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Review Article

Association of diethylhexyl phthalate exposure with serum thyroid hormone levels: a systematic review and meta-analysis

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Abstract: Objective: Evidence suggests that diethylhexyl phthalate (DEHP) may disrupt thyroid hormone homeostasis by targeting multiple components of the hypothalamic-pituitary-thyroid (HPT) axis, potentially harming human health. However, the relationship between DEHP exposure and thyroid function remains debated. We performed a meta-analysis to clarify the association between DEHP exposure and thyroid function. Methods: We searched Medline, Embase, the Cochrane Library, and Web of Science for relevant studies that provided quantitative data on the association between DEHP and thyroid hormones. The ROBINS-E tool was used to assess the quality of included studies. Pearson correlation coefficients or regression coefficients (β) with 95% confidence intervals (CIs) were calculated to evaluate the relationship between DEHP exposure and thyroid hormone levels. Results: Twenty-three studies were included. In adults, thyroxine (TT4) levels (pooled coefficient -0.05, 95% CI [-0.08, -0.03]) and free thyroxine (FT4) levels (pooled coefficient -0.04, 95% CI [-0.06, -0.02]) were negatively associated with urinary DEHP concentration. Additionally, DEHP exposure in adults was positively correlated with thyroid-stimulating hormone (TSH) levels (pooled coefficient 0.03, 95% CI [0.02, 0.04]). In pregnant women, urinary DEHP concentration was negatively correlated with FT4 levels (pooled correlation coefficient -0.04, 95% CI [-0.06, -0.02]). However, no significant association was observed between DEHP exposure and thyroid function in children and adolescents. Conclusion: This meta-analysis demonstrates a significant association between DEHP exposure and serum thyroid hormone levels in adults. However, DEHP exposure appears to have no significant effect on thyroid function in children and adolescents.

Keywords: Diethylhexyl phthalate, thyroid hormone, systematic review, meta-analysis

Introduction

Plastic pollution is a global public health challenge. Phthalate esters (PAEs) are widely used in food and beverage packaging [1], household products [2], toys, pharmaceutical products [3] and so on. Based on side chain differences, PAEs can be divided into two types [4]: high molecular weight PAEs (such as di-iso-octyl phthalate (DEHP), diisonoyl phthalate (DINP)) and low molecular weight PAEs (such as diethyl phthalate (DEP) and butyl benzyl ester (BBzP)). DEHP, the most common phthalate [5], exists widely in the environment [6] because it does not bind to polymers via covalent bonds and is easily released from plastics. Humans are exposed to DEHP through the digestive tract, skin and respiratory tract [7-10]. Once in the body, DEHP is rapidly metabolized into monoesters or hydroxylated metabolites (including mono-(2-ethyl-hexyl) phthalate, MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP). These metabolites have a short elimination half-life and are excreted through urine,

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feces and sweat [11]. Urinary phthalate metabolite levels are commonly used to assess exposure due to their high concentration in urine.

Thyroid hormone (TH) synthesis and secretion are regulated by the hypothalamic-pituitary-thyroid (HPT) axis. TH is a key endocrine hormone that regulates lipid and glucose metabolism, cell growth, and nervous system development. Limited evidence indicates that DEHP can disrupt thyroid hormone homeostasis through multiple targets in the HPT axis, negatively impacting human health [12]. Several observational studies have shown negative correlations between DEHP metabolites and thyroid hormones (triiodothyronine [T3] or thyroxine [T4]) in the general population, pregnant women, and even children [13]. Conversely, other studies found no association between DEHP and thyroid-stimulating hormone (TSH), free thyroxine (FT4), or free triiodothyronine (FT3) [14-17]. However, variations in metabolite types, inconsistent outcome measures, small sample sizes, and unaccounted potential confounders, such as dietary iodine intake, contribute to the controversy regarding the relationship between DEHP exposure and thyroid function.

Therefore, we conducted a systematic review and meta-analysis to clarify the relationship between DEHP exposure and thyroid function.

Methods

This meta-analysis was conducted and reported in accordance with the Preferred Reporting Items For Systematic Reviews And Meta-Analysis (PRISMA) [18]. The study protocol was registered on the PROSPERO website (CRD42022337510).

Search strategy

We performed a literature search in Ovid MEDLINE, Ovid EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception until May 14, 2022, with an updated search conducted on January 29, 2023. Additionally, we manually reviewed the reference lists of relevant studies to identify further eligible studies. When necessary, we contacted authors via email for more information. No language restrictions were applied. The search strategy included a combination of free terms and medical subject headings (MeSH), such as phthalate, diethylhexyl phthalate, Di (2-ethylhexyl) phthalate, Bis (2-ethylhexyl) phthalate, DEHP, and thyroid. The detailed search strategy is provided in the Supplementary Material.

Selection criteria

We included published studies that examined the associations between urinary phthalate metabolites and serum thyroid hormones. The inclusion criteria were as follows: 1) The study population consisted of the general population, including pregnant women and children. 2) The study measured urinary phthalate metabolites (MEHP, MEHHP, MEOHP, and MECPP) to assess DEHP exposure, and serum thyroid hormones (TSH, TT4, FT4, FT3, TT3) to evaluate thyroid function. 3) The study reported correlation or regression coefficients with 95% confidence intervals (CIs) for the association between DEHP exposure and thyroid function. 4) The study design was a prospective cohort or cross-sectional study.

We excluded the following: 1) Studies involving neonates, as they were indirectly exposed to DEHP through their mothers. 2) Reviews, conference abstracts, editorial materials, and animal studies.

Data extraction and quality assessment

Two reviewers (K.X. and H.S.) independently extracted the following data: first author, publication year, study design, location, population, sample size, age, gender, urinary concentrations of DEHP metabolites, thyroid hormones, and statistical analysis methods.

The Risk of Bias (ROB) in Non-Randomized Studies of Environmental Exposures (ROBINS-E) tool was used to assess the risk of bias and the quality of the included studies [19]. This tool evaluates seven domains: bias due to confounding, bias in participant selection, bias in exposure measurement, bias due to deviations from intended exposures, bias due to missing data, bias in outcome measurement, and bias in the selection of reported results. Two reviewers (H.S. and X.Z.) independently assessed the risk of bias, with disagreements resolved through discussion or consensus with a third reviewer (X.C.).

Strategy for data synthesis

Quantitative methods were used for data synthesis. The data were synthesized using meta-analysis to present the primary and secondary outcomes of the studies in a comparative manner. We pooled the β coefficients with 95% confidence intervals (CIs), and correlation coefficients (r) were converted to Fisher's Z-values for pooling. Statistical heterogeneity was assessed using the Chi-square test and I^2, with *p*-values ≤ 0.10 and $I^2 \geq 50\%$ indicating significant heterogeneity. Given the theoretical heterogeneity among the studies, a random-effects model was applied for pooling. Subgroup analyses were conducted based on different populations, such as children, pregnant women, and adults. Sensitivity analysis was performed, and Egger's test was used to assess publication bias. All statistical analyses were conducted using R software (version 4.2.1).

Results

Characteristics of included studies

Figure 1 outlines the study selection process. The electronic searches identified 1,026 potentially relevant studies, of which 64 eligible full texts were evaluated after screening titles and abstracts. After full-text evaluation, 41 studies were excluded. Ultimately, we included 23 cohort or cross-sectional studies [20-42]. The characteristics of the included studies are summarized in **Table 1**. These studies were published between 2007 and 2022, with sample sizes ranging from 61 to 6,003 participants. Six studies involved adults, eight involved pregnant women, eight involved children and adolescents, and one involved participants older than 12 years. Five studies employed Spearman correlation analysis, while the remaining studies used linear regression models.

Quality assessment

The ROBINS-E tool was used to assess risk of bias (ROB) because the included studies involved environmental exposures. Seven domains were evaluated for each study. Two studies did not clearly define certain parameters and were considered to have moderate ROB in those domains. All studies used appropriate methods to assess exposure, resulting in a low ROB for exposure measurement. Eleven studies were cohort studies, where bias due to departures from intended exposures was less likely. Twelve studies were cross-sectional, and sufficient information was not provided to determine ROB in some domains. All studies had low ROB for missing data, outcome measurement, and reported result selection. In total, four studies were judged to have moderate ROB, and the remaining studies had low ROB (Supplementary Table 1).

Associations between DEHP exposure and thyroid function in adults

Eight studies reported associations between DEHP exposure and thyroid function in adults. Meta-analysis showed no correlation between adult DEHP exposure and TT3 levels (pooled coefficient 0.00, 95% CI [-0.03, 0.04], $I^2 = 87\%$; **Table 2**). Subgroup analysis of DEHP metabolites showed no correlation with TT3 levels. However, significant heterogeneity was found among the studies on DEHP and TT3, prompting sensitivity analysis. After excluding one study, a negative correlation between DEHP exposure and TT3 was observed (pooled coefficient -0.00, 95% CI [-0.04, -0.01], $I^2 = 19\%$). Subgroup analysis revealed that both MEHP and MEOHP were negatively correlated with TT3, with correlation coefficients of -0.02 (95% CI [-0.04, -0.00], $I^2 = 70\%$) and -0.06 (95% CI [-0.12, -0.01], $I^2 = 0\%$), respectively (**Table 2**).

