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Review

Association of Di(2-ethylhexyl) Phthalate Exposure with Reproductive Hormones in the General Population and the Susceptible Population: A Systematic Review and Meta-Analysis

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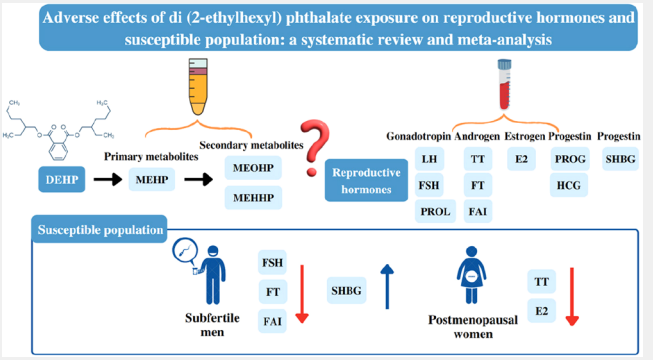
ABSTRACT: Di(2-ethylhexyl) phthalate (DEHP), an environmental endocrine disruptor, has hormone-like activity and endocrine-disrupting effects. However, the types of reproductive hormones associated with DEHP vary across the studies. Thus, we conducted a systematic review and meta-analysis to pool existing epidemiological evidence. We searched three databases up to January 31, 2024, for eligible original studies to ultimately include 37 studies from eight countries with a total of 28 911 participants. DEHP exposure was evaluated with urinary metabolites. Since the main types, production sites, blood concentrations, and functions of reproductive hormones differ between men and women, we reported the combined effect values by gender. Subgroup analyses were conducted by age, subfertility status, and the national sociodemographic index (SDI) level. Furthermore, the effect of maternal exposure during pregnancy on children's reproductive hormone levels was analyzed separately. Overall, in general, in men, DEHP was positively correlated with sex hormone binding-globulin (SHBG) and adversely correlated with total testosterone (TT), free androgen index (FAI), and follicle-stimulating hormone (FSH). Results indicated that among men of reproductive age, DEHP exposure was associated with more significant hormonal suppression in infertile men compared with fertile men. Notably, age subgroup analysis among women revealed that postmenopausal women were more vulnerable to DEHP, which was related to lower TT and estradiol (E_2). However, this study did not observe a significant association between prenatal DEHP metabolites and reproductive hormone levels in children. Our research identifies the most susceptible hormones (androgen suppression) after DEHP exposure and suggests that infertile men and postmenopausal women are in great need of more attention as sensitive populations.



KEYWORDS: *Di(2-ethylhexyl) phthalate, DEHP, Reproductive hormones, Endocrine disruptors, Meta-analysis*

1. INTRODUCTION

Phthalates are a group of semivolatile organic compounds (SVOC) commonly used as plasticizers and softeners in a wide range of household and industrial products, including toys, food packaging, medical devices, building materials, and cosmetics.[1] Among them, di(2-ethylhexyl) phthalate (DEHP) is the most extensively used phthalate derivative in polyvinyl chloride products and the most studied to data.[2,3] As additives not covalently bound to materials, DEHP is easily released through volatilization during manufacture, storage, use, and disposal and easily enters the atmosphere, food, or body fluids.[4] Humans are generally exposed to DEHP through inhalation, ingestion, drinking, and skin contact.[5,6] Studies have identified DEHP as the most hazardous chemical additive to health in plastics on the basis of human health hazard scores.[7] Thus, it is urgent to determine the potential health effects of DEHP.

DEHP is commonly recognized as an endocrine-disrupting chemical because it disrupts the human endocrine system by attaching to molecular targets and interfering with hormonal balance.[8−10] Adverse effects of DEHP exposure on reproductive hormones have been widely reported with plausible mechanisms described. It has been suggested that DEHP exposure blocks the binding of endogenous hormones to receptors mainly through receptor-mediated responses, thereby leading to endogenous hormone antagonistic effects.[11] In addition, DEHP disrupts the synthesis, metabolism, and

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transport of endogenous hormones and their receptors.[12] Studies on rodents have shown that DEHP exhibits antiandrogenic activity resulting in reduced testosterone levels and abnormal reproductive tracts. Epidemiologic studies on populations have shown that DEHP exposure is associated with altered steroid hormone levels in men,[13,14] women,[15,16] and children.[17,18] However, the types of reproductive hormones associated with DEHP and the direction of the association varied across studies.[19−23]

The balance of reproductive hormones in the body is regulated by the hypothalamic−anterior pituitary−gonad (HPG) axis.[24] In brief, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), which subsequently stimulates the synthesis and release of gonadotropins from the anterior pituitary.[18] The gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) stimulate the gonads to synthesize and release reproductive hormones (i.e., steroids). Then, the male testes produce testosterone (T), and the female ovaries produce estradiol (E_2) and progesterone (PROG). Sex hormone binding-globulin (SHBG) is a glycoprotein synthesized by the liver and testes that transplants sex hormones, such as T and E_2, into target cells.[25] Existing studies of reproductive hormones mainly involve three gonadotropins [LH, FSH, and prolactin (PROL)], one estrogen (E_2), one progestin (PROG), one androgen (T), and one carrier (SHBG). There are sex differences in the main types, sites of production, blood concentrations, and functions.[26,27] Moreover, the balance of reproductive hormones varies according to different physiological stages, such as childhood, adulthood, pregnancy, and menopause.[28] Furthermore, disruption of sex steroid hormones is associated with tumors,[29] obesity,[30] metabolic syndrome,[15] and cardiovascular disease.[31] Therefore, exploring the types of hormones affected by DEHP and identifying susceptible populations are crucial to elucidate the mechanism of DEHP on health.

After exposure to DEHP, it is initially metabolized to mono-(2-ethylhexyl) phthalate (MEHP) and then further metabolized to several secondary metabolites, including mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono-[2-(carboxymethyl)-hexyl] phthalate (MCMHP).[32] It is generally believed that MEHP is mainly responsible for the biological activity exerted by DEHP exposure.[2,33] Urine and blood are the most commonly used substrates for DEHP biomonitoring, and the concentration of metabolites found in urine is higher than that in blood because of its rapid metabolism and elimination, which may reflect prolonged exposure.[34] Urine is considered to be the most reliable substrate for the assessment of DEHP exposure.[10] It has been found that the higher detection rates of MEOHP and MEHHP than MEHP in urine suggest that these two oxidative metabolites make low-level exposures more detectable.[35] Thus, the three urinary metabolites, MEHP, MEOHP, and MEHHP, have been widely used to explore the relationship between DEHP exposure and adverse health outcomes. The focus of this study was to use the levels of three metabolites in urine to reflect the body's exposure to DEHP.

On the basis of the heterogeneity of previous studies, a systematic review and meta-analysis were performed to summarize the available results between DEHP exposure and reproductive hormone levels with an aim to (1) identify which reproductive hormone changes are associated with DEHP metabolites concentration, (2) assess the magnitude and direction of the association, and (3) explore susceptible subpopulations.

2. METHODS

2.1. Study Protocol

We conducted this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) rules.[36] The study protocol has been registered with PROSPERO (ID CRD42023429873).

2.2. Search Strategy

We searched for original studies in the Web of Science, PubMed, and The Cochrane Library until January 31, 2024. The keywords covered "DEHP" and "reproductive hormone," and the final search strategies are shown in Table S1. Additionally, the reference lists of the included studies and related reviews were screened for inclusion of all relevant articles. Two authors (X.X.L. and J.T.L.) performed initial screening by title and abstract, respectively, and then obtained the full text for further screening. Data extraction and quality assessment were also performed by the same two authors. Disagreements in the process were arbitrated by a third author (N.W.).

