethylhexyl) phthalate (MEHP) and cortisol concentrations (ß = −0.412, $p = 0.018$) in cord blood without sex-specific differences (Araki et al., 2017). In 2018, an analysis of 287 mother-child pairs showed the opposite with each 10-fold increment of maternal MEHP concentration being associated with 14.2 % (95 % CI: 0.6 %, 29.5 %) increased cortisol levels in cord serum. They also demonstrated that effects were sex-dependant as a positive association between phthalates and glucocorticoids was only observed for female infants (PC ranging from 16.2 % to 55.9 %) while for male infants, a significant association was shown for specific phthalate concentrations where each 10-fold increase was associated with 20.8 %–36.3 % reduction of cortisol concentration (Sun et al., 2018). Differences may be explained by the different covariates included in the analysis (see Table S6). Both studies further demonstrated a negative association between phthalate metabolites and cortisone levels, and a positive association between phthalates and cortisol/cortisone ratio (Araki et al., 2017; Sun et al., 2018). However, recent data suggest that mothers' phthalate and PFAS pollution during pregnancy is not associated with altered hair cortisol levels in 11–14 year old offspring (Sears et al., 2024). Another study showed that the association between bisphenol concentration in mothers and infants' baseline salivary cortisol levels and cortisol reactivity upon a stressor differed according to the sex of the child. Cortisol reactivity was determined by the slope parameter estimates for the linear and quadratic effects of time. The stressor was a blood draw completed by a certified paediatric phlebotomist. Upon each 10-fold increase in maternal BPA concentration female infants showed an 14 % increase in baseline cortisol ($\beta = 0.13$, (95 % CI: 0.01, 0.26)) while results differed for male infants ($\beta = -0.22$ (95 % CI: −0.39, −0.05)) who presented with a 8.1 % decrease in baseline cortisol, but a 17 % increased reactivity ($\beta = 0.30$, (95 % CI: 0.04, 0.56) (Giesbrecht et al., 2017). Association of maternal concentration of organochlorines (OCPs) to cord cortisol levels seems also to differ according to the sex as among female newborns 10-fold increase in p, p′-dichlordiphenyldichlorethan (p,p′- DDD) concentration was associated with increased cortisone levels ($\beta = 0.358$, $p = < 0.05$) while a 10-fold increase in trans-nonachlor and mirex was associated with a decrease in cortisol ($\beta = -0.372$, $p < 0.05$; $\beta = -0.588$, $p < 0.01$) and cortisone concentrations ($\beta = -0.426$, $p < 0,05$; $\beta = -0.572$, $p < 0.05$) in newborn boys (Araki et al., 2018). A recent study of 885 mother-child pairs from 2024 further demonstrated an interquartile range increase in 2,4-dichlorophenoxyacetic acid (2,4 D) concentrations in maternal urine being associated with a decrease in cortisol (−8.67 %, $p < 0.01$), cortisone (−13 %, $p < 0.01$), 11-deoxycortisol (−7.84 %, $p < 0.05$), corticosterone (−8.09 %, $p < 0.05$) and aldosterone (−11.17 %, $p < 0.05$), all measured in spot urine, in one-month-old infants which was significant only for males (Liu et al., 2024).

3.3. Association of EDC concentration with glucocorticoids, mineralocorticoids and ACTH levels in children

Seven studies investigated an association between EDCs, glucocorticoid, mineralocorticoid and ACTH concentrations in children with focus on phthalates (n = 4), bisphenols (n = 2), PFAS (n = 1), POPs (n = 1) and pesticides (n = 1). Two studies investigated infants (<12 months)

Table 2
Association of maternal EDC exposure with glucocorticoids and mineralocorticoids in offspring.

Study	Study population and sample size	Mean age of the child in years (SD)	Mean/median age of the mother in years (SD/range)	Assessment of exposure (biological matrix)	Assessment of outcome (biological matrix)	Key findings
(Goudarzi et al., 2017)	185 mother-child pairs in Japan	0	29.7 (4.7)	PFAS using LC-MS (blood)	Cortisol, cortisone, cortisol/cortisone ratio in cord blood	Association of: • PFOS with decreased cortisol (β = −0.844, p < 0.001) and cortisone (β = −1.15, p < 0.001) • PFOS with increased cortisol/cortisone ratio (β = 0.312, p = 0.032) • Highest quartile of PFOS with decrease of 23.98 ng/mL (95 % CI -47.12, −11.99; p for trend = 0.006) in cortisol and 63.21 ng/mL (95 % CI -132.56, −26.72; p for trend <0.001) in cortisone levels compared with the lowest quartile
(Liu et al., 2020)	374 mother-child pairs in China	0	27.6 (2.9)	PFAS using LC-MS (serum)	Cortisol, 11-deoxycortisol in cord blood	Association of interquartile range increase in: • PFOA (PC = 9.22 %, p < 0.01), PFNA (PC = 11.24 %, p < 0.01), PFDA (PC = 9.35, p < 0.01), PFUDA (PC = 7.64 %, p = 0.02), PFDoA (PC = 7.12 %, p = 0.045), PFHxS (PC = 7.88 %, p = 0.02), PFOS (PC = 6.54 %, p = 0.03) with increased 11-deoxycortisol • PFESA with increased cortisol in females (PC = 13.13 %, p < 0.01)
(Cai et al., 2023)	202 mother-child pairs in China	0	29.3 (4.8)	PFAS using LC-MS (serum)	Cortisol in cord blood	Association of one unit change in PFOS (PC = 16.21 %, p = 0.004), PFOA (PC = 24.4 %, p = 0.025), PFNA (PC = 15.9 %, p = 0.038), PFDA (PC = 17.6 %, p = 0.034), and PFTrDA (PC = 14.16 %, p = 0.021) with increased cortisol
(Liu et al., 2024)	885 mother-child pairs in China	0	30.08 (3.97)	2,4 D using ultraperformance LC-MS (spot urine)	Cortisol, cortisone, 11-deoxycortisol, corticosterone, aldosterone in spot urine	Association of interquartile range increase in 2,4 D with decrease in cortisol (PC = −8.67 %, p < 0.01), cortisone (PC = −13 %, p < 0.01), 11-deoxycortisol (PC = −7.84 %, p < 0.05), corticosterone (PC = −8.09 %, p < 0.05) and aldosterone (PC = −11.17 %, p < 0.05)
(Araki et al., 2018)	232 mother-child pairs in Japan	0	30.45 (4.81)	29 organochlorine pesticides	Cortisol, cortisone in cord blood	Association of 10-fold increase in: • p'p'DDD with increased cortisone (β = 0.358, p < 0.05) in females • Trans-nonachlor with decreased cortisol (ß = −0.372, p < 0.05) and cortisone (ß = −0.426, p < 0.05) in males • Mirex with decreased cortisol (ß = −0.588, p < 0.01) and cortisone (ß = −0.572, p < 0.05) in males
(Sun et al., 2018)	287 mother-child pairs in China	0	28.3 (3.2)	Phthalates using LC-MS (spot urine)	Cortisol, cortisone, cortisol/cortisone ratio in cord blood	Association of 10-fold increase in: • MEHP with increased cortisol (PC = 14.2 %, 95 % CI 0.6 %, 29.5 %), • MBzP with increased cortisol/cortisone ratio (PC = 24.7 %, 95 % CI 4.1 %, 49.5 %) • MECPP with decreased cortisone (PC = −14.4 %, 95 % CI -25.2 %, −2.1 %) • MEOHP with decreased cortisone (PC = −15.5 %, 95 % CI -27.6 %, −1.4 %) Sex-stratified analysis (no exact numbers provided): Association of 10-fold increase in: • MEHP MEHHP, MEOHP, ΣDEHP with increased cortisol in females • MEHP with increased cortisone in females (1st trimester) • MECPP, MEHHP and MEOHP with decreased cortisol and cortisone in males
(Araki et al., 2017)	202 mother-child pairs in Japan	0	29.8 (4.9)	MEHP using GC-MS (blood)	Cortisol, cortisone, cortisol/cortisone ratio in cord blood	Association/correlation of interquartile range increase in: • MEHP with decreased cortisol (Spearman's ρ = −0.273; β = −0.412, p = 0.018) andcortisone (ß = −0.570, p = 0.015) • MEHP with increased cortisol/cortisone ratio (p = 0.036)
(Giesbrecht et al., 2017)	132 mother-child pairs in Kanada	0.25	30.6 (20–42)	BPA using high performance MC/Orbitrap Elite hybrid MS (spot urine)	Cortisol in saliva (before and after stressor)	• Association of 10-fold increase in BPA with increased cortisol (β = 0.13 (95 % CI 0.01, 0.26) in females and decreased cortisol in males (β = −0.22; 95 % CI -0.39, −0.05)