Meta-analysis indicated a negative correlation between adult DEHP exposure and TT4 levels (pooled coefficient -0.05, 95% CI [-0.08, -0.03], $I^2 = 62\%$; **Table 2**). Subgroup analysis showed that MEHHP and MEOHP were negatively correlated with TT4 levels, with correlation coefficients of -0.08 (95% CI [-0.12, -0.05], $I^2 = 58\%$) and -0.05 (95% CI [-0.09, -0.02], $I^2 = 33\%$), respectively (**Table 2**).

A negative correlation was also found between adult DEHP exposure and FT4 levels (pooled coefficient -0.04, 95% CI [-0.06, -0.02], $I^2 = 48\%$; **Table 2**). Subgroup analysis of DEHP metabolites showed that MEHHP and MEOHP were negatively correlated with FT4. The correlation coefficients for MEHHP and MEOHP were -0.07 (95% CI [-0.15, -0.00], $I^2 = 57\%$) and -0.03 (95% CI [-0.06, -0.01], $I^2 = 0\%$), respec-

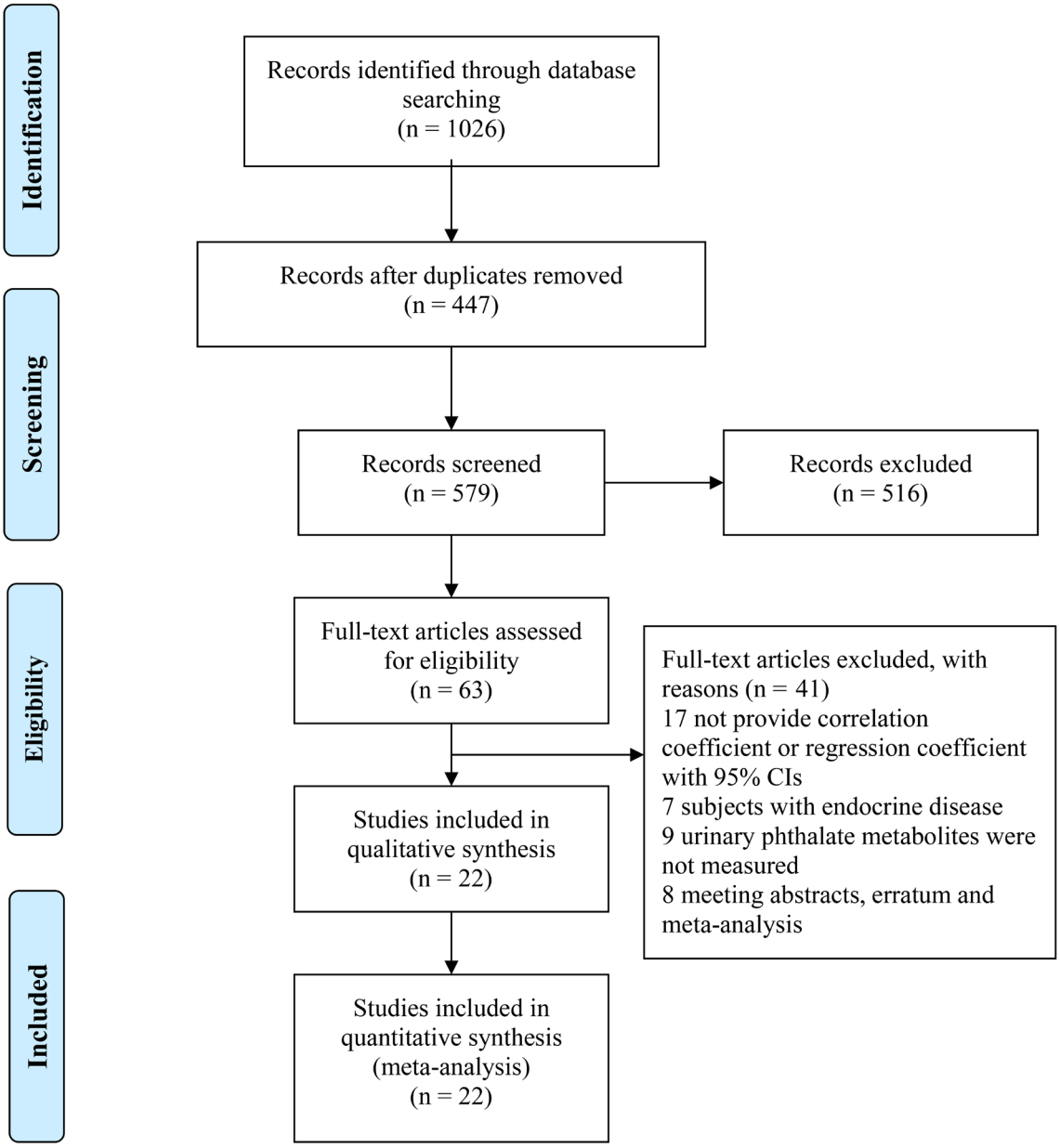

Figure 1. PRISMA flow chart for studies selection.

tively. Significant heterogeneity was noted in the DEHP and FT4 studies, prompting sensitivity analysis. After excluding one study, a stronger negative correlation between DEHP exposure and FT4 was observed (pooled coefficient -0.07, 95% CI [-0.10, -0.04], I^2 = 41%). Subgroup analysis showed that MEHP, MEHHP, and MEOHP were negatively correlated with FT4, with pooled correlation coefficients of -0.14 (95% CI [-0.21, -0.07], I^2 = 0%), -0.04 (95% CI [-0.07, -0.01], I^2 = 0%), and -0.14 (95% CI [-0.24, -0.05], I^2 = 76%), respectively (Supplementary Figure 1).

A positive correlation between adult DEHP exposure and TSH levels was found (pooled coefficient 0.03, 95% CI [0.02, 0.04], I^2 = 0%; **Table 2**). Subgroup analysis showed that MEHHP, MEOHP, and MECPP were positively correlated with TSH, with correlation coefficients of 0.04 (95% CI [0.01, 0.06], I^2 = 30%), 0.03 (95% CI [0.00, 0.05], I^2 = 0%), and 0.03