2.3. Inclusion and Exclusion Criteria

Studies meeting the following criteria were included: (1) original research in English; (2) observational study, including case control, cross-sectional, and prospective and retrospective studies; (3) studies conducted in populations; (4) DEHP exposure evaluated by at least one of the urinary metabolites, including MEHP, MEHHP, and MEOHP; (5) study outcomes were serum reproductive hormone concentrations, which included at least one of LH, FSH, PROL, E_2, PROG, total testosterone (TT), free testosterone (FT), SHBG, free androgen index (FAI), dehydroepiandrosterone (DHEA-S), and human choionic gonadotophin (HCG); and (6) effect sizes were reported as regression coefficient (β), percentage change (PC), mean difference (MD), correlation coefficient (r), and 95% confidence interval (CI).

There were exclusion criteria: (1) if the papers were abstracts, reviews, letters, or conference papers, etc.; (2) if the papers were nonoriginal research or toxicological studies; (3) if DEHP metabolite levels were not measured through urine, and reproductive hormone levels were not measured through the serum; and (4) if effect values were not available or could not be translated.

2.4. Data Extraction and Management

The following information was extracted from each included study: author's name, publication year, study location, study period, population characteristics (age, gender, subfertility status), sample size, study design, exposure, outcomes, effect sizes, and 95% CI.

If studies reported both continuous and categorical outcomes of the DEHP metabolite concentration, we preferred continuous data. Since the distributions of DEHP and reproductive hormones in humans do not satisfy an approximately normal distribution in some studies, different log-transformed methods were used before estimating effect values. For a relatively uniform meta-analysis, we homogenized the results of the different studies.[37] Effect values were converted to the percentage change in reproductive hormone per 1 μg/L increase in the DEHP concentration. When β and P values were reported in the original data, 95% CI values were

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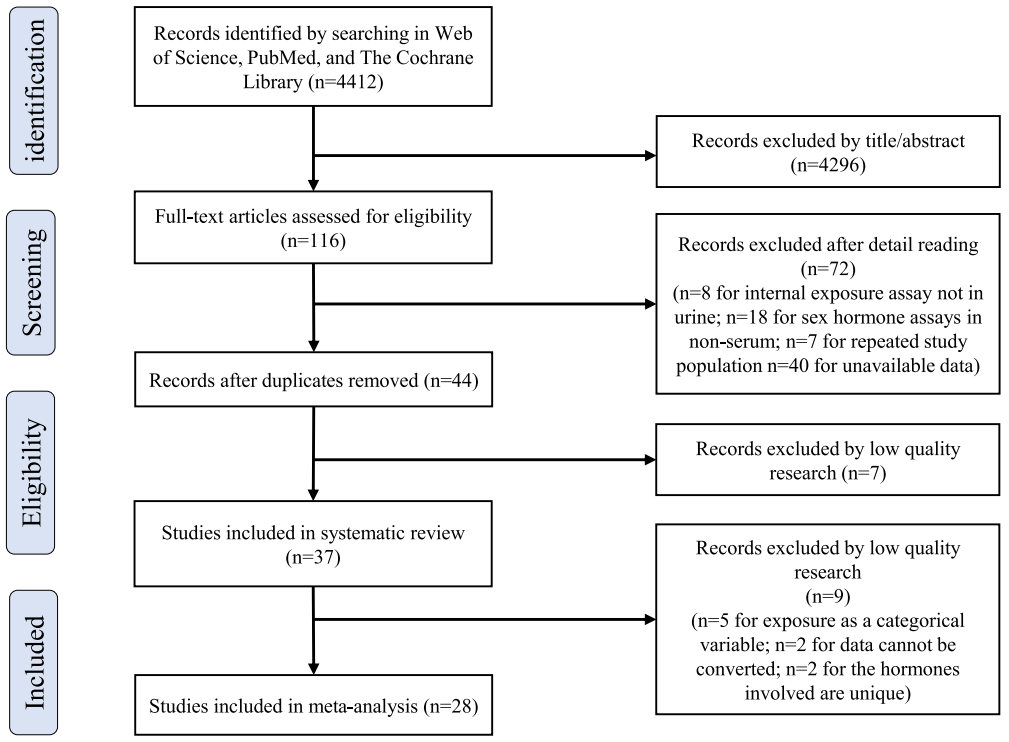

Figure 1. Flowchart of the literature search and selection for meta-analysis.

recalculated using the previous equation.[38] Studies where DEHP metabolites concentration were categorically defined were combined for effect values only in sensitivity analyses.[16,18,21]

2.5. Quality Assessment

A formal quality assessment of screened studies was performed using a systematic and standardized approach referencing the quality assessment methods used in previous meta-analyses related to phthalate.[39] In brief, quality scores were based on 15 items, including study design, study population, measurement of phthalate concentrations, covariate adjustment, interference from other chemicals, exposure-response analysis, and sensitivity analysis. One point was added for methodological strengths, and one point was subtracted for each apparent weakness. All discrepancies in uncertainty were discussed and resolved by consensus among the three evaluating authors. Studies with scores higher than −2 were included in the quantitative analysis of the associations between phthalates and their metabolite levels in humans and reproductive hormones.

2.6. Data Analysis

The I^2 statistics and Cochran's Q test were used to describe heterogeneity.[40] Pooled estimates were calculated on the basis of the random effects model when I^2 values > 50%; if not, the fixed effects model was used.[41] Q-tests with $p < 0.05$ were considered statistically significant for heterogeneity.[42] Publication bias was assessed by funnel plot analysis and Egger's regression test.

We performed subgroup analyses by age, subfertility status, and national sociodemographic index (SDI) level. Studies were separated into three age subgroups on the basis of the characteristics of reproductive hormone distribution at different ages: <20 years, 20−45 years, and >45 years. Additionally, the link between DEHP metabolite concentration and reproductive outcomes has been investigated primarily in infertile males. Because of a more fragile hormonal homeostasis system in infertile men, the association may differ from that in the general population. Therefore, a subgroup analysis on the basis of the reproductive age population was performed. Moreover, SDI is a composite indicator calculated by per capita income, total fertility rate, and average level of education, which represents a country's level of development. Subgroup analyses were performed on the basis of the SDI level of countries to take into account the potential heterogeneity of multiple studies.

Fetuses are more vulnerable to toxic chemicals and exposed to DEHP from maternal to the amniotic fluid. Exposure to hormone mimics during fetal development may be harmful to health after birth, during childhood, or even in adulthood.[43] However, evidence on the impact of fetal exposure to DEHP on reproductive hormones in prepubertal children remains inconsistent. Therefore, the effect of maternal exposure during pregnancy on children's reproductive hormone levels was analyzed separately.

The robustness of the results was verified by a sensitivity analysis. First, the leave-one-out meta-analysis was used to verify whether the combined effect size changed significantly after each study. Besides, the bias caused by using standardized regression coefficients in the meta-analysis to estimate missing correlations was even larger.[44] The quality of the articles reporting a correlation coefficient is relatively low because of other exposures and covariates not being controlled. Therefore, a separate meta-analysis of articles reporting correlation coefficients was conducted for the sensitivity analysis. Among women, hormone levels may be more variable in pregnant women compared with nonpregnant women. So, sensitivity analyses for studies that excluded pregnant women were conducted.