(*continued on next page*)

Table 2 (*continued*)

Study	Study population and sample size	Mean age of the child in years (SD)	Mean/median age of the mother in years (SD/range)	Assessment of exposure (biological matrix)	Assessment of outcome (biological matrix)	Key findings
						• Reactivity increased by 17 % in males (insignificant in females)
(Sears et al., 2024)	205 mother-child pairs in USA	11–14	NA	Phthalates (spot urine), PFAS (serum) using LC-MS	Cortisol, cortisone in hair samples	No association

LC-MS, liquid-chromatography mass spectrometry; GC-MS, gas-chromatography mass spectrometry; DEHP, di(2-ethylhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MBzP, monobenzyl phthalate; MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; PFAS, per- and polyfluoroalkylated substances; PFOS, perfluorooctanesulfonic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexanesulfonic acid; PFDA, Perfluoro-n-decanoic acid; PFUDA, perfluoroundecanoic acid; PFDoA, perfluorododecanoic acid; PFTrDA, perfluorotridecanoic acid; 2,4D, 2,4-dichlorophenoxyacetic acid; BPA, Bisphenol A; DDD, p,p′-dichlordiphenyldichlorethan; PC, percentage change; CI, confidence interval; NA, not available.

and toddlers (1–2 years), three studies pre-/peripubertal children (6–11 years), one study children in early adolescence (11–14 years) and one study children in late adolescence (>16 years). Studies suggest that exposures of phthalates, pesticides and POPs during childhood were associated with higher concentrations of ACTH, glucocorticoids and mineralocorticoids while PFAS and bisphenols were associated with lower concentrations of glucocorticoids. The data are summarised in Table 3 (further information in Supplemental Table S7).

3.3.1. *Infants and toddlers*

Jenkins et al. prospectively investigated an association of phthalates and mineralocorticoid activation and consequently elevated blood

Table 3
Association of EDC concentration and hormone levels in children.

Study	Study population and sample size	Mean age of the child in years (SD)	Sex	Assessment of exposure (biological matrix)	Assessment of outcome (biological matrix)	Key findings
(Jenkins et al., 2019)	18 premature infants in USA	0.55 (0.04) (hypertensives) 0.63 (0.06) (normotensives)	m, f	DEHP using LC-MS (spot-urine)	Cortisol/cortisone ratio, markers of MR activation (ENac, pNCC) in spot urine	Association of: • DEHP with cortisol/cortisone ratio ($\beta = 0.0001$, $p = 0.046$) • Hypertension with ENac ($\beta = 0.703$, $p = 0.0003$), (pNCC) ($\beta = 0.703$, $p = 0.032$)
(Kim et al., 2018)	553 infants in South Korea	0.25; 0.75; 1; 1-25	m, f	Phthalates using LC-MS (spot urine)	Cortisol in spot urine	Association of MEHHP ($\beta = 0.18$, $p < 0.0001$); MEOHP ($\beta = 0.17$, $p < 0.0001$); MiBP ($\beta = 0.13$, $p = 0.0001$); MnBP ($\beta = 0.21$, $p < 0.0001$); and molar sum of metabolites ($\beta = 0.21$, $p < 0.0001$) with increased cortisol
(Zhou et al., 2022)	30 prepubertal girls in China	7.3 (0.679) 7.1 (0.742)	f	Phthalates, BPA, BPB using ultraperformance LC-MS (urine)	Cortisol in serum (no information about timing)	No correlation
(Xu et al., 2014)	45 prepubertal children in China	8	m, f	POPs (PCBs, PBDEs, PCDD/F) using GC-MS (serum)	Cortisol in serum (no information about timing)	Correlation between $\sum$pBDEs and ACTH ($r = 0.61$, $p < 0.05$)
(Mustieles et al., 2018)	172 peripubertal boys in Spain	9.8 (9.7–10.0)	m	BPA using LC-MS (spot urine)	Cortisol in serum (fasting morning samples)	Association of BPA with decreased cortisol (as continuous variable (exponential $\beta = 0.84$, $p = 0.02$); across tertiles (exponential $\beta = 0.83$ (second tertile), exponential $\beta = 0.77$ (third tertile); p-trend = 0.04)
(Sears et al., 2024)	205 adolescents in USA	11–14	m, f	Phthalates (spot urine), PFAS (serum) using LC-MS	Cortisol in hair samples	Association of interquartile range increase in: • PFOS PFOA, PFHxS with decreased cortisol • Log2-transformed PFOS concentration during childhood with approximately 20 % lower hair concentrations • Log2-transformed PFNA concentrations at age 8 years with approximately 15 % higher hair cortisol concentration • All phthalate metabolites, driven by MEP, MiBP, and MBzP with increased cortisol (difference in log10cortisol = 0.13; 95 % CI 0.03 %, 0.22 %)
(Freire et al., 2021)	117 adolescents in Spain	16–17	m	Pesticides using ultra-high-performance LC-MS (urine)	ACTH, cortisol in serum (non-fasting, afternoon)	• Interaction of 1N with ACTH in Cyp2D6 G1846A polymorphism ($p = 0.02$) • Interaction of ETU with cortisol in poor CYP2D6 metabolizer (40 % variation in detected versus undetected ETU (95 % CI 2, 91; $p < 0.05$))

ACTH, adrenocorticotropic hormone; MR, mineralocorticoid receptor; EnaC; epithelial sodium channel; pNCC, phosphorylated (activated) sodium chloride cotransporter; DEHP, di(2-ethylhexyl) phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MBzP, monobenzyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; MEP, monoethyl phthalate; MiBP, monoisobutyl phthalate; MnBP, mono-n-butyl phthalate; ETU, ethylenethiourea; 1N, 1-naphthol; PFOS, perfluorooctanesulfonic acid; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexanesulfonic acid; LC-MS, liquid chromatography–mass spectrometry; GC-MS, gas chromatography–mass spectrometry; BP, bisphenol; PFAS, per- and polyfluoroalkyl substances; POPs, persistent organic pollutants; ETU, ethylenethiourea; 1N, 1-naphthol; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyls; PCDD/F, polychlorinated dibenzo-p-dioxins and dibenzofurans; f, female; m, male; CI, confidence interval.

pressure in hypertensive premature infants being exposed to di(2-ethylhexyl) phthalate (DEHP) by intravenous and respiratory tubing. DEHP levels in urine were positively associated with hypertension (β = 5.0389, p = < 0.0001). The magnitude of the coefficient decreases toward zero when urinary cortisol/cortisone ratio was added to the analysis, suggesting that the cortisol/cortisone ratio may mediate the effect of intravenous DEHP exposure on systolic blood pressure (SBP) index. In addition, renin levels were suppressed and urinary exosome expression analysis by Western Blot revealed a significant increase in markers of mineralocorticoid receptor (MR) activation, epithelial sodium channel (EnaC) (β = 0.703, p = 0.0003) and phosphorylated (activated) sodium chloride cotransporter (pNCC) (β = 0.703, p = 0.032) in hypertensive infants (Jenkins et al., 2019). However, direct regression analysis between MR activation markers or mineralocorticoid hormones and DEHP levels were not reported, hormones were measured in spot urine and the size of the study population was quite small (n = 18). In accordance with Jenkins et al., urinary phthalate concentrations were positively correlated with urinary cortisol concentrations in spot urine in early childhood (<15-months) (association of cortisol with molar sum of phthalate metabolites, β = 0.29 and p < 0.0001) (Kim et al., 2018).