Table 1. Characteristics of included studies

Study	Study design	Sample collection time	Location	Population	Sample	Age (years)	Gender	Urinary concentrations of Diethylhexyl Phthalate (DEHP) metabolites				Thyroid hormone	Statistical analysis
								MEHP	MEHHP	MEOHP	MECPP		
Albert 2018 [20]	Cross-sectional study	2009-2012	Canada	Adults	153	25.9 (6.1)	All M	3.1 (1.4-6.2)	13 (5-22)	8.4 (3.4-15)	13 (6-25)	TSH/FT3/FT4	Linear regression models
Choi 2020 [21]	Cross-sectional study	2015-2017	Korea	Adults	1254	47 (15)	M: 630 F: 624	-	-	-	-	TT4/TT3/FT4/FT3/TSH	Linear regression analysis
Huang HBP 2017 [25]	Cross-sectional study	2013	Taiwan	Adults (≥ 18 years) Minors (< 18 years)	358	Adults 53.4 (17.3) Minors 12.6 (3.2)	Adults M: 129, F: 150 Minors M: 47, F: 32	Adults 6.7 (2.5-12.1) Minors 7.4 (2.4-12.6)	Adults 16.4 (9.8-30.1) Minors 25.5 (13.6-39.4)	Adults 10.2 (5.6-16.9) Minors 19.6 (9.3-32.3)	Adults 20.2 (10.9-31.9) Minors 34.7 (18.4-63.6)	TSH/FT4/TT4/TT3	Multivariable linear regression models
Huang HB 2021 [26]	Cross-sectional study	2013	Taiwan	Adults	217	52.7 (17.5)	M: 104 F: 113	7.0 (3.1-12.1)	15.9 (9.8-30.1)	9.93 (5.5-16.4)	19.9 (10.9-32.4)	TSH/FT4/TT4/TT3	Multiple regression models
Huang PCW 2020 [27]	Cross-sectional study	2013	Taiwan	Adults	266	53.6 (17.0)	M: 124 F: 142	6.8	16.46	10.28	20.30	TT4/TT3/FT4/TSH	Multivariate linear regressions
Park 2017 [31]	Cross-sectional study	2012-2014	Korean	Adults	6003	-	M: 2638 F: 3365	-	19.3 (10.7-32.1)	13.2 (7.7-22.4)	21.3 (12.8-34.8)	TSH/TT4/TT3	Multiple linear regression models
Derakhshan 2021 [22]	Cohort study	2007-2010	The Netherlands	Pregnant women	1996	30.9 (4.9)	All F	3.7 (0.7-26.8)	16.9 (2.9-110)	11.2 (1.9-72.3)	15.9 (3.3-95.5)	TSH/FT4/TT4/FT3/TT3	Multivariable linear regression
Huang HB 2018 [24]	Cohort study	2013-2014	Taiwan	Pregnant women	98	35.0 (3.5)	All F	-	-	-	-	TSH/FT4/TT4/TT3	Linear mixed models
Huang PC 2021 [28]	Cohort study	2005-2006	Taiwan	Pregnant women	61	34.0 (3.5)	All F	-	-	-	-	TT4/TT3/FT4/TSH	Spearman correlation
Huang PC 2007 [29]	Cohort study	2005-2006	Taiwan	Pregnant women	76	33.6 (3.3)	All F	20.6 (13.1-38.6)	-	-	-	TT4/TT3/FT4/TSH	Spearman correlation
Huang PC 2016 [30]	Cohort study	2013-2014	Taiwan	Pregnant women	97	35.1 (3.5)	All F	5.1	5.7	5.6	9.5	TT4/TT3/FT4/TSH	Spearman correlation
Kuo 2015 [33]	Cohort study	2009-2010	Taiwan	Pregnant women	148	29.4 (4.9)	All F	7.71	14.52	13.4	-	TT4/TT3/FT4/TSH	Spearman correlation
Yao 2016 [40]	Cohort study	-	China	Pregnant women	2521	26.3 (3.5)	All F	-	-	-	-	TT4/TT3/FT4/TSH	Spearman correlation
Huang PC 2020 [27]	Cohort study	2012-2016	Taiwan	Children	166	6.1 (2.4)	M: 106 F: 66	4.99 (1.8-9.9)	21.7 (11.4-38.8)	16 (7.5-29.4)	-	TT4/TT3/FT4/TSH	Generalized estimating equation
Kim 2018 [32]	Cross-sectional study	-	Korea	Children and adolescents	302	M: 9 (0.8) F: 8.7 (3.7)	M: 138 F: 164	7.8 (3.3-10.4)	-	-	-	TSH/TT3/TT4	Multiple linear regression
Meeker 2011 [34]	Cross-sectional study	2007-2008	United States	Adults and Adolescents	1760	-	Adults M: 737, F 668 Adolescents M: 185, F: 170	2.6 (< LOD-5.2)	20.6 (9.8-37.0)	11.2 (5.43-20.5)	30.6 (15.4-50.8)	TT4/TT3/FT4/FT3/TSH	Multivariable linear regression
Morgenstern 2017 [35]	Cohort study	1998-2006	United States	Children	229	3	M: 109 F: 119	-	-	-	-	FT4/TSH	Multiple linear regression models

Tsai 2016 [37]	Cross-sectional study	2012-2013	Taiwan	Children and Adolescents	250	7.6 (1.2)	M: 146 F: 104	4.8 (1.9-9.8)	20.6 (10.3-35.9)	14.7 (7.3-26.9)	-	FT4/TT3/ TT4 TSH	Multivariate linear regression models
Weng 2017 [38]	Cross-sectional study	2013-2014	Taiwan	Children	189	9-10	M: 92 F: 97	4.4 (1.3-9.4)	17.2 (8.0-33.4)	11.1 (5.4-21.9)	-	FT4/TT4/ FT3/TT3/ TSH	Generalized linear model
Wu 2017 [39]	Cross-sectional study	2013	China	Children aged 5-7 years	216	-	M: 107 F: 109	Urban 6 (3.6-13.2) Rural 4 (3.2-6.3)	Urban 15.4 (8.6-27.5) Rural 24.4 (10-93.9)	Urban 8.3 (5.2-13.7) Rural 5.6 (4.1-12.3)	-	FT4/FT3/ TSH	Multiple linear regression models
Zhao 2022 [41]	Cross-sectional study	2017	China	Students aged 16-19 years	347	-	M: 116 F: 231	-	-	-	-	TT4/TT3/ FT4/FT3/ TSH	Multivariate linear regression
Kim 2017 [32]	Cohort study	2007-2008	Korea	Population (≥ 12 years)	1829	-	M: 960 F: 869	2.1 (0.8-5.3)	20 (9.1-46.6)	11.2 (5.2-25.6)	29.8 (14.7-65.9)	TSH/FT4/ TT4/FT3/ TT3	Multivariate linear regression analyses
Yang 2022 [42]	Cohort study	2019-2020	China	Pregnant women	325	30.8 (3.9)	All F	20.70 (14-33.8)	7.67 (5.13-12.6)	13.30 (8.37-20)	24.20 (16-38.6)	TSH/FT4	

M: male, F: female.

Table 2. Results of meta-analysis and heterogeneity test of the correlation between Diethylhexyl Phthalate (DEHP) and thyroid hormone in adults

Factors	No.	Sample size	Heterogeneity		Effect Model	β	95% CI
			P (Q)	I^2 (%)			
TT3							
MEHP	4	2108	3.07	2.3	RE	-0.01	(-0.07, 0.04)
MEHHP	7	11194	22.31	73.1	RE	-0.00	(-0.05, 0.05)
MEOHP	6	9365	51.77	90.3	RE	-0.03	(-0.13, 0.06)
MECPP	6	9365	81.93	93.9	RE	0.05	(-0.05, 0.14)
Pooled correlation	-	-	-	87	RE	0.00	(-0.03, 0.04)
TT4							
MEHP	4	2108	6.37	53	RE	-0.01	(-0.08, 0.06)
MEHHP	7	11194	14.25	58	RE	-0.08	(-0.12, -0.05)
MEOHP	6	9365	7.47	33	RE	-0.05	(-0.09, -0.02)
MECPP	6	9365	25.51	80	RE	-0.02	(-0.09, 0.06)
Pooled correlation	-	-	-	62	RE	-0.05	(-0.08, -0.03)
FT4							
MEHP	5	2261	9.28	57	RE	-0.07	(-0.15, -0.00)
MEHHP	7	5344	4.33	0	RE	-0.03	(-0.06, -0.01)
MEOHP	6	3515	21.62	77	RE	-0.09	(-0.18, 0.01)
MECPP	6	3515	5.82	14	RE	-0.02	(-0.05, 0.01)
Pooled correlation	-	-	-	48	RE	-0.04	(-0.06, -0.02)
TSH							
MEHP	4	2108	1.93	0	RE	0.03	(-0.01, 0.07)
MEHHP	7	11194	8.56	30	RE	0.04	(0.01, 0.06)
MEOHP	6	9365	4.24	0	RE	0.03	(0.00, 0.05)
MECPP	6	9365	2.14	0	RE	0.03	(0.01, 0.05)
Pooled correlation	-	-	-	0	RE	0.03	(0.02, 0.04)

RE: Random effects model, MEHP: mono-(2-ethyl-hexyl) phthalate, MEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate, MEOHP: mono-(2-ethyl-5-oxohexyl) phthalate, MECPP: mono-(2-ethyl-5-carboxypentyl) phthalate.

(95% CI [0.01, 0.05], I^2 = 0%), respectively (**Table 2**).

No publication bias was detected based on the funnel plot and Egger's test (Supplementary Figure 4).

Associations between DEHP exposure and thyroid function in pregnant women

A total of eight studies reported the association between DEHP exposure and thyroid function in pregnant women. The meta-analysis results showed no correlation between maternal DEHP exposure and TT3 (pooled coefficient -0.02, 95% CI [-0.04, 0.00], I^2 = 35%). However, subgroup analysis of different DEHP metabolites revealed that MECPP was negatively correlated with TT3 in pregnant women (pooled coefficient -0.09, 95% CI [-0.15, -0.02], I^2 = 35%) (**Table 3**).

Maternal DEHP exposure was negatively correlated with TT4 (pooled coefficient -0.03, 95% CI [-0.04, -0.01], I^2 = 0%). Subgroup analysis indicated a negative correlation between maternal MEHHP exposure and TT4 levels (pooled coefficient -0.04, 95% CI [-0.07, -0.01], I^2 = 0%) (**Table 3**).