All statistical analyses were performed with Stata 13.0 and R v3.1.0.

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3. RESULTS

3.1. Characteristics of Included Studies

As shown in Figure 1, 4412 studies were initially searched. After reviewing the abstracts and removing duplications, 116 articles underwent a full-text review, and finally, 44 articles met the criteria. After quality assessment, a total of 37 studies were considered high quality, while the other 7 were of low quality. The details of the scores for each article are shown in Table S2. Ultimately, this systematic review comprised 37 studies, of which 28 were included in the meta-analysis.[13−15,17,19,20,22,23,45−64] Five articles[16,18,21,65,66] included exposure as a categorical variable, two studies[67,68] had data that could not be transformed, and two studies[69,70] had a unique hormone that was not included in the meta-analysis.

Table 1 presents the characteristics of studies included in the systematic review. There were 28 cross-sectional studies, three mother−infant cohort studies, three case control studies, and two panel studies. These studies were conducted in eight countries. There were 27 articles for males and 22 articles for females in this systematic review. The number of meta-analyses was 20 for males and 12 for females, with 4 articles containing both genders. Study subjects were composed of newborns, children, adolescents, adults, infertile populations, pregnant women, and workers, involving a total of 28 911 participants.

Liquid chromatography−tandem mass spectrometry (LC-MS), high-performance liquid chromatography/tandem mass spectrometry (HPLC-MS), and ultrahigh-performance liquid chromatography−tandem mass spectrometry (UPLC-MS) were used to determine the concentration of DEHP metabolites. These methods are currently recognized with reliable results, low limits of detection, and good reproducibility.[71−73] Reproductive hormone levels in serum were detected by enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), chemiluminescence immunoassay (CLIA), electrochemiluminescence immunoassay (ECLIA), and LC-MS. LC-MS was the most sensitive method, but CLIA and ECLIA were the most commonly used methods.[74,75] However, there is no uniform standard for reproductive hormone testing. The hormone levels obtained in different laboratories by different methods may differ. Therefore, the effect values in this meta-analysis were converted to relative changes in reproductive hormones to avoid the effects of assay methods.[76]

Among the five metabolites of DEHP, the most frequently measured, MEHP, MEHHP, and MEOHP, were meta-analyzed in this study. The number of studies on various DEHP included in this review is as follows: MEHP (N = 38), MEHHP (N = 30), and MEOHP (N = 29). TT, E_2, FSH, and SHBG were the hormones with the highest numbers of studies at 30, 27, 21, and 18, respectively. Meta-analysis was conducted when the number of articles was more or equal to three.

3.2. Association between DEHP and Reproductive Hormones in Males

A pooled analysis of 20 studies estimated the association between urinary DEHP metabolite concentrations and male reproductive hormones, as shown in Figure 2. Overall, in males, DEHP levels were positively correlated with SHBG and negatively correlated with TT, FAI, and FSH. For each 1 μg/L increase in MEHHP, MEHP, and MEOHP, FAI levels changed by −0.07799% (95% CI: −0.12216%, −0.03382%), −0.22769% (95% CI: −0.33557%, −0.11981%), and −0.14837% (95% CI: −0.22017%, −0.07656%), respectively. There were negative correlations between MEHP and TT [−0.03649% (95% CI: −0.06640%, −0.00658%)] and MEOHP and FSH [−0.00733% (95% CI: −0.01410%, −0.00056%)]. The analysis between MEOHP and SHBG showed a positive correlation with pooled coefficients of 0.00605% (95% CI: 0.00229%, 0.00981%). There was no evidence of a relationship between DEHP and LH, inhibin B, FT, E_2, DHEA-S, or PROG.

3.3. Association between DEHP and Reproductive Hormones in Females

As shown in Figure 3, the pooled analysis did not reveal a significant correlation between DEHP metabolite concentration and the levels of TT, SHBG, E_2, PROG, and FT. For the association of DEHP metabolites with PROL, three articles presented completely disparate findings with a cumulative effect value for MEHP of 0.13881% (95% CI: −0.17846%, 0.45607%). Significant results were reported among articles insufficient for meta-analysis. Adibi et al. found significant associations between MEHP with disrupting placental HCG in pregnant women, thus leading to shortened anogenital distance in boys.[69] Higher exposure to several phthalates, including all metabolites of DEHP, was associated with lower HCG[77] and higher FSH.[17,64]

3.4. Subgroup Analyses

Subgroup analyses were conducted by age, subfertility status, and the national SDI level.

In the age subgroup analysis of women, all study subjects in the high-age groups were postmenopausal women. Above all, postmenopausal women were more sensitive to DEHP than younger women (Figure 4). The results showed that in women over 45 years old, with each 1 μg/L increase in MEHHP, MEHP, and MEOHP, TT levels changed by −0.04539% (95% CI: −0.07296%, −0.01782%), −0.04828% (95% CI: −0.07605%, −0.01486%), and −0.04828% (95% CI: −0.07605%, −0.02050%), respectively. Increases in MEOHP were linked to decreases in E_2 [−0.05349% (95% CI: −0.08825%, −0.01873)]. In contrast, the age subgroup of males did not show any statistically diverse outcomes (Table S4).

In infertile men, an increased DEHP metabolite concentration was associated with reduced FT, FSH, and FAI concentrations (Figure 5). The meta-analysis found that each 1 μg/L MEHHP, MEHP, and MEOHP increase was associated with −0.02783% (95% CI: −0.05509%, −0.00056%), −0.16234% (95% CI: −0.32093%, −0.00375%), and −0.04718% (95% CI: −0.08824%, −0.00612%) change in FAI, respectively. Increases in MEHHP and MEOHP were linked to decreases in FT [−0.00497% (95% CI: −0.00980%, −0.00014)] and FSH [−0.00750% (95% CI: −0.01489%, −0.00011)], and increases in MEOHP were linked to decreases in FSH [−0.00801% (95% CI: −0.01551%, −0.00050)]. Al-Saleh et al. observed that DEHP metabolites were associated with low PROL levels.[47] Chang et al. reported no associations between DEHP metabolites and inhibin B in infertile men.[14] However, the meta-analysis in fertile men of reproductive age did not find a significant association between DEHP and alterations in TT, SHBG, LH, FSH, or E_2 (Table S5). The association of DEHP with other hormones was not meta-analyzed because of the insufficient number of articles. Only two articles reported a significant negative correlation between MEOHP and FAI.[55,58] There was only one study in a