3.3.2. Prepubertal children

In contrast to infants and toddlers, there was no significant correlation between serum steroid hormone and phthalate and bisphenol concentrations in prepubertal girls (Zhou et al., 2022). However, urinary BPA concentrations in peripubertal boys were significantly associated with lower cortisol concentrations in the serum, both when BPA concentrations were treated as continuous variable (exponential β = 0.84, p = 0.02) and across tertiles (β = 0.83 (second tertile), β = 0.77 (third tertile); p-trend = 0.04) (Mustieles et al., 2018). The differences in study results may not only be based on the sex of the study population, but also on the timing of sample collection as Mustieles et al. determined cortisol concentrations in fasting blood samples in the morning (Mustieles et al., 2018), whereas Zhou et al. (2022) did not provide information on the timing of cortisol measurement. In 2014, a significant correlation with ACTH concentrations in prepubertal children was shown for several subtypes (congeners) of flame retardants BDEs ($\sum$ PBDEs and ACTH: Pearson r = 0.61, p < 0.05) (Xu et al., 2014). Results should be interpreted cautiously as authors did not provide information about the timepoint of ACTH measurement.

3.3.3. Adolescents

Freire et al. investigated late adolescents (>16 years) and found a significant interaction, expressed as the percentage variation in hormone concentration for detected versus undetected pesticide metabolite, of 1-naphthol and ACTH (p = 0.02) in subjects with the CYP2D6 G1846A polymorphism and further between ethylenethiourea and cortisol (p < 0.05) in poor CYP2D6 metabolizers (Freire et al., 2021). Cortisol measurement was conducted in the afternoon in non-fasting blood samples which limits comparability with other study results. Another recent study investigated the association of phthalate and PFAS concentrations during childhood with hormone concentration in adolescents and found that 1-quartile increase in all childhood phthalate metabolites was associated with 35 % higher adolescent hair cortisol (difference of log10cortisol = 0.13; 95 % CI: 0.03, 0.22). In contrast, interquartile range increases of PFAS concentrations in childhood were associated with approximately 20 % lower hair cortisol concentrations. They further found that the association between childhood phthalate mixtures and hair cortisol varied by race as a quartile increase in all phthalate metabolites was associated with 86 % higher hair cortisol among black participants (difference of log10cortisol = 0.27; 95 % CI: 0.07, 0.47) (Sears et al., 2024).

3.4. Association of EDC concentration with glucocorticoids and mineralocorticoids in adults

Seven studies investigated an association between EDC and glucocorticoid and mineralocorticoid concentrations in adults with focus on POPs (n = 5), pesticides (n = 4), phthalates (n = 1), bisphenols (n = 1), and PFAS (n = 1). Studies suggest that exposure of most EDCs in adults was associated with higher glucocorticoid and lower mineralocorticoid concentrations. Data are summarised in Table 4 (further information in Supplemental Table S8).

In 2023, it was shown, that in 264 childbearing-aged women individual metabolites of phthalates (mPAE) and molar sums of mPAEs ($\sum$mPAEs) were negatively associated with cortisol levels (−0.17 change of steroid concentration per interquartile range (IQR) increase in $\sum$mPAEs, p = 0.03) but positively with cortisone concentrations (0.37 change of steroid concentration per IOR increase in $\sum$mPAEs, p < 0.01) in follicular fluid. For details about associations of different mPAE, please see Table S8. The mixture of mPAEs was also negatively associated with cortisol (β = −0.38, 95 % CI: −0.68, −0.09) and corticosterone (β = −0.47, 95 % CI: −0.85, −0.09) levels (Li et al., 2023). Further investigations of an association between certain EDCs, in particular 140 pesticides, four PCBs, BPA and bisphenol S (BPS) with hair cortisol, cortisone, tetrahydrocortisol and cortisol/cortisone ratio in hair samples of 196 adult women was conducted in 2024. There was a significant association of at least 10 to 17 biomarkers for each hormone. The strongest association was found for imidacloprid (IMI) with a 2-standard deviation-increase in log10-transformed IMI concentrations being associated with a 30.4 % (95 % CI: 15.9, 46.8 %, p < 0.05) increase in hair cortisol levels and 39.6 % (95 % CI: 23.1, 58.3 %, p < 0.05) increase in hair cortisone levels. They also demonstrated a positive association between BPA and cortisol/cortisone ratio, and BPS and hair cortisol, tetrahydrocortisol, tetrahydrocortisone and cortisone levels (p < 0.05) (Peng et al., 2024). Another study group focused on adult Vietnamese women investigating the relationship between steroid hormone levels in saliva and serum, and dioxin concentrations in breast milk. The levels of cortisol and cortisone of women from the dioxin hotspot region were significantly higher than those of women from an unexposed area (p < 0.001), and these levels were further positively associated with dioxin concentrations in all subjects (r^2 = 0.114, p < 0.001 (salivary cortisol); r^2 = 0.109, p < 0.001 (salivary cortisone); r^2 = 0.066, p < 0.01 (serum cortisol), r^2 = 0.142, p < 0.001 (serum cortisone) (Kido et al., 2014). Three study groups studied PCBs association with cortisol levels in 63, 112 and 196 adults, respectively, all demonstrating no significant association (Gaum et al., 2020; Jansen et al., 2020; Peng et al., 2023). In 2007, another study investigated 6β-hydroxycortisol/cortisol ratio in the urine to investigate CYP3A4 activity and found the ratio was weakly positively correlated with PCB levels (β = 0.093, p = 0.054) and further with organochlorines (OCPs), in particular p, p′-dichlordiphenyldichlorethylene (p,p′-DDE) (β = 0.073, p = 0.081), dichloro-diphenyl-trichloroethane (o,p′-DDT) (β = 0.065, p = 0.069) and hexachlorobenzene (HCB) (β = 0.137, p = 0.02) in men (Petersen et al., 2007). In farmworkers of northern Thailand, cortisone, dehydrocorticosterone (DHC) and deoxycorticosterone (DOC) levels, all measured in non-fasting afternoon blood samples, were negatively associated with thiamethoxam (THX) concentration. Contradictory, in the same study population DHC levels were positively associated with IMI concentrations (Suwannarin et al., 2021).

4. Discussion

To our best knowledge, this review is the first to provide a comprehensive overview of epidemiological studies investigating the association of common EDCs with altered concentrations of glucocorticoids, mineralocorticoids and ACTH in human specimen and a potential connection to metabolic disorders. Overall, even though largely understudied, EDCs of several classes of chemicals are potentially interfering

Table 4
Association of EDC concentration and hormone levels in adults.