A negative correlation between DEHP exposure and FT4 levels was also found (pooled coefficient -0.04, 95% CI [-0.06, -0.02], I^2 = 55%). Subgroup analysis showed that maternal MECPP exposure was negatively correlated with FT4 levels (pooled coefficient -0.05, 95% CI [-0.09, -0.01], I^2 = 0%). Due to significant heterogeneity between studies on DEHP and FT4 in pregnant women, a sensitivity analysis was conducted. After excluding one study, a negative correlation was observed between DEHP exposure and FT4 in pregnant women (pooled

Table 3. Results of meta-analysis and heterogeneity test of the correlation between Diethylhexyl Phthalate (DEHP) and thyroid hormone in pregnant women

Factors	No.	Sample size	Heterogeneity		Effect Model	COR	95% CI
			P (Q)	I^2 (%)			
TT3							
MEHP	7	5115	4.63	0	RE	-0.01	(-0.04, 0.02)
MEHHP	5	4978	8.05	50.3	RE	-0.02	(-0.08, 0.03)
MEOHP	5	4978	3.25	0	RE	-0.00	(-0.03, 0.03)
MECPP	3	2309	2.12	5.5	RE	-0.09	(-0.15, -0.02)
Pooled correlation	-	-	-	35	RE	-0.02	(-0.04, 0.00)
TT4							
MEHP	7	5115	3.14	0	RE	-0.02	(-0.05, 0.01)
MEHHP	5	4978	1.71	0	RE	-0.04	(-0.07, -0.01)
MEOHP	5	4978	3.18	0	RE	-0.01	(-0.03, 0.02)
MECPP	3	2309	2.16	7.4	RE	-0.03	(-0.01, 0.04)
Pooled correlation	-	-	-	0	RE	-0.03	(-0.04, -0.01)
FT4							
MEHP	8	5440	15.44	54.7	RE	-0.01	(-0.07, 0.04)
MEHHP	6	5303	12.95	61.4	RE	-0.03	(-0.10, 0.03)
MEOHP	6	5303	13.64	63.3	RE	-0.03	(-0.10, 0.04)
MECPP	4	2634	0	0	RE	-0.05	(-0.09, -0.01)
Pooled correlation	-	-	-	55	RE	-0.04	(-0.06, -0.02)
TSH							
MEHP	8	5440	13.34	45.7	RE	0.02	(-0.03, 0.07)
MEHHP	6	5303	17.6	71.6	RE	0.02	(-0.05, 0.09)
MEOHP	6	5303	12.22	59.1	RE	-0.01	(-0.08, 0.06)
MECPP	4	2634	5.86	48.8	RE	0.02	(-0.06, 0.10)
Pooled correlation	-	-	-	64	RE	0.01	(-0.02, 0.05)

RE: Random effects model, MEHP: mono-(2-ethyl-hexyl) phthalate, MEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate, MEOHP: mono-(2-ethyl-5-oxohexyl) phthalate, MECPP: mono-(2-ethyl-5-carboxypentyl) phthalate.

coefficient -0.06, 95% CI [-0.07, -0.04], I^2 = 0%). Subgroup analysis revealed negative correlations between FT4 levels and exposures to MEHHP (pooled coefficient -0.06, 95% CI [-0.09, -0.04], I^2 = 0%), MEOHP (pooled coefficient -0.05, 95% CI [-0.08, -0.02], I^2 = 0%), and MECPP (pooled coefficient -0.05, 95% CI [-0.09, -0.01], I^2 = 0%) in pregnant women (Supplementary Figure 2).

No significant association was found between maternal DEHP exposure and TSH levels in this meta-analysis (pooled coefficient 0.00, 95% CI [-0.04, 0.04], I^2 = 64%) (**Table 3**). Even after sensitivity analysis, no correlation was observed between maternal DEHP exposure and TSH (Supplementary Figure 3). The funnel plot and Egger's test revealed no significant publication bias (Supplementary Figure 5).

Associations between DEHP exposure and thyroid function in children and adolescents

Eight studies examined the association between DEHP exposure and thyroid function in children and adolescents. The meta-analysis results showed that DEHP exposure was positively correlated with TT3 in children and adolescents (pooled coefficient 0.05, 95% CI [0.02, 0.09], I^2 = 76%; **Table 4**). Subgroup analysis of different DEHP metabolites revealed a negative correlation between MEOHP and TT3 in children and adolescents (pooled coefficient 0.09, 95% CI [0.02, 0.15], I^2 = 39%; **Table 4**). No significant correlation was found between DEHP exposure and TT4, FT4, or TSH in children and adolescents.

The funnel plot and Egger's test revealed no significant publication bias between DEHP

Table 4. Results of meta-analysis and heterogeneity test of the correlation between Diethylhexyl Phthalate (DEHP) and thyroid hormone in children and adolescents

Factors	No.	Sample size	Heterogeneity		Effect Model	β	95% CI
			P (Q)	I^2 (%)			
TT3							
MEHP	7	1572	8.40	29	RE	0.05	(-0.01, 0.11)
MEHHP	7	1572	4.55	0	RE	0.04	(-0.01, 0.09)
MEOHP	7	1572	9.84	38	RE	0.09	(0.02, 0.15)
MECPP	3	751	8.46	76	RE	-0.01	(-0.19, 0.17)
Pooled correlation	-	-	-	31	RE	0.05	(0.02, 0.09)
TT4							
MEHP	7	1572	1.87	0	RE	0.02	(-0.03, 0.07)
MEHHP	7	1572	9.52	37	RE	0.01	(-0.05, 0.08)
MEOHP	7	1572	9.67	38	RE	0.01	(-0.05, 0.08)
MECPP	3	751	5.70	65	RE	-0.04	(-0.17, 0.08)
Pooled correlation	-	-	-	19	RE	0.01	(-0.03, 0.04)
FT4							
MEHP	7	1550	4.89	0	RE	-0.01	(-0.06, 0.04)
MEHHP	8	1800	16.20	56	RE	0.03	(-0.04, 0.10)
MEOHP	8	1800	9.56	27	RE	-0.00	(-0.06, 0.05)
MECPP	4	979	0.87	0	RE	-0.01	(-0.07, 0.06)
Pooled correlation	-	-	-	20	RE	0.00	(-0.02, 003)
TSH							
MEHP	8	1800	8.30	0	RE	0.01	(-0.04, 0.06)
MEHHP	8	1800	4914.96	100	RE	0.56	(-0.50, 0.95)
MEOHP	8	1800	7.20	3	RE	0.05	(-0.00, 0.10)
MECPP	4	979	5.77	48	RE	0.03	(-0.06, 0.12)
Pooled correlation	-	-	-	99	RE	0.20	(-0.13, 0.49)

RE: Random effects model, MEHP: mono-(2-ethyl-hexyl) phthalate, MEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate, MEOHP: mono-(2-ethyl-5-oxohexyl) phthalate, MECPP: mono-(2-ethyl-5-carboxypentyl) phthalate.

exposure and TT3, TT4, or FT4. However, in the analysis of DEHP exposure and TSH, the funnel plot was asymmetrical, and Egger's test showed a *p*-value of 0.04, indicating potential publication bias (Supplementary Figure 6).

Sensitivity analysis

To evaluate the stability of the results, sensitivity analysis was performed by omitting one study at a time and checking the consistency of the overall effect estimates. The results indicated that excluding individual studies did not significantly alter the statistical outcomes, demonstrating that the meta-analysis results were stable (Supplementary Figure 7).

Discussion

Thyroid-related medical conditions, such as thyroid dysfunction, thyroid nodules, and autoimmune thyroiditis, have increased globally in recent years, posing a significant threat to human health [17]. A key factor contributing to this rise is widespread exposure to environmental endocrine disruptors. In 2011, a major food safety incident involving DEHP-contaminated food occurred in Taiwan, raising concerns about its safety and potential health impacts. Current research indicates that DEHP and its metabolites can disrupt the regulation of the hypothalamic-pituitary-thyroid (HPT) axis and affect the thyroid endocrine system [43].

DEHP influences thyroid homeostasis through multiple mechanisms. First, it exhibits T3 antagonistic activity and inhibits the expression of the endogenous thyroid hormone receptor-beta (TRβ) gene [44]. DEHP exposure has also been found to suppress thyroid hormone receptor (THR)-mediated transcription, suggest-

ing that it may interfere with THR-regulated gene expression [45]. Animal studies have further shown that DEHP exposure can antagonize thyroid function to varying degrees [46]. For example, changes in the TSH/TSHR signaling pathway [47], proteins related to tyrosine hydroxylase (TH) synthesis, and deiodinase activity [48] have been observed, which in turn disrupt the HPT axis and alter TH levels. DEHP exposure can also lead to oxidative stress, increasing reactive oxygen species (ROS), activating the Ras/Akt/TRHr pathway, and ultimately decreasing TH levels [49]. Additionally, histological analyses have revealed that DEHP exposure can cause thyroid follicular hypertrophy and proliferation, leading to thyroid damage and inflammatory infiltration [50], which can impair iodine uptake by thyroid follicular cells [51].

Although numerous epidemiological studies have investigated the effects of DEHP exposure on thyroid function, meta-analyses have been hindered by significant heterogeneity between studies. These differences may be due to various confounding factors. A Chinese study found that MEHP and MECPP levels were higher in women than in men, and higher in minors than in adults [52]. Moreover, women are generally more susceptible to thyroid disease, and greater DEHP exposure in this population may increase the risk of thyroid dysfunction. Lifestyle factors, such as the use of personal care products and food packaging, also influence DEHP exposure. DEHP is widely present in packaging materials and can leach into food, with frequent consumption of plastic-wrapped or microwave-heated fast food potentially increasing exposure [53]. Occupational exposure to DEHP is also common in industries such as polyvinyl chloride (PVC) film manufacturing, rubber boot production, and PVC flooring and window installation, where exposure levels are significantly higher [54]. Given the wide range of DEHP exposure sources, including sex, diet, and occupation, controlling for all confounding factors in studies is challenging.