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Table 1. Principal Characteristics of Studies Included in the Systemic Review and Meta-Analysis[a]

study	data period	location	population	sex: *N*	DEHP exposure type	reproductive hormone type	statistical analysis	study design	effect value type	significance result
Zhu et al. (2022)[63]	2015−2016	United States	adults	M: 1056 F: 1108	MEHP, MEHHP, MEOHP	E_2, TT, SHBG	linear regression model	cross-sectional study	β	MEHP-TT (−), E_2 (+) MEHHP-TT (−), SHBG (+) MEOHP-TT (−), SHBG (+)
Dubey et al. (2022)[15]	2013−2016	United States	female participants aged 15 years or older	F: 7561	MEHP, MEHHP, MEOHP	TT, SHBG	generalized linear model with a Poisson family distribution and log link	cross-sectional study	β	MEHHP-SHBG (−)
Bigambo et al. (2022)[49]	2013−2016	United States	girls aged 12−19 years	F: 279	MEHHP, MEOHP	TT, E_2, SHBG	multivariate linear regression	cross-sectional study	β	none
Long et al. (2021)[67]	2013−2016	United States	women over the age of 20	F: 545	MEHP, MEHHP, MEOHP	TT, E_2, FT, FAI, SHBG	survey-weighted multivariable linear regression models	cross-sectional study	PC	MEHP-TT, FT, BT, FAI (−) MEHHP- E_2 (−) MEOHP- E_2, FT, BT, FAI (−)
Xie et al. (2015)[62]	2013−2014	China	57 boys with CDGP (cases) and 110 controls	M: 167	MEHP, MEHHP, MEOHP	TT	multiple linear regression models	case-control study	β	none
Wei-Hsiang Chang et al. (2015)[14]	2010−2012	China	infertile men (25−45 years old) fertile men (21−40 years old)	M: 176	MEHP, MEHHP, MEOHP	FSH, LH, TT, E_2, SHBG, inhibin B, FT, FAI	linear regression models	case-control study	β	MEHP-TT (−)
Cao et al. (2020)[16]	2015−2017	China	173 women determined to meet the diagnosis of POF and 246 healthy women <40 years	F: 419	MEHP, MEHHP, MEOHP	E_2, FSH	binary logistic regression models	case-control study	OR	MEHHP-FSH (−) MEOHP-FSH (−)
Bustamante-Montes et al. (2021)[50]		Mexico	mother−infant	mother−infant: 83	MEHP	TT, FSH, LH, inhibin B	generalized estimating equations (GEE) models	mother−infant cohort	β	MEHP-inhibin B (−)
Meeker et al. (2009)[58]	January 2000 to May 2004	United States	men who were partners in subfertile couples seeking treatment	M: 425	MEHP, MEHHP, MEOHP	FSH, LH, inhibin B, TT, SHBG, FAI, E_2, PROL	multivariable linear regression	cross-sectional study	β	MEHP-E_2, TT (−), TT/E_2 (+) MEOHP-FAI (−)
Mendiola et al. (2012)[13]	1999−2005	United States	Study for Future Families (SFF): men who were partners of pregnant women; Massachusetts General Hospital (MGH): men with male factor infertility, as well as men who are partners of women with female factor infertility	M: 850	MEHP, MEHHP, MEOHP	FSH, LH, TT, E_2, SHBG, FAI, FT	Mann−Whitney U test and Pearson correlation coefficients	cross-sectional study	β, r	MEHP-TT, E_2, FAI, FT (−), TT/E_2 (+) MEHHP-FT, FAI (−), SHBG (+) MEOHP-FT, FAI (−), SHBG (+)
Jurewicz et al. (2013)[57]	2007	Poland	men who were attending an infertility clinic	M: 269	MEHP	TT, E_2, FSH	linear regression model	cross-sectional study	β	MEHP-TT (−)

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Table 1. continued

study	data period	location	population	sex: *N*	DEHP exposure type	reproductive hormone type	statistical analysis	study design	effect value type	significance result
Ferguson et al. (2014)[56]	1994–2004 recruit 2010 follow-up	Mexico	boys	M: 118	MEHP, MEHHP, MEOHP	DHEA-S, E_2, inhibin B, SHBG, TT, FT	linear regression models	cross-sectional study	PC	MEHP-FT (−), SHBG (+) MEHHP-SHBG (+) MEOHP-SHBG (+)
Pan et al. (2015)[19]	2012–2014	China	male partners of infertile couples	M: 1066	MEHP, MEHHP, MEOHP	TT, LH, FSH, E_2, SHBG, FAI, FT	multivariate linear regression models	cross-sectional study	PC	MEHP- E_2, INSL3 (−)
Axelsson et al. (2015)[48]		Sweden	young men	M: 314	MEHP, MEHHP, MEOHP	TT, FT, LH, FSH, E_2, SHBG	regression models	cross-sectional study	β	none
Wang et al. (2016)[20]	from March to June 2013	China	male partners of couples attending an infertility clinic	M: 483	MEHP, MEHHP, MEOHP	TT, FT, LH, FSH, E_2, SHBG, FAI	multivariate linear regression models	cross-sectional study	β, PC	MEHP-TT, E_2, FT (−)
Chang et al. (2017)[52]	November 2010 to March 2014	China	male partners of subfertile and fertile couples	M: 290	MEHP, MEHHP, MEOHP	TT, E_2, LH, FSH, SHBG	multiple linear regression	cross-sectional study	PC	MEHP-TT, TT/LH (−), E_2 (+) MEHHP-TT, TT/LH (−), E_2, SHBG (+) MEOHP-TT (−), E_2, SHBG (+)
Chen et al. (2017)[21]	2013	China	male students	M: 796	MEHP, MEHHP, MEOHP	E_2, FSH, LH, PROL, PROG, TT	linear regression or mixed model	cross-sectional study	PC	MEHP-PROG (−) MEHHP-TT (−) MEOHP- E_2, TT, PROG (−)
Albert et al. (2018)[46]	2009–2012	Canada	men aged between 18 and 41 years	M: 117	MEHP, MEHHP, MEOHP	LH, TT, TSH	unadjusted linear regression models	cross-sectional study	PC	none
Al-Saleh et al. (2019)[47]	2015–2017	Saudi Arabia	men attending an in vitro fertilization clinic	M: 599	MEHP, MEHHP, MEOHP	FSH, LH, E_2, PROL, TT	Pearson correlation coefficients	cross-sectional study	β	MEHHP-FSH (−) MEOHP-FSH PROL (−)
Chang et al. (2019)[22]	2015–2017	China	elderly men with urologist-diagnosed benign prostatic hyperplasia (BPH) and prostatic enlargement	M: 207	MEHP, MEHHP, MEOHP	LH, FSH, SHBG, inhibin B, E_2, TT, FT	multivariate linear regressions	cross-sectional study	β	MEHP- E_2 (+) MEHHP- E_2 (+) MEOHP- E_2 (+)
Henrotin et al. (2020)[68]	2015–2018	French	male workers from factories in the plastics industry	M: 97	MEHP	TT, FT, FSH, LH, E_2,	Wilcoxon signed-rank test	panel study	β	MEHP-TT (+)
Wang et al. (2020)[59]	2015	China	male partners of couples and diagnosed as infertile	M: 88	MEHP, MEHHP	FSH, TT, LH	multiple linear regression analysis	cross-sectional study	β	none
Du et al. (2018)[55]	2016	China	women seeking infertility treatment	F: 415	MEHP, MEHHP, MEOHP	AMH, inhibin B	multivariable linear regression	cross-sectional study	β	MEHP-inhibin B (−)