Study	Study population and sample size	Mean age in years (SD)	Sex	Assessment of exposure (biological matrix)	Assessment of outcome (biological matrix)	Key findings
(Li et al., 2023)	264 woman in childbearing age in China	30	f	Phthalates using ultraperformance LC-MS (follicular fluid)	Cortisol, cortisone, corticosterone in follicular fluid	Association of interquartile range increase in: • mEP with decreased corticosterone (β = −0.26; p = 0.019) and cortisol (β = −0.23; p = 0.008) • mEOHP with decreased corticosterone (β = −0.3; p < 0.001) and cortisol (β = −0.27; p < 0.001), increased cortisone (β = 0.41; p=<0.001) • mEHP with decreased corticosterone (β = −0.16; p = 0.043) and cortisol (β = −0.21; p = 0.001), increased cortisone (β = 0.35; p < 0.001) • ∑mDEHP with decreased corticosterone (β = −0.20; p = 0.025) and cortisol (β = −0.25; p < 0.001), increased cortisone (β = 0.42; p < 0.001) • Mixture of phthalates with decreased corticosterone (β = −0.47, 95 % CI -0.85, −0.09) and cortisol (β = −0.38, 95 % CI -0.68, −0.09) • ∑mPAEs with decreased cortisol (β = −0.17; p = 0.03), increased cortisone (β = 0.37; p < 0.001) • ∑mDBP (β = 0.32; p = 0.01), mBP (β = 0.35; p < 0.001), miBP (β = 0.34; p < 0.001) with increased cortisone
(Peng et al., 2024)	196 women in China	34.1 (5.77)	f	BPA BPS 140 pesticides 4 PCB 7 BDE using GC-MS (hair)	Cortisol, cortisone, cortisol/cortisone ration, tetrahydrocortisol, tetrahydrocortisone in hair samples	Association of 2 standard-deviation increase in log10-transformed: • Imidacloprid (PC = 30.4 % (95 % CI: 15.9, 46.8 %), thiamethoxam (PC = 23.0 %, 95 % CI 8.35 %, 39.7 %) and 4 other pesticides, (p < 0.05) with increased cortisol • Imidacloprid (PC = 39.6 %, 95 % CI 23.1, 58.3 %, p < 0.05) and 10 other pesticides with increased cortisone • 7 pesticides with increased tetrahydrocortisol • Imidacloprid (PC = 30.6 %; 95 % CI 15.4 %, 47.7 %) and 11 other pesticides with increased tetrahydrocortisone • Tebuconazole with decreased cortisol (PC = −11.3 %, 95 %CI 23 %, 2.14 %; p < 0.05) • 7 pesticides with cortisol/cortisone (positive and negative), (p < 0.05) • BPS with increased cortisol, tetrahydrocortisol, tetrahydrocortisone and cortisone, (p < 0.05)
(Gaum et al., 2020)	112 former employees of recycling company in Germany	47.3 (12.5)	m, f	14 PCBs 15 OH-PCB using GC-MS (plasma)	Cortisol in plasma (no information about timing)	No association
(Jansen et al., 2020)	63 patients before and after bariatric surgery in Norway	47 (43–50)	m, f	PFAS, pesticides, persistent organic pollutants using LC-MS (serum)	Cortisol in serum (between 10AM and 1PM preoperatively; between 8AM and 10AM at 1 year follow-up)	No association
(Kido et al., 2014)	109 Women in Vietnam	27.3 (3.68) (exposed) 26.1 (2.82) (non-exposed)	f	Dioxin using GC-MS (breast milk)	Cortisol in saliva, serum (between 8 and 10 a.m.)	Correlation of dioxin with salivary cortisol (r^2 = 0.114, p < 0.001); salivary cortisone (r^2 = 0.109, p < 0.001); serum cortisol (r^2 = 0.066, p < 0.01); and serum cortisone (r^2 = 0.142, p < 0.001)
(Petersen et al., 2007)	308 adults in Faroe Island	38 (18–60)	m, f	∑PCB, PCB-TEQ, pesticides using GC-MS (serum)	6β-hydroxycortisol/cortisol in diurnal urine	Association of ∑PCB (β = 0.093; p = 0.054); PCB-TEQ (β = 0.095; p = 0.036); DDE (β = 0.073; p = 0.081); HCB (β = 0.137; p = 0.02); DDT (β = 0.065; p = 0.069) with increased 6β-hydroxycortisol/cortisol ratio in males
(Suwannarin et al., 2021)	143 Farmworkers in Thailand	30.1 (5.8)	m	Pesticides using LC-MS (spot urine)	Cortisone, 11-dehydrocorticosterone, deoxycorticosterone in serum (non-fasting, between 5AM and 12 a.m.)	Association of: • Clothianidin, thiamethoxam with decreased cortisone • Thiamethoxam with decreased dehydrocorticosterone and deoxycorticosterone • Imidacloprid with increased dehydrocorticosterone

PCB, polychlorinated biphenyls; PCB–TEQ, [(PCB-105 + PCB-118 + 5 * PCB-156) * 10]; PBDE, polybrominated diphenyl ethers; mPAE, individual metabolites of phthalates; ∑, molar sum; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MBzP, monobenzyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; MEP, monoethyl phthalate; MiBP, monoisobutyl phthalate; MnBP, mono-n-butyl phthalate; mMP, monomethyl phthalate; BP, bisphenol; PFAS, per- and polyfluoroalkyl substances; HCB; hexachlorobenzene; DDE, p,p'-dichlorodiphenyldichloroethylene; DDT, dichloro-diphenyl-trichloroethane; f, female; m, male; PC, percentage change; CI, confidence interval.

with glucocorticoid and mineralocorticoid metabolism altering steroid hormone concentrations. Children and pregnant woman were amongst the most studied populations due to the known impact of EDCs on fertility (Green et al., 2021) and fetal development (Rolfo et al., 2020). Most investigated EDCs were pesticides and phthalates. All but three studies showed significant associations between specific EDCs and hormone levels. Results differed according to age and sex of the study population, especially among children, as well as analysed matrices, and measured hormone parameters and EDC metabolites. Only one study investigated a connection between EDC concentration, hormone level and metabolic features (Jenkins et al., 2019). However, heterogeneity amongst study methodologies impairs the comparability of the studies and did not allow meta-analysis.

There are a few aspects, which we would like to discuss to guide future investigations of EDC research.

4.1. Missing connection of EDC concentration, hormone levels and steroid-sensitive metabolic phenotypes

An association between various EDCs and components of the metabolic syndrome has been previously shown by many epidemiological studies, summarised 2021 by Haverinen et al. (2021). Pan et al. further summarised associations between PFAS and hypertension (Pan et al., 2023), Arab et al. between pesticides and insulin-resistance-related metabolic diseases (Arab and Mostafalou, 2023), Varghese et al. between bisphenols and obesity (Varghese and Hall, 2023). In addition, *in vitro* studies demonstrated that EDCs alter steroid hormone secretion and interact with steroid hormone receptors on a cellular level (summarised by Zhang et al. (2019). Our search revealed only one study that investigated a potential connection between DEHP exposure and arterial hypertension mediated by altered glucocorticoid levels (Jenkins et al., 2019). However, even though some studies that demonstrated an association between EDC levels and steroid hormone concentration did not analyse a further connection to specific clinical features at all, others did their analysis within a different research objective, e.g. the influence of EDCs on fetal development or onset of puberty. Therefore, they measured glucocorticoids alongside other hormones like androgens and investigated further associations to other clinical features e.g. birth weight or tanner stadium rather than features of the metabolic syndrome. To accurately determine the mechanism by which EDCs contribute to the development of the metabolic syndrome and to uncover in the future not only associations but also causalities, future studies should in a first step include hormone diagnostics alongside clinical and biochemical parameters like lipids, degree of hypertension and HbA1c level in association to EDC pollution and conduct formal mediation analyses. Eventually randomized withdrawal studies should be conducted to determine changes in those parameters upon reduced exposure to EDCs by lifestyle modification.