Previous research has shown inconsistent associations between DEHP exposure and thyroid function in pregnant women. A study by Huang et al. in Taiwan found that urinary MEOHP levels were negatively correlated with TSH levels in pregnant women, and urinary MECPP levels were negatively correlated with T3 levels [24]. Another repeated measures analysis in Puerto Rico observed a significant negative association between urinary DEHP metabolites and FT4 levels, but no significant association with TSH levels [43]. Our subgroup analysis revealed a significant negative correlation between DEHP and FT4, but no correlation between DEHP and TSH. The duration of exposure in the studies ranged from 18 to 39 weeks of gestation, and previous research has shown that different windows of DEHP exposure during pregnancy can affect thyroid hormone levels differently. This suggests that the timing of DEHP exposure may be a critical factor in determining thyroid dysfunction risk in pregnant women [24]. Other factors, such as iodine intake, nutritional status, and varying detection methods, may also influence thyroid hormone levels. Inadequate adjustment for these confounders could lead to overestimation or underestimation of the true association between DEHP exposure and thyroid function. To address these issues, future studies should collect and test biomarkers at multiple time points across different gestational weeks for longitudinal analyses. This approach would help generate more consistent and robust results, improving our understanding of the potential health risks associated with long-term DEHP exposure.

There is a notably increased demand for thyroid hormone during pregnancy due to changes in hormone metabolism, binding proteins, placental thyroid hormone transfer, and fetal depletion [55]. Both hyperthyroidism and hypothyroidism in pregnant women are associated with adverse birth outcomes, such as preterm birth and low birth weight [56]. In particularly vulnerable populations, like fetuses, even subtle changes in thyroid hormone levels - within the normal range - can lead to serious health effects, including neurocognitive problems [57]. Given this, maternal DEHP exposure may critically impact fetal thyroid hormone homeostasis, especially during the first trimester when the fetus is entirely dependent on the mother's thyroid hormone. After the first trimester, the fetus begins producing sufficient thyroid hormone on its own, but DEHP exposure should be minimized, if not avoided, during this early period.

In a study by Wu et al., involving 216 primary caregivers of children aged 5-7 years affected by the 2011 Taiwan food scandal, higher DEHP

exposure was significantly associated with decreased serum TSH levels in children [50]. Similarly, a Danish study of 845 children aged 4-9 years reported an inverse relationship between DEHP metabolites and FT3/TT3 levels [58]. However, a contrasting U.S. study involving adolescents aged 12-19 found a positive association between DEHP metabolites and T3 and TSH levels [34]. Our meta-analysis identified a positive correlation between MEOHP and TT3 in children, while other DEHP metabolites were not significantly linked to thyroid dysfunction. These varying results could stem from differences in race, age, exposure levels, and exposure duration across studies.

Moreover, increased public awareness of DEHP's harmful effects in recent years has likely prompted parents to limit their children's exposure to DEHP-contaminated food and household products, which could explain the lack of significant associations between DEHP exposure and thyroid dysfunction in some studies. This points to the importance of continued education and proactive measures to reduce DEHP exposure, particularly among vulnerable groups such as children and pregnant women.

Our research has several strengths:

Small changes in TH levels due to exposure to environmental endocrine disruptors may not be easily detectable in small populations [59]. Therefore, including a large number of epidemiological studies with a substantial sample size in this meta-analysis enhances the robustness of our findings. We conducted subgroup analyses to explore sources of heterogeneity, identify windows of susceptibility, and examine vulnerable populations. The findings from these studies can guide the assessment of DEHP's impact on thyroid function across different populations and inform the development of targeted interventions to improve public health.

However, several limitations of this review should be acknowledged. DEHP is non-persistent in the body and is rapidly metabolized, meaning its concentrations in urine samples may be significantly lower than in dust samples, which introduces uncertainty in exposure assessment [60]. Relying on a single type of sample to assess long-term exposure may lead to random errors. Additionally, urine composition can vary depending on the time of sampling, such as between first-morning fasting urine and 24-hour total urine [61]. To better reflect chronic exposure, future studies should collect multiple samples to improve exposure assessment. The use of urine samples to assess DEHP exposure may vary by region, potentially influencing the conclusions.

Different phthalates can coexist, and the "cocktail effect" of phthalate mixtures cannot be entirely ruled out. This means the effect of DEHP on thyroid function may be confounded by other phthalates. Most studies to date have focused on the relationship between a single phthalate and thyroid function, with few evaluating the effects of multiple phthalates.

Non-English-language studies were excluded, and the heterogeneity of the included studies may have affected the meta-analysis results. Finally, the majority of the studies originated from countries in Asia and North America, such as China, Korea, and the United States. There is a lack of relevant studies from other regions, particularly Europe. In summary, more high-quality studies providing detailed data are necessary. The results of our meta-analysis are crucial for environmental and health research, and future studies should focus on identifying potential mechanisms.

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Disclosure of conflict of interest

None.

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Supplementary Material

Search strategy and number of per database

MEDLINE (Ovid), Embase (Ovid) and Cochrane Central Register of Controlled Trials (Ovid)

1. exp Diethylhexyl Phthalate/
2. (phthalate or Di-2-ethylhexyl phthalate or Bis-2-ethylhexyl phthalate or DEHP).mp
3. 1 or 2
4. (thyroid or tsh or t3 or t4 or thyroxine or triiodothyronine).mp
5. 3 and 4

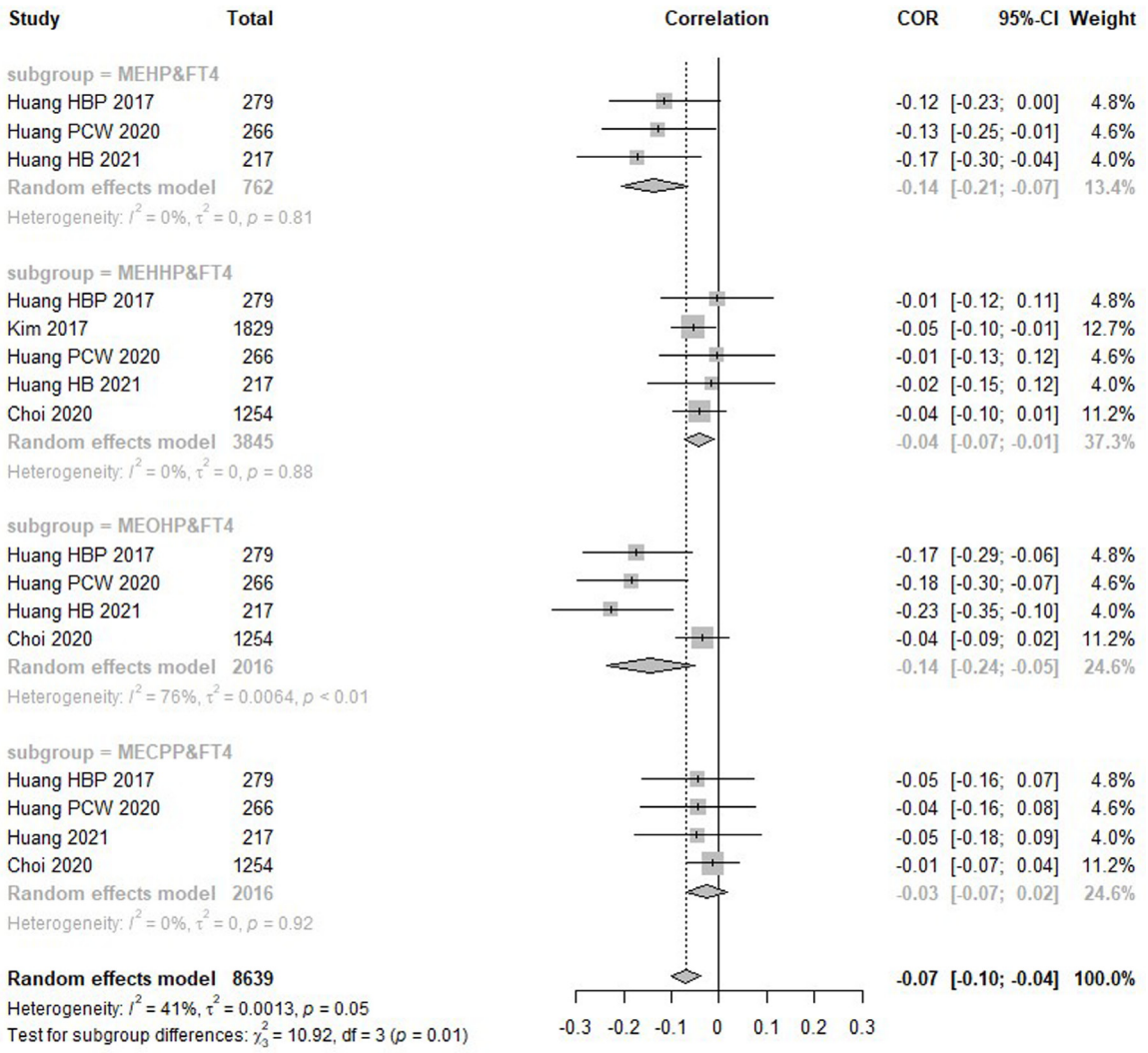
Web of Science

TS=(Diethylhexyl Phthalate or phthalate or Di-2-ethylhexyl phthalate or Bis-2-ethylhexyl phthalate or Bis (2-ethylhexyl) phthalate or DEHP) AND TS=(thyroid or tsh or t3 or t4 or thyroxine or triiodothyronine)