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Table 1. continued

study	data period	location	population	sex: *N*	DEHP exposure type	reproductive hormone type	statistical analysis	study design	effect value type	significance result
										MEOHP-inhibin B (−)
Watkins et al. (2014)[60]	1997−2004, recruit 2010 follow-up	Mexico	pregnant women and their offspring	F: 128	MEHP, MEHHP, MEOHP	E_2, TT, SHBG, DHEA-S, inhibin B	linear regression	mother−infant cohort	PC	none
Sathyanarayana et al. (2017)[23]	2010−2012	United States	The Infant Development and the Environment Study	mother−infant: 591	MEHP, MEHHP, MEOHP	FT, TT, E_2	multiple linear regression	cross-sectional study	PD	MEHP-E_2 (−) MEOHP- E_2 (−)
Cathey et al. (2019)[51]	2012−2017	United States	pregnancy 16 to 20 weeks and 24 to 28 weeks station	F: 677	MEHP, MEHHP, MEOHP	E_2, SHBG, PROG, TT	linear mixed model	cross-sectional study	PC	none
Su et al. (2014)[17]	2001−2009	China	children 8 years old and their mothers	F: 69 M: 61	MEHP	E_2, FSH, FT, PROG, TT	simple linear and binary logistic regression analyses	cross-sectional study	β	MEHP-PROG (+)
Chen et al. (2017)[53]	2006−2008	China	adults (aged 20−30)	M: 313 F: 473	MEHP, MEHHP, MEOHP	TT	generalized additive models	cross-sectional study	β	MEHP-TT (−)
Wen et al. (2017)[18]	2011	China	children aged <12 years old in issue of the illegal use of phthalates as clouding agents in food products	F: 90 M: 132	MEHP, MEHHP, MEOHP	LH, FSH, E_2, TT, FT, SHBG	Spearman's correlation	cross-sectional study	*r*, OR	MEHP-FSH (−) MEHHP-FSH (−) MEOHP-FSH (−)
Wen et al. (2017)[61]	2000−2001, recruit 2003, 2006, 2009, 2012 follow-up	China	mother−infant	F: 97 M: 94	MEHP	E_2, TT, FT, PROG	generalized estimating equation (GEE) linear regression analysis	cross-sectional study	β	none
Zhang et al. (2019)[65]	2014−2015	China	residents aged 11−88 years	F: 58 M: 48	MEHP, MEHHP, MEOHP	FSH, PROL, LH, E_2, PROG, TT	multivariate binary logistic regression models	cross-sectional study	RR	MEHP-TT, FSH (−) MEHHP-TT, LH (+) MEOHP-TT, FSH, LH, PROG (−)
Aimuzi et al. (2022)[45]	2013−2016	United States	participants aged 12−19 years old	M: 319 F: 294	MEHP, MEHHP, MEOHP	TT, E_2, SHBG, FAI, FT	multiple linear regression	cross-sectional study	β	MEHP- E_2 (−) MEHHP- E_2, TT/E_2 (−) MEOHP- E_2, TT/E_2 (−)
Adibi et al. (2015)[69]	2010−2012	United States	pregnant women	F: 541	MEHP	HCG	multiple linear regression	mother−infant cohort	β	MEHP-HCG (−)
Ding et al. (2023)[54]	1996−2003	United States	female aged 42 to 52 years	F: 3302	MEHP, MEHHP, MEOHP	AMH, FSH, SHBG	multivariable linear mixed-effect models	panel study	PC	MEHP-AMH (−) MEHHP-AMH (−) MEOHP-AMH (−)
Derakhshan et al. (2023)[77]	2007−2010	Sweden	pregnant women	F: 2039	MEHP, MEHHP, MEOHP	HCG	multivariable linear regression model	cross-sectional study	β	MEHP- HCG (−)

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Table 1. continued

study	data period	location	population	sex: *N*	DEHP exposure type	reproductive hormone type	statistical analysis	study design	effect value type	significance result
										MEHHP- HCG (−)
										MEOHP- HCG (−)
Liu et al. (2023)[66]	2017−2020	China	child	F: 399 M: 430	MEHP, MEHHP, MEOHP	TT, E_2	generalized linear models	panel study	β	none
Nobles et al. (2023)[64]	2007−2011	United States	women attempting pregnancy	F: 1228	MEHP, MEHHP, MEOHP	E_2, FSH, LH, PROG	generalized linear models	cross-sectional study	PC	MEHP- FSH (+)
										MEHHP- FSH (+)
										MEOHP- FSH (+)

[a]TT, total testosterone; SHBG, sex hormone binding-globulin; LH, luteinizing hormone; FT, free testosterone; BT, bioavailable testosterone; FSH, follicle-stimulating hormone; FAI, free androgen index; E_2, estradiol; DHEA-S, dehydroepiandrosterone; PROG, progesterone; HCG, human choionic gonadotophin; AMH, anti-Müllerian hormone; PROL, prolactin; F, female; M, male; β, regression coefficient; PC, percentage change; PD, percent difference; *r*, correlation coefficient; OR, odds ratio; RR, relative risk; (+), positive correlation; (−), negative correlation; *N*, sample size.

female infertile population that reported the association of DEHP metabolites with inhibin B. Therefore, a subgroup analysis by fertility was not available among women.

Additionally, analysis by country subgroups indicated that the association between MEHHP, MEOHP, and FSH was significantly negative in high-middle SDI countries (Tables S6 and S7). Furthermore, a total of five studies investigated the association between prenatal DEHP metabolite concentration and reproductive hormone levels in children, and no significant relationship was observed in this meta-analysis (Table S8).

3.5. Sensitivity Analysis and Publication Bias

The leave-one-out meta-analysis was used to evaluate the stability of the pooled estimates. The results are presented in Figures S1−S15, which suggest that the pooled effect estimates between all DEHP metabolites with reproductive hormones (TT, SHBG, LH, inhibin B, FSH, FAI) remained stable, except for PROL, FT, and E_2 in males and PROG in female. In addition, the results of the combined articles reporting correlation coefficients also showed that MEHP was negatively correlated with FT and FAI, and all DEHP metabolites were positively correlated with FSH in males (Figures S16 and S17). Moreover, meta-analyses conducted in studies excluding pregnant women did not reverse the pooled effects in females (Figures S20).

Although Egger's tests revealed publication bias in the association of DEHP metabolite concentrations with TT, PROL, FT, and FSH ($P < 0.05$) (Table S9), further trim-and-fill analyses indicated no reversal of the pooled effect values before and after adjustment; thus, the results are robust (Table S10).

4. DISCUSSION

A total of 37 articles from eight countries were examined in this systematic review and meta-analysis to assess the relationship between urinary levels of DEHP metabolites and serum reproductive hormones. There was significant gender specificity in the association of DEHP with reproductive hormones. A pooled analysis of 20 studies conducted in men showed that DEHP was positively correlated with SHBG and negatively correlated with TT, FAI, and FSH. However, DEHP was not significantly associated with reproductive hormones in overall women. It is noteworthy, however, that an age subgroup analysis of women showed that postmenopausal women were more sensitive to DEHP, which was associated with lower TT and E_2. Furthermore, no significant association between DEHP and reproductive hormone alterations was found in men of childbearing age. However, in infertile men, increased concentrations of DEHP metabolites were associated with reduced FT, FSH, and FAI levels.

The association of TT with DEHP is the most studied among all of the reproductive hormones. TT is crucial for the male reproductive system, as well as male fertility. Low TT levels can cause adverse conditions (e.g., prostatic enlargement, decreased fertility, decreased bone mineral density,[78] osteoporosis, and depression[79]). Numerous studies revealed that both high- and low-dose exposure to DEHP decreased circulating testosterone concentrations in adult animals.[80,81] Although the mechanism underlying how DEHP exposure affects TT has not been fully demonstrated, the available experimental studies provide several possible avenues of explanation. First, studies in rats have shown that DEHP-induced reductions in testosterone are achieved by repressing some genes involved in cholesterol