4.2. Confounders and differences in study results

The differences and inconclusiveness of study results might not solely be based on different study designs, study populations or analytical methods. In general, besides typical confounders like BMI and age results of those kind of studies are biased by several other aspects. First, a singular measurement of certain EDCs may not be representative as measured concentration depends on half-life and time as well as possible local EDC accumulation in target tissues. Repeated measurement or measurement of 24h-urine or alternate matrices like hair or nails can be more reliable (Padmanabhan et al., 2021). In addition, biases due to diet, physical activity, and medication, which were not listed as typical confounders in most of the included studies, must always be considered depending on the specific EDCs. When analysing cortisol concentrations as an outcome parameter, it is essential to consider the circadian rhythm of cortisol secretion. Although most of the included studies used standardized specimen collection, such as diurnal urine samples or morning fasting serum, some studies still measured cortisol in spot urine or blood samples collected at any time of day or provided no information regarding the specimen collection method. This variability undermines the comparability of study participants within a single study, thereby affecting the overall study quality, and further hinders the ability to compare findings across different studies. A well-known effect measure modifier, considered by most studies, is sex. As shown in Table 2, EDCs association to hormone concentrations in children differed in many studies according to their sex which is not surprising as males and females respond differently to stressors (Verma et al., 2011). Future studies must always incorporate the sex in their analysis to understand the sex-specific action of EDCs. A dose-dependent effect of EDCs must also be considered in the analysis as some EDCs have a non-monotonic effect, i.e. they have no effect when the concentration is low, but also not when it is too high (Vandenberg et al., 2012). Therefore, interquartile analysis might be helpful and provide insight into dose-dependent effects of EDCs.

Besides this, interaction or co-exposure with other EDCs must also be considered as confounder. Only one study adjusted their model for concentration of another chemical (Araki et al., 2017), while most studies simply investigated a single EDC or EDC class. Therefore, there is little to no knowledge about additive and interactive effects of EDCs. Humans are constantly and simultaneously exposed to mixtures of different chemicals from different classes of EDCs. Future studies should analyse mixed exposure of EDCs by adjusting the impact of a specific EDC exposure to exposure of other EDCs or by applying statistical methods such as the Bayesian mixture model to represent a more realistic analysis. Furthermore, studies must be combined with *in vitro* or *in vivo* experiments to determine additive, synergistic/antagonistic and interactive effects. This is also supported by the WHO/UNEP which called for the development of novel test methods for the investigation of the effects of simultaneous exposure to multiple EDCs (Wan et al., 2022).

4.3. Public health related aspects and perspectives

Given the extensive impact of corticosteroids on the human physiology, there may exist additional, yet unidentified health consequences upon EDC exposure mediated by corticosteroid disruption, e.g. effects on immune function and mental health. A comprehensive understanding of EDCs including their mechanistic action will support the need for risk assessment and reduction at a policy level. Additionally, it could support the development of secondary prevention or (if necessary) therapeutic strategies, given that primary prevention – through exposure restriction – is constrained by the global presence of EDCs, as well as the lack of awareness among numerous political systems. As most discussions focus on stricter legal regulations of EDCs and prevention strategies for minimized exposure, we believe that negative results of studies are sometimes neglected and ultimately not published. However, it should not be forgotten that EDCs have great benefits and that life without most of these chemicals would be restrictive in many ways. A good example is the medical sector, as various EDCs are used in the manufacturing of many medical products e.g. ventilation tubes (North and Halden, 2013). Substitutes are rare and their safety for the endocrine system is not always proven or even studied. One example are BPA substitutes such as

BPS and BPF which are likely to be prevalent in products labelled BPA-free. However, Peng et al. indicated an even stronger influence of BPS in regards on glucocorticoid concentrations than BPA, which is supported by Potzl et al. who suggested similar adverse health effect of BPS and BPF as for BPA (Potzl et al., 2024; Peng et al., 2024). For this reason, a detailed study of the influence of EDCs on the endocrine system and its publication is of importance, regardless of the results and whether they meet scientific expectations. Furthermore, systematic reviews should assess and visualize publication bias whenever possible by using tools like funnel plots. From a future research perspective EDCs may also contribute to the development or the extent of diseases which are primarily based on cortisol or aldosterone excess, like Cushing's syndrome or primary aldosteronism. To date, no study has specifically focused on EDCs influence on those endocrine diseases, which would therefore be an interesting topic for future research projects.

4.4. Strengths and limitations

The main strength of this review is that it is the first of its kind and therefore complements the many existing reviews on the association between EDCs and components of metabolic syndrome and cardiovascular diseases, as well as *in vitro* and *in vivo* studies investigating altered hormone secretion upon EDC exposure. We furthermore analysed studies that focused on different types of EDCs in different study populations ranging from newborns to adults. We had no restrictions on the geographic origin of the study. We thus provide a holistic overview of the association of EDCs with altered hormone levels. In addition, only studies in which EDC concentrations were measured directly and exposure was not determined by questionnaires or surveys were considered, which allows the reduction of exposure misclassification.

The major limitation of our review is that we could not summarise the results in a meta-analysis due to differences in study design, study population, analytical method, and measured hormones and chemicals. In addition, visualizing data across different studies using forest plots or to assess publication bias was challenging, as the studies assessed various outcomes and outcome measures (e.g., β-estimates, percentage change, etc.). In addition, some reports are based on cohorts with a small number of cases, which impairs statistical power and generalizability of study results and thus a possible conclusion. We further did only search PubMed and Cochrane library and not additionally in further databases like Web of Science or Embase.

5. Summary

Despite the growing awareness and interest in the topic in recent years, this detailed analysis about epidemiological studies investigating the effects of EDCs on corticosteroids or disruption of the HPA axis revealed that only a limited number of studies overlap in terms of investigated chemical, age group and study methodology, making meaningful summary of the data by meta-analysis challenging. However, most of the studies demonstrated an effect of several types of EDCs on these hormones. To gain a holistic knowledge of EDCs influence on steroid hormone balance studies should be optimized by improved selection of the study population and more representative measurements of EDC and hormone levels and by linking both parameters to clinical features. In addition, studies should be complemented with *in vitro* experiments and additionally evaluate the human risk for corticosteroid hormone disruption upon the exposure of EDC mixtures.

In conclusion, investigating endocrine disruptors and their effects on mineralocorticoid and glucocorticoid function is a research priority. These hormones are integral to a wide range of physiological processes in humans, and any disruption can have widespread and profound consequences for health. Understanding these influences is crucial for developing strategies to mitigate potential risks associated with endocrine disruptors and inform future research and policy decisions.

CRediT authorship contribution statement

Isabel Stüfchen: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Júnia R.O.L. Schweizer:** Writing – review & editing, Formal analysis. **Friederike Völter:** Writing – review & editing, Formal analysis. **Elisabeth Nowak:** Writing – review & editing, Methodology. **Leah Braun:** Writing – review & editing. **Julien Kocabiyik:** Writing – review & editing. **Michael Mederos y Schnitzler:** Writing – review & editing. **Tracy Ann Williams:** Writing – review & editing. **Sonja Kunz:** Writing – review & editing. **Martin Bidlingmaier:** Writing – review & editing. **Martin Reincke:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2025.121438.

Data availability

Data will be made available on request.

References

Arab, A., Mostafalou, S., 2023. Pesticides and insulin resistance-related metabolic diseases: evidences and mechanisms. Pestic. Biochem. Physiol. 195, 105521. https://doi.org/10.1016/j.pestbp.2023.105521.

Araki, A., Mitsui, T., Goudarzi, H., Nakajima, T., Miyashita, C., Itoh, S., Sasaki, S., Cho, K., Moriya, K., Shinohara, N., Nonomura, K., Kishi, R., 2017. Prenatal di(2-ethylhexyl) phthalate exposure and disruption of adrenal androgens and glucocorticoids levels in cord blood: The Hokkaido Study. Sci. Total Environ. 581–582, 297–304. https://doi.org/10.1016/j.scitotenv.2016.12.124.

Araki, A., Miyashita, C., Mitsui, T., Goudarzi, H., Mizutani, F., Chisaki, Y., Itoh, S., Sasaki, S., Cho, K., Moriya, K., Shinohara, N., Nonomura, K., Kishi, R., 2018. Prenatal organochlorine pesticide exposure and the disruption of steroids and reproductive hormones in cord blood: the Hokkaido study. Environ. Int. 110, 1–13. https://doi.org/10.1016/j.envint.2017.10.006.