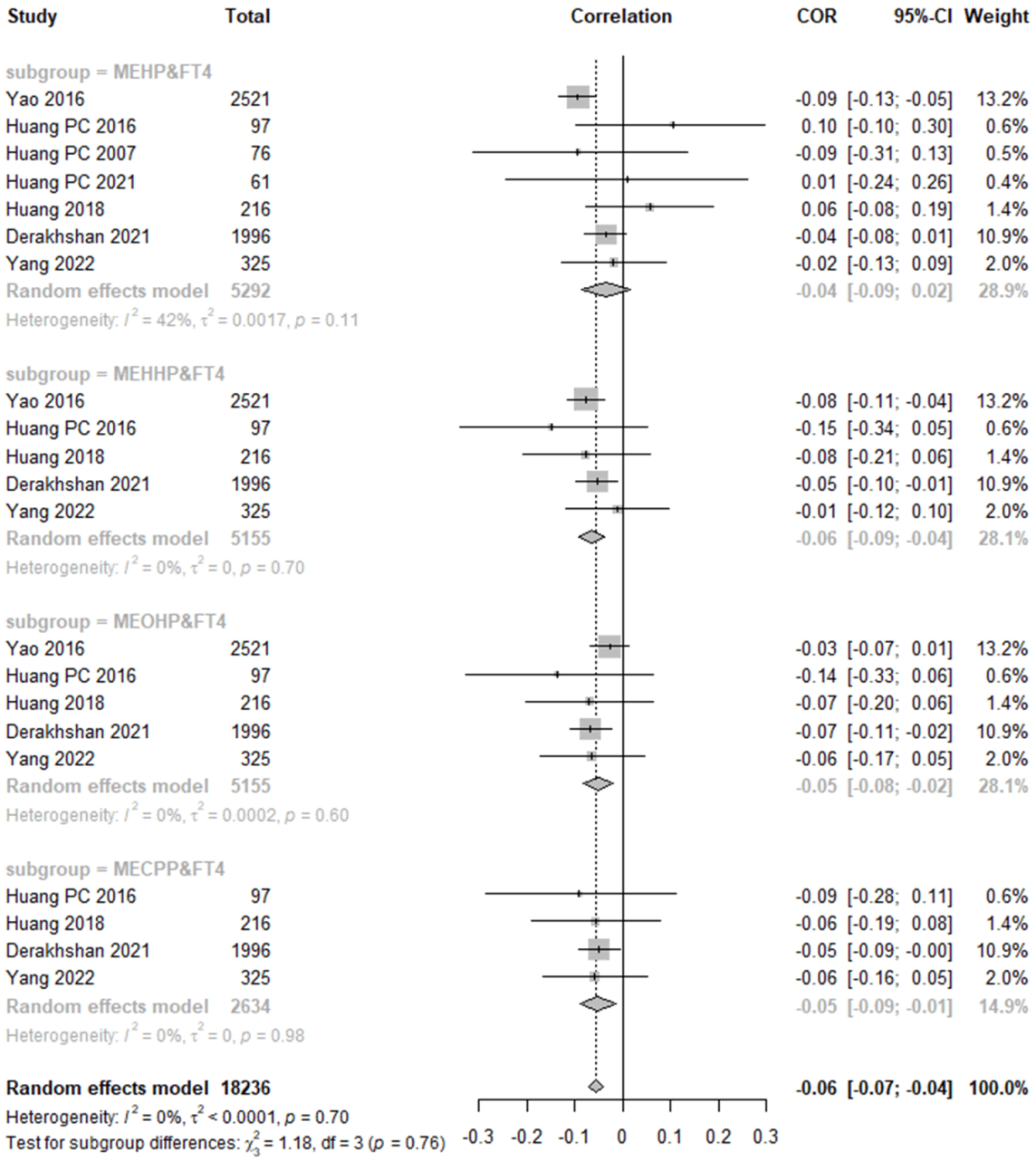
Supplementary Table 1. ROBINS-E evaluation of included studies

Studies	Domains							Overall bias
	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of exposures	Bias due to departures from intended exposures	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	
Albert 2018 [20]	Low	Low	Low	NI	Low	Low	Low	Low
Choi 2020 [21]	Low	Low	Low	NI	Low	Low	Low	Low
Huang HBP 2017 [23]	Low	Low	Low	NI	Low	Low	Low	Low
Huang HB 2021 [26]	Low	Low	Low	NI	Low	Low	Low	Low
Huang PCW 2020 [31]	Low	Low	Low	NI	Low	Low	Low	Low
Park 2017 [36]	Low	Low	Low	NI	Low	Low	Low	Low
Derakhshan 2021 [22]	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Huang HB 2018 [24]	Low	Low	Low	Low	Low	Low	Low	Low
Huang PC 2021 [28]	Low	Low	Low	Low	Low	Low	Low	Low
Huang PC 2007 [29]	Low	Low	Low	Low	Low	Low	Low	Low
Huang PC 2016 [30]	Low	Low	Low	Low	Low	Low	Low	Low
Kuo 2015 [33]	Moderate	Low	Low	NI	Low	Low	Low	Moderate
Yao 2016 [40]	Low	Low	Low	Low	Low	Low	Low	Low
Huang PC 2020 [27]	Low	Low	Low	Low	Low	Low	Low	Low
Kim 2018 [32]	Moderate	Low	Low	NI	Low	Low	Low	Moderate
Meeker 2011 [34]	Low	Low	Low	NI	Low	Low	Low	Low
Morgenstern 2017 [35]	Low	Low	Low	Low	Low	Low	Low	Low
Tsai 2016 [37]	Low	Low	Low	NI	Low	Low	Low	Low
Weng 2017 [38]	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Wu 2017 [39]	Low	Low	Low	NI	Low	Low	Low	Low
Zhao 2022 [41]	Low	Low	Low	NI	Low	Low	Low	Low
Kim 2017 [32]	Low	Low	Low	Low	Low	Low	Low	Low
Yang 2022 [42]	Low	Low	Low	Low	Low	Low	Low	Low

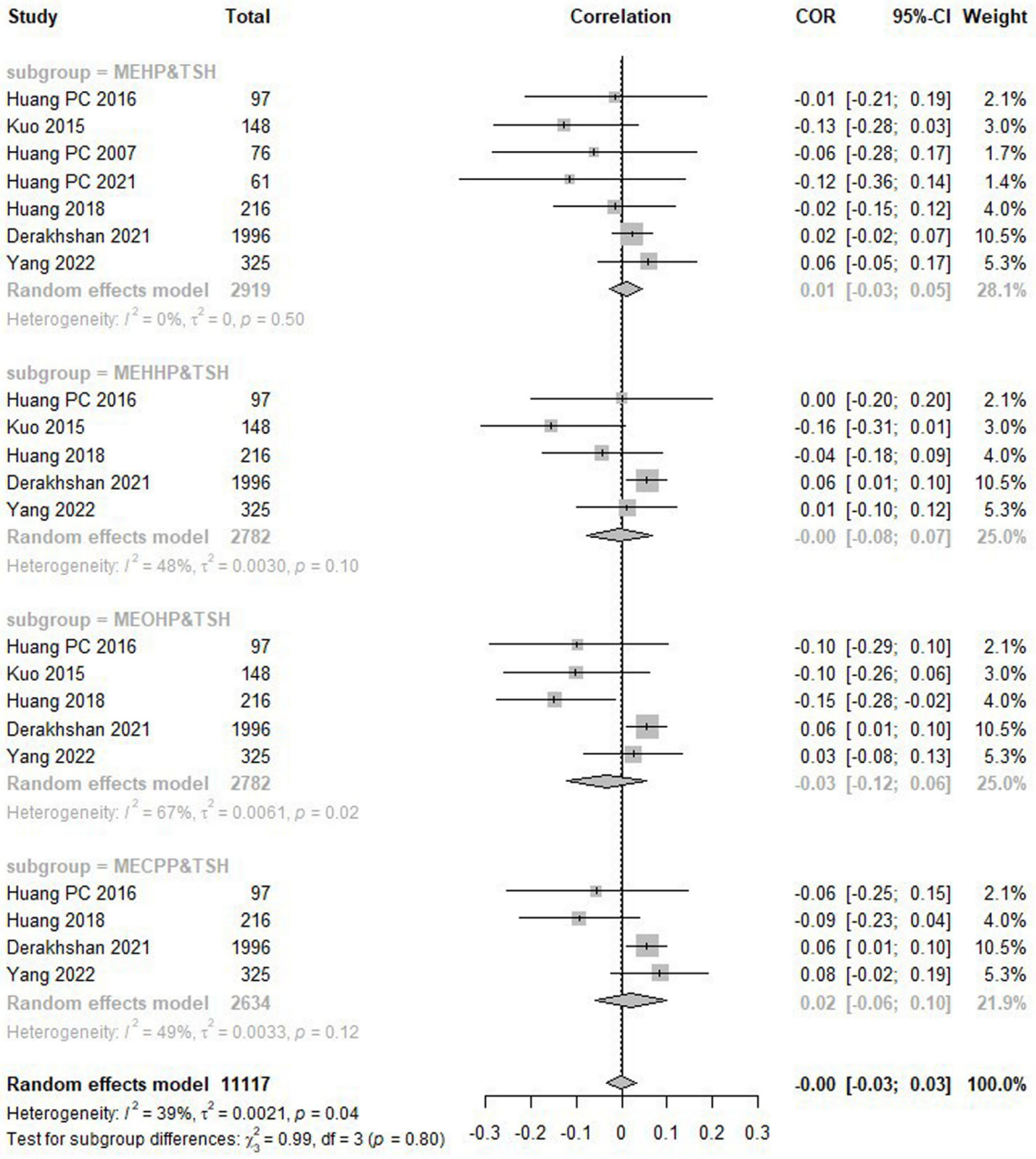
NI: No information.