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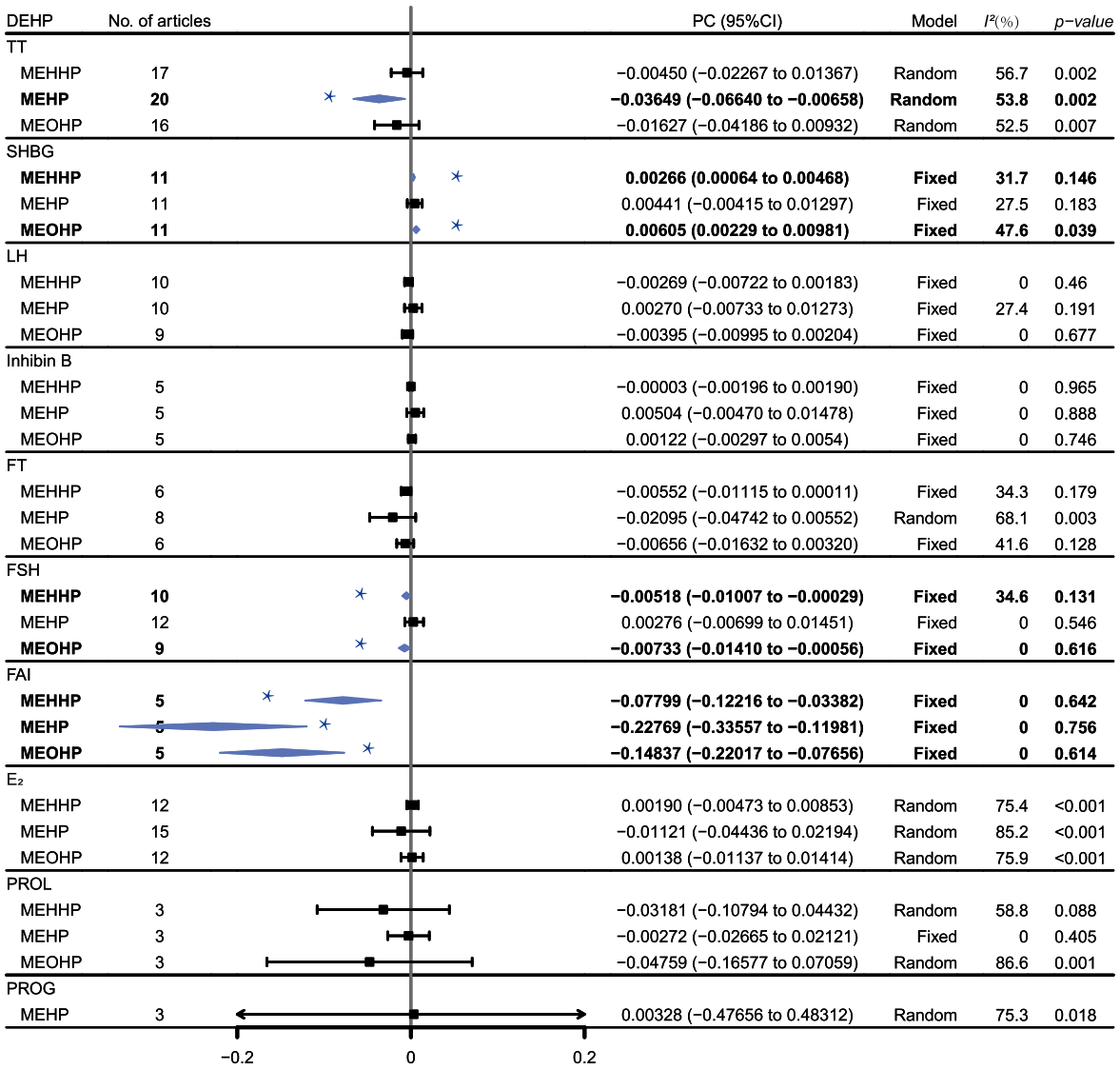

Figure 2. Forest plot of urinary DEHP metabolites associated with reproductive hormones in men. MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl)-hexyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; TT, total testosterone; SHBG, sex hormone binding-globulin; LH, luteinizing hormone; FT, free testosterone; FSH, follicle-stimulating hormone; FAI, free androgen index; E_2, estradiol; DHEA-S, dehydroepiandrosterone; PROG, progesterone; PC, percentage change; *p*-value, Cochran's Q test for heterogeneity.

transport and metabolism or genes encoding steroidogenic enzymes.[82] In addition, DEHP is a peroxisome proliferator that can produce a lot of reactive oxygen species (ROS) in vivo.[83] Prenatal exposure to DEHP leads to a decrease in antioxidant capacity by reducing riboflavin[84] and biotin[85] metabolism. Excessive ROS production and inadequate antioxidant defense mechanisms can lead to the development of oxidative stress, which in turn affects HPG and disrupts hormone secretion.[86] Finally, experimental studies revealed pathways by which DEHP reduces testosterone synthesis, including by inhibiting aromatase transcription and activating peroxisome proliferation-activated receptors (PPARs) in granulosa cells[87] and inhibiting the differentiation of Leydig cells during regeneration.[88]

TT, FT, and FAI are common clinical indexes of androgen. Androgens were much higher in men than in postmenopausal women. In the body, most of the circulating testosterone is bound to a protein (SHBG or albumin), while the remaining testosterone (about 2%) is free or unbound, called FT. FAI, calculated as the ratio of TT to SHBG, reflects the status of biologically active androgens.[89] We also found a significant negative correlation between DEHP and FAI, which indicates that DEHP not only lowers the TT concentration but also dramatically inhibits the bioactivity of testosterone in men.

SHBG was negatively associated with MEHHP in postmenopausal women and positively associated with MEOHP in men. SHBG is a serum glycoprotein regulated by the reproductive hormone levels in the body. The opposite effects of SHBG by estrogens and androgens, whereby androgens decrease while estrogens raise SHBG concentration,[18,90] may be responsible for this phenomenon.

The primary female reproductive hormone is E_2, which also controls the menstrual cycle and is essential for the growth and upkeep of female reproductive tissues.[91] Exposure to DEHP has been documented to cause both increases and decreases in E_2 levels in humans and animals. Our meta-analysis revealed significant changes in E_2 associated with the DEHP metabolite concentration among postmenopausal women. As an endo-

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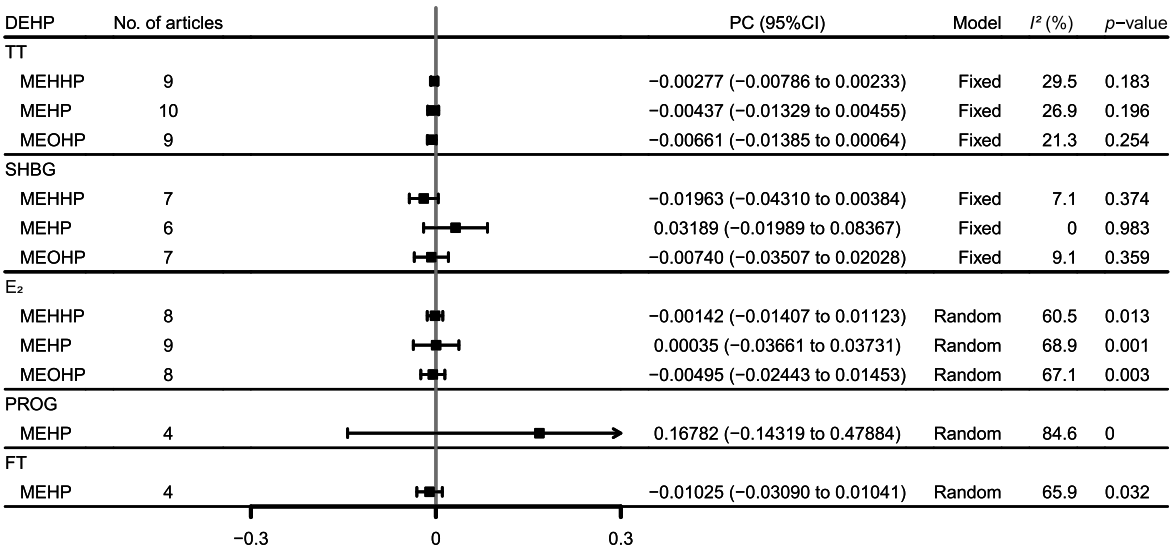

Figure 3. Forest plot of urinary DEHP metabolites associated with reproductive hormones in women. MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl)-hexyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; TT, total testosterone; SHBG, sex hormone binding-globulin; E_2, estradiol; FT, free testosterone; PROG, progesterone; PC, percentage change; *p*-value, Cochran's Q test for heterogeneity.