Bonato, M., Corra, F., Bellio, M., Guidolin, L., Tallandini, L., Irato, P., Santovito, G., 2020. PFAS environmental pollution and antioxidant responses: an overview of the impact on human field. Int. J. Environ. Res. Publ. Health 17. https://doi.org/10.3390/ijerph17218020.

C., M. D. P. A. R. C., 1973. Adrenocortical function in persons occupationally exposed to pesticides. J. Occup. Med. 15, 26–28.
Cai, D., Li, Q.Q., Mohammed, Z., Chou, W.C., Huang, J., Kong, M., Xie, Y., Yu, Y., Hu, G., Qi, J., Zhou, Y., Tan, W., Lin, L., Qiu, R., Dong, G., Zeng, X.W., 2023. Fetal glucocorticoid mediates the association between prenatal per- and polyfluoroalkyl substance exposure and neonatal growth index: evidence from a birth cohort study. Environ. Sci. Technol. 57, 11420–11429. https://doi.org/10.1021/acs.est.2c08831.
Caroccia, B., Caputo, I., Rossi, F.B., Piazza, M., Pallafacchina, G., Paolo Rossi, G., 2023. Endocrine disruptors and arterial hypertension: a developing story. Steroids 199, 109292. https://doi.org/10.1016/j.steroids.2023.109292.
Cecchi, A., Rovedatti, M.G., Sabino, G., Magnarelli, G.G., 2012. Environmental exposure to organophosphate pesticides: assessment of endocrine disruption and hepatotoxicity in pregnant women. Ecotoxicol. Environ. Saf. 80, 280–287. https://doi.org/10.1016/j.ecoenv.2012.03.008.
Chai, Y., Wang, H., Tang, D., Wu, Y., Sun, Z., Zeng, Y., Zhang, B., Niu, B., Dong, X., 2024. Changes of serum cortisol during pregnancy and labor initiation: an onsite cross-sectional study. Front. Endocrinol. 15, 1379693. https://doi.org/10.3389/fendo.2024.1379693.
Chronister, B.N.C., Yang, K., Yang, A.R., Lin, T., Tu, X.M., Lopez-Paredes, D., Checkoway, H., Suarez-Torres, J., Gahagan, S., Martinez, D., Barr, D., Moore, R.C., Suarez-Lopez, J.R., 2023. Urinary glyphosate, 2,4-D and DEET biomarkers in relation to neurobehavioral performance in Ecuadorian adolescents in the ESPINA cohort. Environ. Health Perspect. 131, 107007. https://doi.org/10.1289/EHP11383.
Dreyer, A.F., Jensen, R.C., Glintborg, D., Schmedes, A.V., Brandslund, I., Nielsen, F., Kyhl, H.B., Jensen, T.K., Andersen, M.S., 2020. Perfluoroalkyl substance exposure early in pregnancy was negatively associated with late pregnancy cortisone levels. J. Clin. Endocrinol. Metab. 105. https://doi.org/10.1210/clinem/dgaa292.
Egalini, F., Marinelli, L., Rossi, M., Motta, G., Prencipe, N., Rossetto Giaccherino, R., Pagano, L., Grottoli, S., Giordano, R., 2022. Endocrine disrupting chemicals: effects on pituitary, thyroid and adrenal glands. Endocrine 78, 395–405. https://doi.org/10.1007/s12020-022-03076-x.
Erkudov, V.O., Rozumbetov, K.U., Gonzalez-Fernandez, F.T., Pugovkin, A.P., Nazhimov, I.I., Matchanov, A.T., Ceylan, H.I., 2023. The effect of environmental disasters on endocrine status, hematology parameters, body composition, and physical performance in young soccer players: a case study of the aral sea region. Life 13. https://doi.org/10.3390/life13071503.
Farnbach, K., Iragorri, S., Al-Uzri, A., Rozansky, D., Forbush, R., Jenkins, R., 2019. The changing spectrum of hypertension in premature infants. J. Perinatol. 39, 1528–1534. https://doi.org/10.1038/s41372-019-0457-z.
Freire, C., Suarez, B., Vela-Soria, F., Castiello, F., Reina-Perez, I., Andersen, H.R., Olea, N., Fernandez, M.F., 2021. Urinary metabolites of non-persistent pesticides and serum hormones in Spanish adolescent males. Environ. Res. 197, 111016. https://doi.org/10.1016/j.envres.2021.111016.
Gaum, P.M., Vida, V.S., Schettgen, T., Esser, A., Kraus, T., Gube, M., Lang, J., 2020. Cross-sectional and longitudinal effects of PCB exposure on human stress hormones in the German HELPcB surveillance program. Int. J. Environ. Res. Publ. Health 17. https://doi.org/10.3390/ijerph17134708.
Giesbrecht, G.F., Ejaredar, M., Liu, J., Thomas, J., Letourneau, N., Campbell, T., Martin, J.W., Dewey, D., Team, A.P.S., 2017. Prenatal bisphenol a exposure and dysregulation of infant hypothalamic-pituitary-adrenal axis function: findings from the APrON cohort study. Environ. Health 16, 47. https://doi.org/10.1186/s12940-017-0259-8.
Giesbrecht, G.F., Liu, J., Ejaredar, M., Dewey, D., Letourneau, N., Campbell, T., Martin, J. W., Team, A.P.S., 2016. Urinary bisphenol A is associated with dysregulation of HPA-axis function in pregnant women: findings from the APrON cohort study. Environ. Res. 151, 689–697. https://doi.org/10.1016/j.envres.2016.09.007.
Gore, A.C., Chappell, V.A., Fenton, S.E., Flaws, J.A., Nadal, A., Prins, G.S., Toppari, J., Zoeller, R.T., 2015. EDC-2: the endocrine society's second scientific statement on endocrine-disrupting chemicals. Endocr. Rev. 36, E1–E150. https://doi.org/10.1210/er.2015-1010.
Goudarzi, H., Araki, A., Itoh, S., Sasaki, S., Miyashita, C., Mitsui, T., Nakazawa, H., Nonomura, K., Kishi, R., 2017. The association of prenatal exposure to perfluorinated chemicals with glucocorticoid and androgenic hormones in cord blood samples: the hokkaido study. Environ. Health Perspect. 125, 111–118. https://doi.org/10.1289/EHP142.
Green, M.P., Harvey, A.J., Finger, B.J., Tarulli, G.A., 2021. Endocrine disrupting chemicals: impacts on human fertility and fecundity during the peri-conception period. Environ. Res. 194, 110694. https://doi.org/10.1016/j.envres.2020.110694.
Hamid, N., Junaid, M., Pei, D.S., 2021. Combined toxicity of endocrine-disrupting chemicals: a review. Ecotoxicol. Environ. Saf. 215, 112136. https://doi.org/10.1016/j.ecoenv.2021.112136.
Haverinen, E., Fernandez, M.F., Mustieles, V., Tolonen, H., 2021. Metabolic syndrome and endocrine disrupting chemicals: an overview of exposure and health effects. Int. J. Environ. Res. Publ. Health 18. https://doi.org/10.3390/ijerph182413047.
Hu, X., Zhao, Y., Chen, B., Liang, Y., Li, L., Xie, C., Zhang, Y., Lin, Z., Xie, A., Chen, S., 2014. [11beta-hydroxysteroid dehydrogenase type 2 enzyme activity effect after exposures phthalate esters in maternal]. Zhonghua Yufang Yixue Zazhi 48, 800–804.
J, C. N. W., 1972. Cortisol metabolism in persons occupationally exposed to DDT. Arch. Environ. Health 24. https://doi.org/10.1080/00039896.1972.10666062.
Jansen, A., Berg, J.P., Klungsoyr, O., Muller, M.H.B., Lyche, J.L., Aaseth, J.O., 2020. The influence of persistent organic pollutants on thyroidal, reproductive and adrenal hormones after bariatric surgery. Obes. Surg. 30, 1368–1378. https://doi.org/10.1007/s11695-019-04273-w.