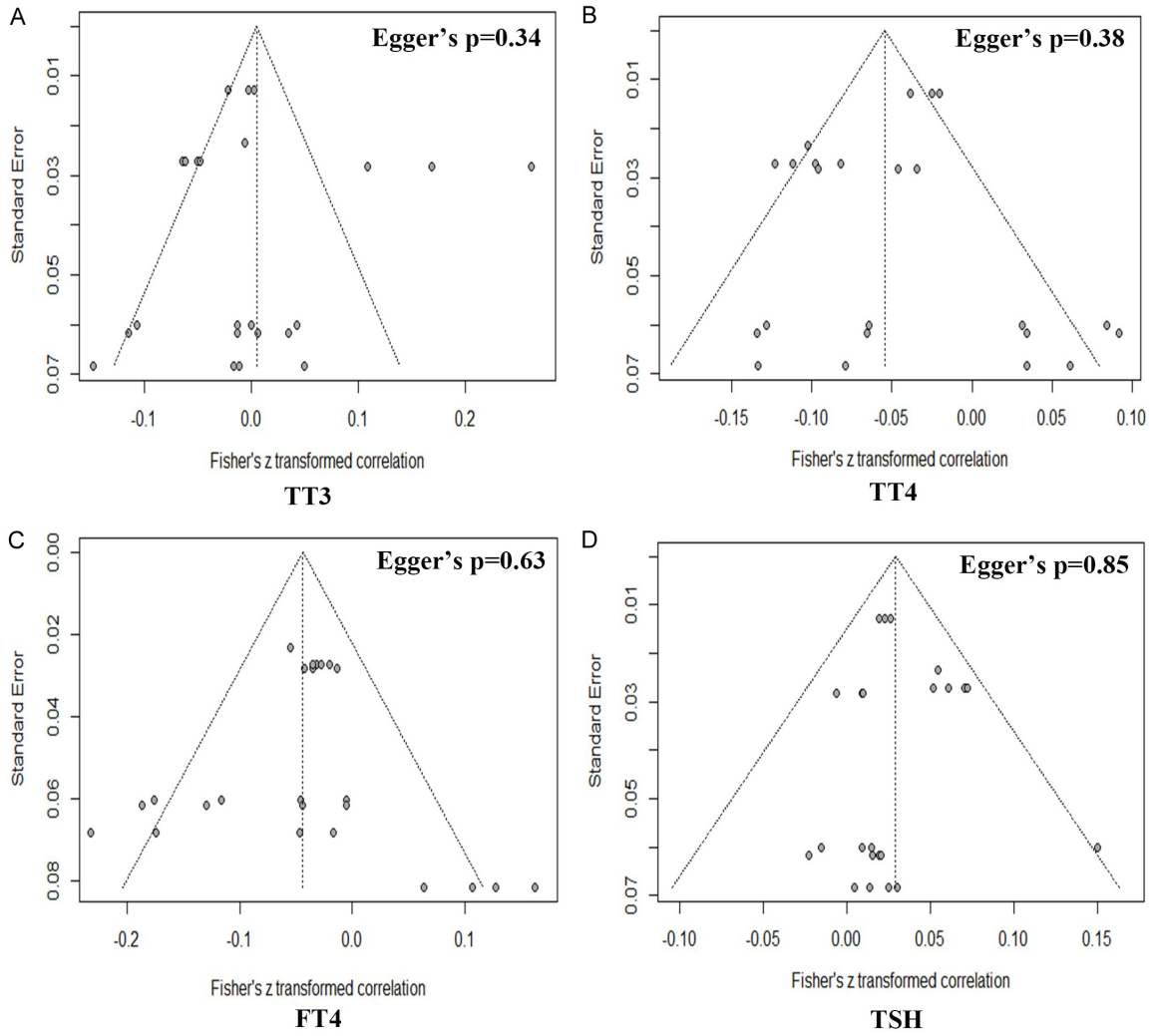
Supplementary Figure 1. Forest plot of the correlation between Diethylhexyl Phthalate (DEHP) and Free Thyroxine (FT4) in adults (sensitivity analysis).



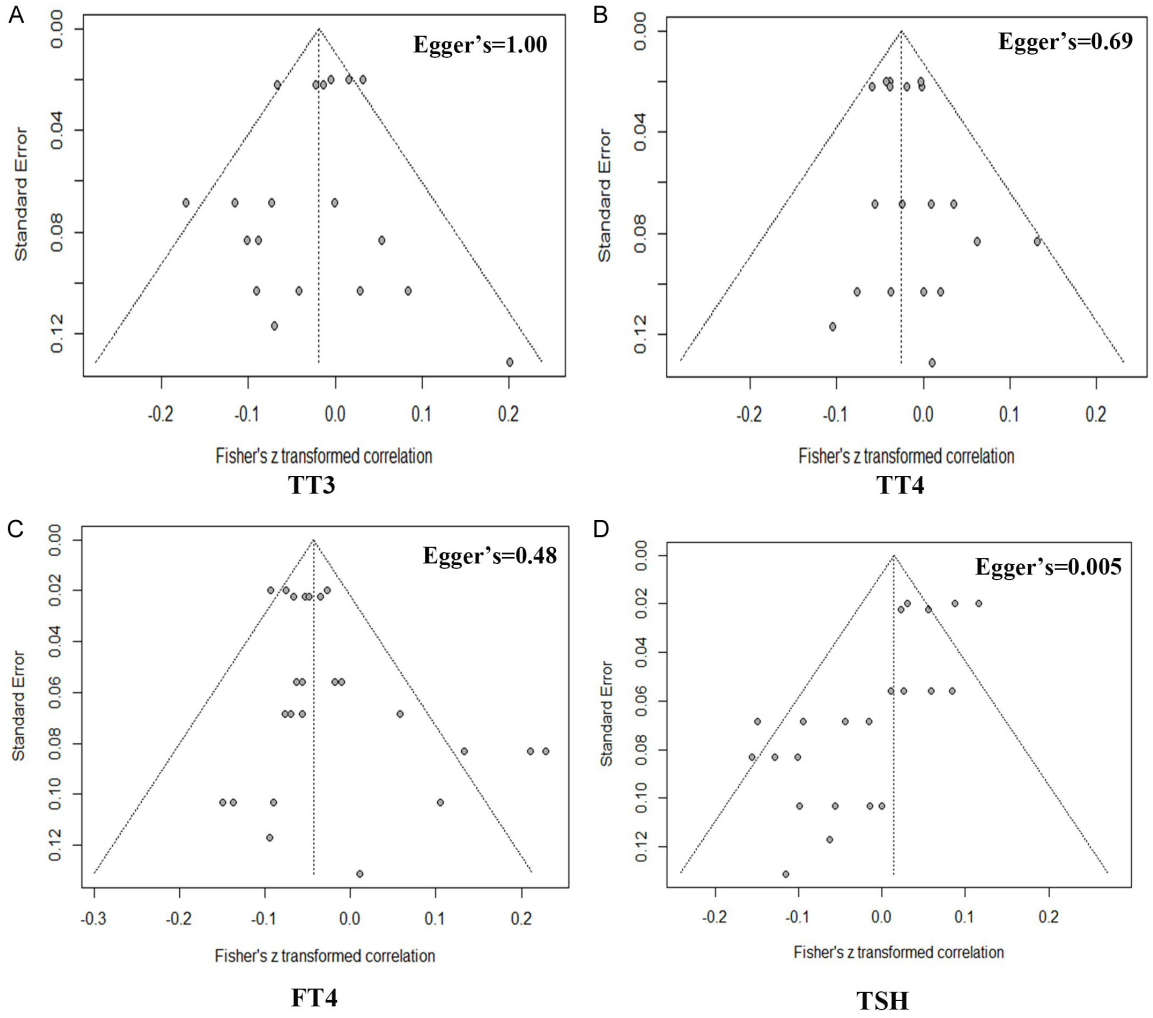
Supplementary Figure 2. Forest plot of the correlation between Diethylhexyl Phthalate (DEHP) and Free Thyroxine (FT4) in pregnant women (sensitivity analysis).