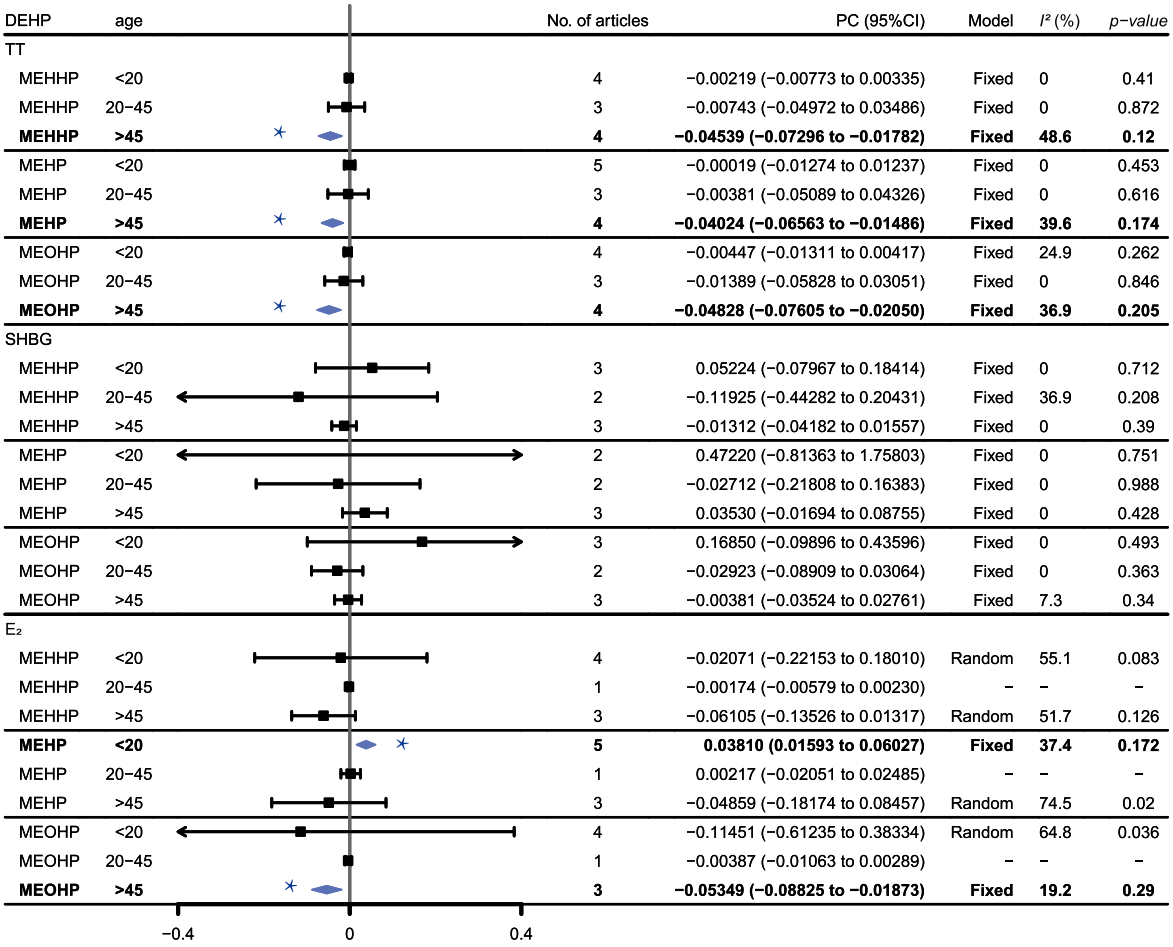

Figure 4. Forest plot of urinary DEHP metabolites associated with reproductive hormones in women of different age groups. MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl)-hexyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; TT, total testosterone; SHBG, sex hormone binding-globulin; PC, percentage change; *p*-value, Cochran's Q test for heterogeneity.

crine-disrupting chemical (EDCs), DEHP mimics naturally occurring estrogen, thereby competing with endogenous estrogen and binding to the ER to ultimately interfere with or prevent the metabolism of the hormone or receptor in the liver.[92] Furthermore, Takeuchi et al. indicated that DEHP exhibited not only estrogen receptor (ER) α-mediated

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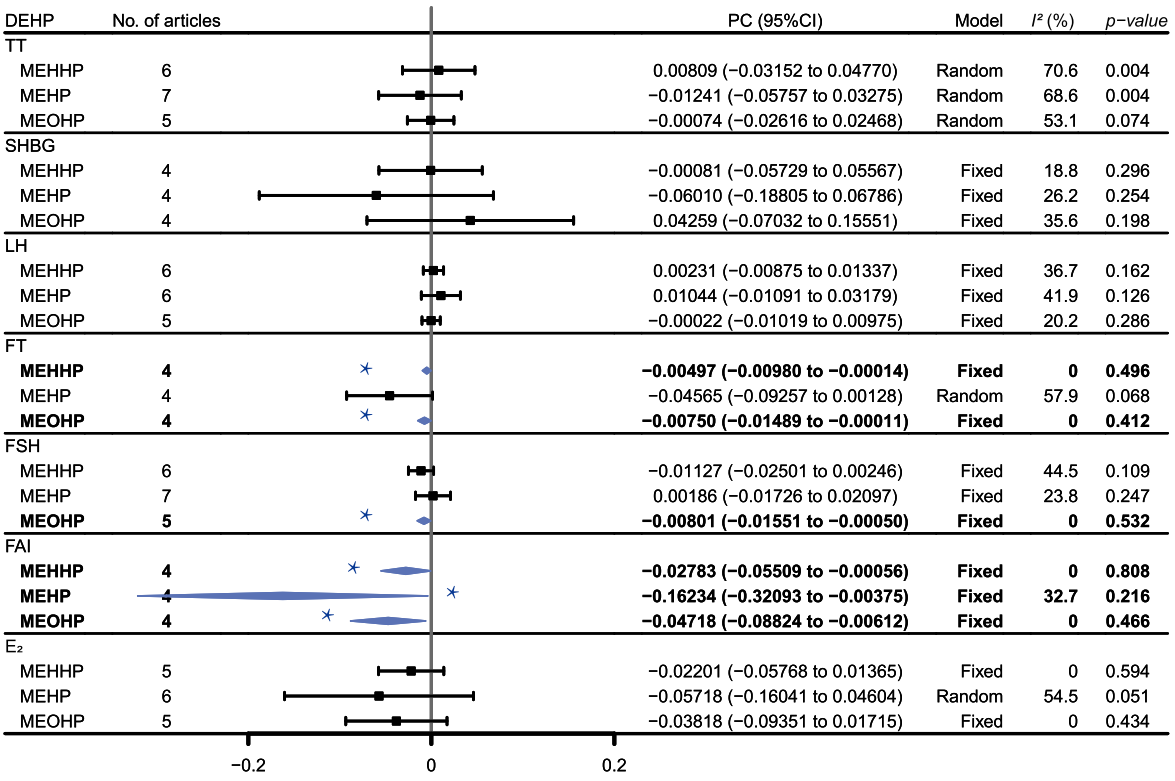

Figure 5. Forest plot of urinary DEHP metabolites associated with reproductive hormones in infertile men. MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl)-hexyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; TT, total testosterone; SHBG, sex hormone binding-globulin; LH, luteinizing hormone; FT, free testosterone; FSH, follicle-stimulating hormone; FAI, free androgen index; E_2, estradiol; PC, percentage change; *p*-value, Cochran's Q test for heterogeneity.

estrogenic activity but also ER β-mediated antiestrogenic activity in a dose-dependent manner.[78] Hence, DEHP may cause hormonal disorders through the ER.