Jenkins, R., Tackitt, S., Gievers, L., Iragorri, S., Sage, K., Cornwall, T., O'Riordan, D., Merchant, J., Rozansky, D., 2019. Phthalate-associated hypertension in premature infants: a prospective mechanistic cohort study. Pediatr. Nephrol. 34, 1413–1424. https://doi.org/10.1007/s00467-019-04244-4.
Jenkins, R.D., 2023. Phthalates cause a low-renin phenotype commonly found in premature infants with idiopathic neonatal hypertension. Pediatr. Nephrol. 38, 1717–1724. https://doi.org/10.1007/s00467-022-05773-1.
Joseph, D.N., Whirledge, S., 2017. Stress and the HPA Axis: balancing homeostasis and fertility. Int. J. Mol. Sci. 18. https://doi.org/10.3390/ijms18102224.
Jumes, J.J., Jaques, H.S., Dalla Vecchia, M.F., Ferreira, M.O., Orrutea, J.F.G., Machado, M.G., Mezoni, M.F., Silva, R., Almeida, R.F., Rech, D., Kawassaki, A.C.B., Panis, C., 2024. Occupational exposure to pesticides deregulates systemic cortisol levels in women with breast cancer and correlates with poor prognosis features. Braz. J. Med. Biol. Res. 57, e13060. https://doi.org/10.1590/1414-431X2023e13060.
Kido, T., Dao, T.V., Ho, M.D., Duc Dang, N., Pham, N.T., Okamoto, R., Pham, T.T., Maruzeni, S., Nishijo, M., Nakagawa, H., Honma, S., Le, S.K., Nguyen, H.N., 2014. High cortisol and cortisone levels are associated with breast milk dioxin concentrations in Vietnamese women. Eur. J. Endocrinol. 170, 131–139. https://doi.org/10.1530/EJE-13-0410.
Kim, J.H., Lee, J., Moon, H.B., Park, J., Choi, K., Kim, S.K., Kim, S., 2018. Association of phthalate exposures with urinary free cortisol and 8-hydroxy-2'-deoxyguanosine in early childhood. Sci. Total Environ. 627, 506–513. https://doi.org/10.1016/j.scitotenv.2018.01.125.
Kongtip, P., Nankongnab, N., Kallayanatham, N., Pengpumkiat, S., Gore, R., Pundee, R., Konthonbut, P., Woskie, S.R., 2021. Disruption of the diurnal cortisol hormone pattern by pesticide use in a longitudinal study of farmers in Thailand. Ann Work Expo Health 65, 406–417. https://doi.org/10.1093/annweh/wxaa124.
Li, Y., Xiao, N., Liu, M., Liu, Y., He, A., Wang, L., Luo, H., Yao, Y., Sun, H., 2023. Dysregulation of steroid metabolome in follicular fluid links phthalate exposure to diminished ovarian reserve of childbearing-age women. Environ. Pollut. 330, 121730. https://doi.org/10.1016/j.envpol.2023.121730.
Liu, H., Pan, Y., Jin, S., Li, Y., Zhao, L., Sun, X., Cui, Q., Zhang, B., Zheng, T., Xia, W., Zhou, A., Campana, A.M., Dai, J., Xu, S., 2020. Associations of per-/polyfluoroalkyl substances with glucocorticoids and progestogens in newborns. Environ. Int. 140, 105636. https://doi.org/10.1016/j.envint.2020.105636.
Liu, J., Yang, T., Li, Y., Li, S., Li, Y., Xu, S., Xia, W., 2024. Associations of maternal exposure to 2,4-dichlorophenoxyacetic acid during early pregnancy with steroid hormones among one-month-old infants. Sci. Total Environ. 912, 169414. https://doi.org/10.1016/j.scitotenv.2023.169414.
Macedo, S., Teixeira, E., Gaspar, T.B., Boaventura, P., Soares, M.A., Miranda-Alves, L., Soares, P., 2023. Endocrine-disrupting chemicals and endocrine neoplasia: a forty-year systematic review. Environ. Res. 218, 114869. https://doi.org/10.1016/j.envres.2022.114869.
Manh, H.D., Kido, T., Okamoto, R., Xianliang, S., Viet, N.H., Nakano, M., Tai, P.T., Maruzeni, S., Nishijo, M., Nakagawa, H., Suzuki, H., Honma, S., Van Tung, D., Nhu, D.D., Hung, N.N., Son Le, K., 2013. The relationship between dioxins and salivary steroid hormones in Vietnamese primiparae. Environ. Health Prev. Med. 18, 221–229. https://doi.org/10.1007/s12199-012-0310-x.
Martocchia, A., Gallucci, M., Noale, M., Maggi, S., Cassol, M., Stefanelli, M., Postacchini, D., Proietti, A., Barbagallo, M., Dominguez, L.J., Ferri, C., Desideri, G., Toussan, L., Pastore, F., Falaschi, G.M., Paolisso, G., Falaschi, P., Investigators, A., 2022. The increased cortisol levels with preserved rhythmicity in aging and its relationship with dementia and metabolic syndrome. Aging Clin. Exp. Res. 34, 2733–2740. https://doi.org/10.1007/s40520-022-02262-1.
Moola, S., Munn, Z., Sears, K., Sfetcu, R., Currie, M., Lisy, K., Tufanaru, C., Qureshi, R., Mattis, P., Mu, P., 2015. Conducting systematic reviews of association (etiology): the Joanna Briggs Institute's approach. Int. J. Evid. Base. Healthc. 13, 163–169. https://doi.org/10.1097/XEB.0000000000000064.
Mustieles, V., Lascouts, A., Pozo, O.J., Haro, N., Lyon-Caen, S., Jedynak, P., Bayat, S., Thomsen, C., Sakhi, A.K., Sabaredzovic, A., Slama, R., Ouellet-Morin, I., Philippat, C., 2023. Longitudinal associations between prenatal exposure to phthalates and steroid hormones in maternal hair samples from the SEPAGES cohort. Environ. Sci. Technol. 57, 19202–19213. https://doi.org/10.1021/acs.est.3c03401.
Mustieles, V., Ocon-Hernandez, O., Minguez-Alarcon, L., Davila-Arias, C., Perez-Lobato, R., Calvente, I., Arrebola, J.P., Vela-Soria, F., Rubio, S., Hauser, R., Olea, N., Fernandez, M.F., 2018. Bisphenol A and reproductive hormones and cortisol in peripubertal boys: the INMA-Granada cohort. Sci. Total Environ. 618, 1046–1053. https://doi.org/10.1016/j.scitotenv.2017.09.093.
Nhu Dd, K.T., Naganuma, R., Suzuki, H., Kuroda, N., Honma, S., Tai, P.T., Maruzeni, S., Nishijo, M., Nakagawa, H., Hung, N.N., 2010. Salivary cortisol and cortisone levels, and breast milk dioxin concentrations in Vietnamese primiparas. Toxicol. Environ. Chem. 92. https://doi.org/10.1080/02772248.2010.484247.
North, E.J., Halden, R.U., 2013. Plastics and environmental health: the road ahead. Rev. Environ. Health 28, 1–8. https://doi.org/10.1515/reveh-2012-0030.
Padmanabhan, V., Song, W., Puttabyatappa, M., 2021. Praegnatio perturbatio-impact of endocrine-disrupting chemicals. Endocr. Rev. 42, 295–353. https://doi.org/10.1210/endrev/bnaa035.
Page, M.J., Mckenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hrobjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., Mcdonald, S., Mcguinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71. https://doi.org/10.1136/bmj.n71.
Pan, K., Xu, J., Long, X., Yang, L., Huang, Z., Yu, J., 2023. The relationship between perfluoroalkyl substances and hypertension: a systematic review and meta-analysis. Environ. Res. 232, 116362. https://doi.org/10.1016/j.envres.2023.116362.