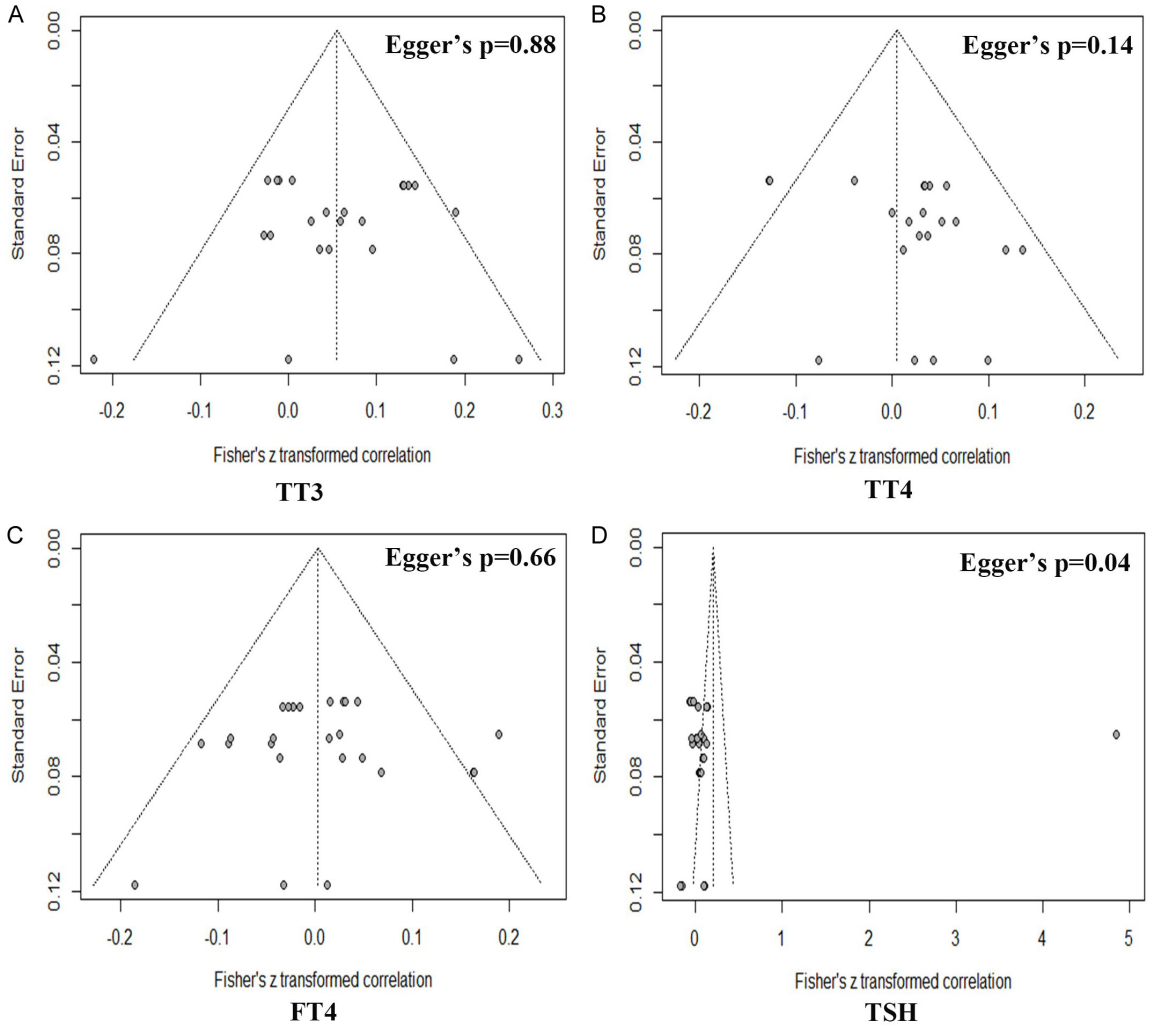
Supplementary Figure 3. Forest plot of the correlation between Diethylhexyl Phthalate (DEHP) and Thyroid-stimulating hormone (TSH) in pregnant women (sensitivity analysis).



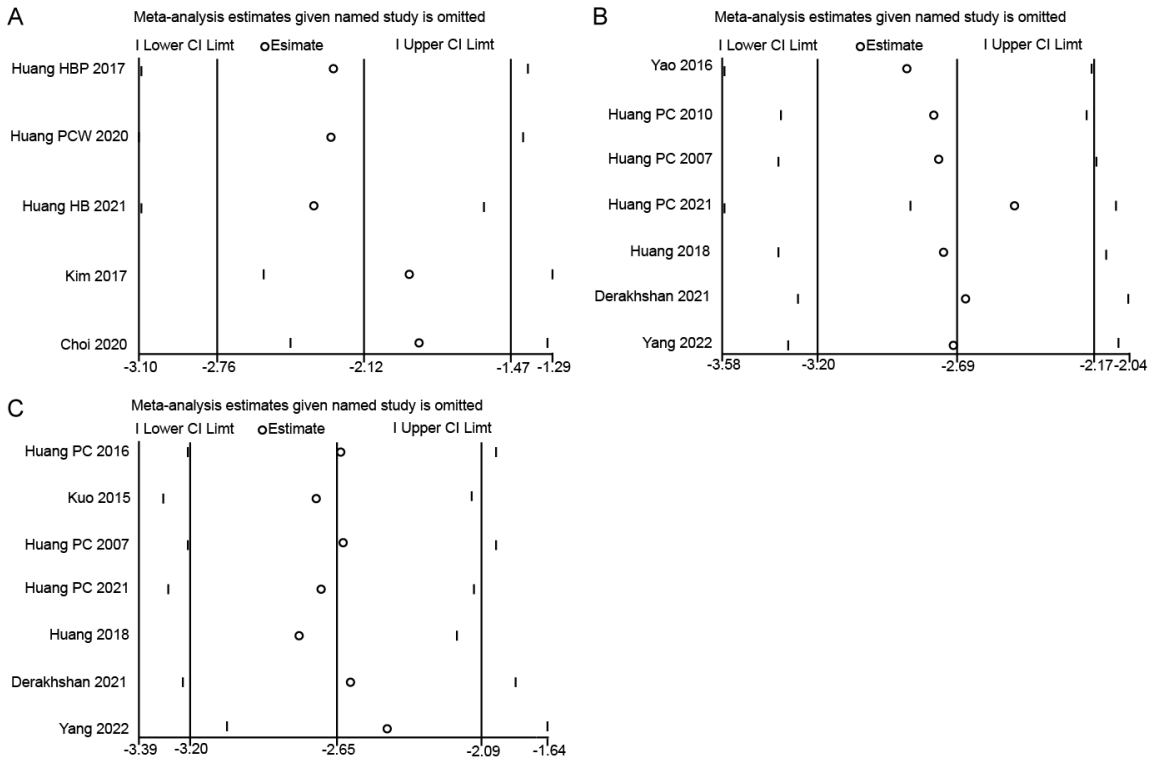
Supplementary Figure 4. Funnel plot and Egger's test of the correlation between Diethylhexyl Phthalate (DEHP) and thyroid hormone in adults. A. Correlation between DEHP exposure and TT3 in adults; B. Correlation between DEHP exposure and TT4 in adults; C. Correlation between DEHP exposure and FT4 in adults; D. Correlation between DEHP exposure and TSH in adults.



Supplementary Figure 5. Funnel plot and Egger's test of the correlation between Diethylhexyl Phthalate (DEHP) and thyroid hormone in pregnant women. A. Correlation between DEHP exposure and TT3 in pregnant women; B. Correlation between DEHP exposure and TT4 in pregnant women; C. Correlation between DEHP exposure and FT4 in pregnant women; D. Correlation between DEHP exposure and TSH in pregnant women.



Supplementary Figure 6. Funnel plot and Egger's test of the correlation between Diethylhexyl Phthalate (DEHP) and thyroid hormone in children and adolescents. A. Correlation between DEHP exposure and TT3 in children and adolescents; B. Correlation between DEHP exposure and TT4 in children and adolescents; C. Correlation between DEHP exposure and FT4 in children and adolescents; D. Correlation between DEHP exposure and TSH in children and adolescents.



Supplementary Figure 7. Sensitivity analysis (A) for the included studies in adults; (B) for the included studies in pregnant women; (C) for the included studies in children and adolescents.