Subfertility is the failure to conceive after one year of unprotected intercourse.[93] It is reported that subfertility affects 15% of couples worldwide, involving 48.5 million couples.[93] Men were fully responsible for 20−30% of subfertility cases.[94] In our meta-analysis, subjects of the subfertility subgroup are mainly recruited among partners of infertile couples seeking treatment in clinics. The results show that among men of reproductive age, exposure to DEHP was associated with more significant hormonal suppression in infertile men compared with that in fertile men. A previous review summarized the relationship between phthalate (PAE) exposure and male reproductive outcomes, ultimately finding moderate evidence of increased DEHP metabolites related to shorter anogenital distance and lower semen quality.[95] Studies revealed that the adverse effects of DEHP exposure on sperm concentration may be partially mediated by reproductive hormones, thereby further contributing to fertility problems in reproductive-age men.[14,47,52] Hence, we cannot determine whether infertile men are more sensitive or whether infertility is also a health effect of DEHP exposure. Finally, we found evidence of negative associations between MEOHP and FSH. FSH usually reflects the feedback between the testes and the hypothalamus/pituitary gland on the status of spermatogenesis, and its elevation indicates abnormal spermatogenesis.[96]

Age subgroup analysis revealed that postmenopausal women (>45 years old) were more sensitive to DEHP by showing a significant decrease in TT and E_2 concentrations. Although several studies have revealed this phenomenon, it still has not been addressed why and how postmenopausal women become particularly susceptible to plasticizers.[54,67] It seems not to be the result of exposure levels. Long et al. found that postmenopausal women had lower DEHP exposure than premenopausal women.[67] However, the study by Ding et al. showed no appreciable variations in the concentrations of DEHP metabolites across menopausal stages.[54] Alternatively, postmenopausal women have lower TT with reproductive aging and declining ovarian functions compared with premenopausal women. The reproductive hormones of postmenopausal women tend to stabilize independently of the menstrual cycle,[97] which may explain their greater sensitivity to DEHP. There were no significant differential results for age subgroup analysis in males, partly because of the existing studies focused on men of reproductive age.

Several studies have found that PAE was associated with multiple adverse health outcomes by affecting reproductive hormone levels. Two studies conducted in China showed that LH and androstenedione mediated the association between serum PAE concentration sperm concentration and sperm motility.[59,98] Studies in older men indicated that exposure to DEHP promoted benign prostatic hyperplasia by increasing the level of dihydrotestosterone, E_2, and ROS production. Adibi et al. confirmed HCG partially mediates PAE concerning anogenital distance in males and females.[69] In addition, PAE exposure during pregnancy increases the risk of developing postpartum depression by decreasing maternal progesterone concentrations.[99] Finally, some studies link exposure to phthalate metabolites to female obesity,[15] metabolic syndrome, the timing of menarche,[49] premature ovarian failure,[16] delayed pubarche,[100] and self-reported sleep disruptions.[101]

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The usage of DEHP is expanding as economies grow, which harms ecosystems and public health.[102] Our study demonstrates the hormone-disrupting effects of DEHP, especially in infertile men and postmenopausal women. Therefore, attention should be paid to taking measures to minimize the adverse effects of DEHP. First, governments can innovate technologies to reduce the emission rate of DEHP by adopting non/low-toxicity alternatives to plasticizers or by replacing polymers without plasticizers.[103,104] The use of phthalates in food and mother and child products should be restricted or suspended,[105] and it is necessary to develop new technologies to improve the degradation rate of DEHP to reduce the burden of DEHP deposition in the environment.[106] Besides, individuals, especially vulnerable populations, can also effectively reduce the burden of DEHP in the body by reducing dietary intake and changing personal habits and behaviors,[105,107] such as by (1) reducing drinking from plastic cups; (2) reducing the use of plastic packaging for food, especially meat and fat-rich food; (3) avoiding repeated use of disposable plastic packaging; (4) limiting microwaving food in cartons, plastic boxes, or plastic packaging; and (5) stopping use of cosmetics or by using less-scented personal care products.

4.1. Strengths and Limitations of This Study

In conclusion, this systematic review and meta-analysis provide the most updated and comprehensive analysis to date of the relationship between urinary DEHP metabolites and serum reproductive hormones, thereby contributing to clarifying the mechanisms of DEHP effects on human health. Nevertheless, several limitations must be considered in this study. First, only minor studies used the sum of DEHP metabolites (ΣDEHP) involving different types of DEHP metabolites. Therefore, the relationship between ΣDEHP and reproductive hormones is still inconclusive. Additionally, only a few studies of male children, adolescents, and older adults limits our further assessment of differences in male age subgroups.

4.2. Future Directions

Several potential future extensions of this work are proposed in this paper. First, the half-life of DEHP is very short (<24 h). DEHP is rapidly metabolized after absorption and does not bioaccumulate in the body. However, most of the existing studies used a single urine spot to represent DEHP exposure and ignored the changes in exposure over time. Therefore, more studies with higher sensitivity (i.e., taking into account different exposure time windows with repeated exposure measurements) would be informative. In addition, studies in women should take full account of factors affecting the circulating levels of reproductive hormones, such as menstrual cycle, menstrual status, etc. Moreover, research is urgently needed to determine whether hormone effects from DEHP exposure result in later adverse health outcomes.

5. CONCLUSIONS

This systematic review and meta-analysis provide evidence that DEHP metabolites are associated with altered reproductive hormones, including TT, FAI, FSH, and SHBG. DEHP mainly exerts antiandrogenic effects on the human body. Postmenopausal women are more vulnerable to the association of DEHP with lower TT and E_2. Furthermore, the significant changes in hormones are found in infertile men rather than fertile men, which means DEHP may contribute to other adverse reproductive health outcomes by altering hormone levels. Overall, our findings may provide support for understanding the relationship between DEHP metabolites and reproductive hormones. As the annual production and use of plastics increase dramatically, policymakers should consider the health risks of using DEHP as an additive.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.4c00046.

Additional results from this manuscript in Tables S1−S10 and Figures S1−S20 (PDF)

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#X.L. and C.X. contributed equally to this study. X.L., S.W., and L.H.: Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, and Writing - review and editing. J.L., N.W., and J.S.: Data curation, Formal analysis, Visualization, and Writing - review and editing. J.Y., L.L., and R.S.: Formal analysis, Methodology, Data curation, and Writing - review and editing. W.Y. and R.P.: Formal analysis, and Methodology. H.S. and C.X.: Supervision, Conceptualization, Validation, Writing - original draft, and Writing review and editing.

Notes

The authors declare no competing financial interest.

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