Pecori Giraldi, F., Ferrau, F., Ragonese, M., Cannavo, S., 2024. Endocrine disruptors, aryl hydrocarbon receptor and cortisol secretion. J. Endocrinol. Investig. 47, 2407–2419. https://doi.org/10.1007/s40618-024-02371-w.

Peng, F.J., Palazzi, P., Mezzache, S., Adelin, E., Bourokba, N., Bastien, P., Appenzeller, B. M.R., 2023. Association between environmental exposure to multiclass organic pollutants and sex steroid hormone levels in women of reproductive age. Environ. Sci. Technol. 57, 19383–19394. https://doi.org/10.1021/acs.est.3c06095.

Peng, F.J., Palazzi, P., Mezzache, S., Adelin, E., Bourokba, N., Bastien, P., Appenzeller, B. M.R., 2024. Glucocorticoid hormones in relation to environmental exposure to bisphenols and multiclass pesticides among middle aged-women: results from hair analysis. Environ. Pollut. 348, 123839. https://doi.org/10.1016/j.envpol.2024.123839.

Petersen, M.S., Halling, J., Damkier, P., Nielsen, F., Grandjean, P., Weihe, P., Brosen, K., 2007. Polychlorinated biphenyl (PCB) induction of CYP3A4 enzyme activity in healthy Faroese adults. Toxicol. Appl. Pharmacol. 224, 202–206. https://doi.org/10.1016/j.taap.2007.07.002.

Potzl, B., Kurzinger, L., Kendl, S., Stopper, H., Kurlbaum, M., Fassnacht, M., Dischinger, U., 2024. Disruptive effects of plasticizers bisphenol A, F, and S on steroidogenesis of adrenocortical cells. Front. Endocrinol. 15, 1387133. https://doi.org/10.3389/fendo.2024.1387133.

Reincke, M., Fleseriu, M., 2023. Cushing syndrome: a review. JAMA 330, 170–181. https://doi.org/10.1001/jama.2023.11305.

Rolfo, A., Nuzzo, A.M., De Amicis, R., Moretti, L., Bertoli, S., Leone, A., 2020. Fetal-maternal exposure to endocrine disruptors: correlation with diet intake and pregnancy outcomes. Nutrients 12. https://doi.org/10.3390/nu12061744.

Russell, G., Lightman, S., 2019. The human stress response. Nat. Rev. Endocrinol. 15, 525–534. https://doi.org/10.1038/s41574-019-0228-0.

Sears, C.G., Liu, Y., Lanphear, B.P., Buckley, J.P., Meyer, J., Xu, Y., Chen, A., Yolton, K., Braun, J.M., 2024. Evaluating mixtures of urinary phthalate metabolites and serum per-/polyfluoroalkyl substances in relation to adolescent hair cortisol: the HOME study. Am. J. Epidemiol. 193, 454–468. https://doi.org/10.1093/aje/kwad198.

Silvia, S.C., Magnarelli, G., Rovedatti, M.G., 2020. Evaluation of endocrine disruption and gestational disorders in women residing in areas with intensive pesticide application: an exploratory study. Environ. Toxicol. Pharmacol. 73, 103280. https://doi.org/10.1016/j.etap.2019.103280.

Suarez-Lopez, J.R., Nguyen, A., Klas, J., Gahagan, S., Checkoway, H., Lopez-Paredes, D., Noble, M., 2021. Associations of acetylcholinesterase inhibition between pesticide spray seasons with depression and anxiety symptoms in adolescents, and the role of sex and adrenal hormones on gender moderation. Expo Health 13, 51–64. https://doi.org/10.1007/s12403-020-00361-w.

Sun, X., Li, J., Jin, S., Li, Y., Liu, W., Zhao, H., Zhou, Y., Jiang, Y., Liu, H., Xia, W., Cai, Z., Xu, S., Shen, X., 2018. Associations between repeated measures of maternal urinary phthalate metabolites during pregnancy and cord blood glucocorticoids. Environ. Int. 121, 471–479. https://doi.org/10.1016/j.envint.2018.09.037.

Suwannarin, N., Prapamontol, T., Isobe, T., Nishihama, Y., Hashimoto, Y., Mangklabruks, A., Pantasri, T., Chantara, S., Naksen, W., Nakayama, S.F., 2021. Exposure to organophosphate and neonicotinoid insecticides and its association with steroid hormones among male reproductive-age farmworkers in northern Thailand. Int. J. Environ. Res. Publ. Health 18. https://doi.org/10.3390/ijerph18115599.

Vandenberg, L.N., 2014. Low-dose effects of hormones and endocrine disruptors. Vitam. Horm. 94, 129–165. https://doi.org/10.1016/B978-0-12-800095-3.00005-5.

Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs JR., D.R., Lee, D.H., Shioda, T., Soto, A.M., Vom Saal, F.S., Welshons, W.V., Zoeller, R.T., Myers, J.P., 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr. Rev. 33, 378–455. https://doi.org/10.1210/er.2011-1050.

Varghese, S.V., Hall, J.M., 2023. Bisphenol A substitutes and obesity: a review of the epidemiology and pathophysiology. Front. Endocrinol. 14, 1155694. https://doi.org/10.3389/fendo.2023.1155694.

Verma, R., Balhara, Y.P., Gupta, C.S., 2011. Gender differences in stress response: role of developmental and biological determinants. Ind. Psychiatry J. 20, 4–10. https://doi.org/10.4103/0972-6748.98407.

Verplanke, A.J., Bloemen, L.J., Brouwer, E.J., Van Sittert, N.J., Boogaard, P.J., Herber, R. F., De Wolff, F.A., 2000. Occupational exposure to cis-1,3-dichloropropene: biological effect monitoring of kidney and liver function. Occup. Environ. Med. 57, 745–751. https://doi.org/10.1136/oem.57.11.745.

Wan, M.L.Y., Co, V.A., El-Nezami, H., 2022. Endocrine disrupting chemicals and breast cancer: a systematic review of epidemiological studies. Crit. Rev. Food Sci. Nutr. 62, 6549–6576. https://doi.org/10.1080/10408398.2021.1903382.

Xu, P., Lou, X., Ding, G., Shen, H., Wu, L., Chen, Z., Han, J., Han, G., Wang, X., 2014. Association of PCB, PBDE and PCDD/F body burdens with hormone levels for children in an e-waste dismantling area of Zhejiang Province, China. Sci. Total Environ. 499, 55–61. https://doi.org/10.1016/j.scitotenv.2014.08.057.

Yang, J., Zhang, K., Shen, C., Tang, P., Tu, S., Li, J., Chen, L., Yang, W., 2023. The association of hypertension with perfluoroalkyl and polyfluoroalkyl substances. Int. Heart J. 64, 1079–1087. https://doi.org/10.1536/ihj.23-036.

Yu, S., Ren, J., Lv, Z., Li, R., Zhong, Y., Yao, W., Yuan, J., 2022. Prediction of the endocrine-disrupting ability of 49 per- and polyfluoroalkyl substances: in silico and epidemiological evidence. Chemosphere 290, 133366. https://doi.org/10.1016/j.chemosphere.2021.133366.

Zhang, J., Yang, Y., Liu, W., Schlenk, D., Liu, J., 2019. Glucocorticoid and mineralocorticoid receptors and corticosteroid homeostasis are potential targets for endocrine-disrupting chemicals. Environ. Int. 133, 105133. https://doi.org/10.1016/j.envint.2019.105133.

Zhou, F., Jin, Z., Zhu, L., Huang, F., Ye, A., Hou, C., 2022. A preliminary study on the relationship between environmental endocrine disruptors and precocious puberty in girls. J. Pediatr. Endocrinol. Metab. 35, 989–997. https://doi.org/10.1515/jpem-2021-0691.