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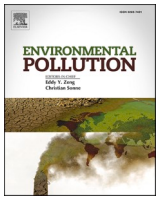

Review

Phthalate exposure and the metabolic syndrome: A systematic review and meta-analysis☆

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ABSTRACT

Phthalates are chemicals widely used in plastic-based consumer products, and human exposure is universal. They are classified as endocrine disruptors, and specific phthalate metabolites have been associated with an increased risk of cardiometabolic diseases. The aim of this study was to assess the association between phthalate exposure and the metabolic syndrome in the general population. A comprehensive literature search was performed in four databases (Web of Science, Medline, PubMed, and Scopus). We included all the observational studies that evaluate the association between phthalate metabolites and the metabolic syndrome available until January 31st, 2023. Pooled Odds Ratios (OR) and their 95% confidence intervals were calculated by using the inverse-variance weighted method. Nine cross-sectional studies and 25,365 participants aged from 12 to 80 were included. Comparing extreme categories of phthalate exposure, the pooled ORs for the metabolic syndrome were: 1.08 (95% CI, 1.02–1.16, $I^2 = 28\%$) for low molecular weight phthalates, and 1.11 (95% CI, 1.07–1.16, $I^2 = 7\%$) for high molecular weight phthalates. For individual phthalate metabolites, the pooled ORs that achieved statistical significance were: 1.13 (95% CI, 1.00–1.27, $I^2 = 24\%$) for MiBP; 1.89 (95% CI, 1.17–3.07, $I^2 = 15\%$) for MMP in men; 1.12 (95% CI, 1.00–1.25, $I^2 = 22\%$) for MCOP; 1.09 (95% CI, 0.99–1.20, $I^2 = 0\%$) for MCPP; 1.16 (95% CI, 1.05–1.28, $I^2 = 6\%$) for MBzP; and 1.16 (95% CI, 1.09–1.24, $I^2 = 14\%$) for DEHP (including ΣDEHP and its metabolites). In conclusion, both low molecular weight and high molecular weight phthalates were associated with an 8 and 11% higher prevalence of the MetS, respectively. The exposure to six specific phthalate metabolites was associated with a higher prevalence of the MetS.

Abbreviations: Low molecular weight (LMW), High molecular weight (HMW); Mono-n-butyl phthalate (MnBP), Mono-ethyl phthalate (MEP); Mono-isobutyl phthalate (MiBP), Mono-methyl phthalate (MMP); Mono-carboxynonyl phthalate (MCNP), Mono-carboxyoctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP), Mono-(3-carboxypropyl) phthalate (MCPP); Mono-benzyl phthalate (MBzP), Molar sum of DEHP (ΣDEHP); Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP); Mono(2-ethylhexyl) phthalate (MEHP), Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP); Mono(2-carboxymethylhexyl) phthalate (MCMHP), Dibutyl phthalate (DBP); Diethyl phthalate (DEP), Di-isobutyl phthalate (DiBP); Dimethyl phthalate (DMP), Di-isodecyl phthalate (DiDP); Di-isononyl phthalate (DiNP), Di-n-octyl phthalate (DnOP); Butyl benzyl phthalate (BzBP), Di(2-ethylhexyl) phthalate (DEHP).

☆ This paper has been recommended for acceptance by Da Chen.

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1. Introduction

Phthalates are chemical substances widely used as plasticizers as they give extensibility and elasticity to plastic (Phthalates Factsheet | National Biomonitoring Program | CDC n, 2022; Giuliani et al., 2020). They have been used in the plastic industry since the 1930s (Vieira et al., 2011). Humans are universally exposed to them as they are widely used in plastic-based consumer products (Giuliani et al., 2020). Based on their molecular weight, they are classified into low molecular weight (LMW) and high molecular weight (HMW) phthalates. LMW phthalates (such as DMP, DEP, and DiBP) are used as solvents, fixatives, and adhesives in cosmetics and personal care products (Serrano et al., 2014; Su et al., 2019). On the other hand, HMW phthalates (such as DiDP, DiNP, DEHP, DnOP, and BzBP) are well known for their use as plasticizers in PVC materials, such as food packaging, flooring, and medical devices (Serrano et al., 2014). HMW phthalates represent 80% of the phthalates used in manufacturing plastic products in Europe (Giuliani et al., 2020).

There are many phthalate exposure pathways such as inhalation, dermal contact, or iatrogenic exposure, but ingestion through the diet is considered the main one (Giuliani et al., 2020; Committee on the Health Risks, 2008). Thus, during processing, storing, and food preparation, phthalates leak from plastic materials into food and beverages (Giuliani et al., 2020). After exposure, phthalates are quickly metabolized, then transformed into primary and secondary metabolites, and finally excreted in urine (Committee on the Health Risks, 2008).

Phthalates have been classified as endocrine disruptors (Schug et al., 2016). As such, exposure to these chemicals has been associated with several health outcomes, including shortened anogenital distance in children (Zarean et al., 2019), female infertility (Trnka et al., 2021), and endometriosis (Chou et al., 2020), but also with other health conditions such as childhood atopic dermatitis (Jung et al., 2020), childhood allergies (Ait Bamai et al., 2018), as well as urothelial (Chou et al., 2021) and thyroid cancers (Liu et al., 2020). Moreover, epidemiological studies have shown a positive association between higher levels of specific phthalate metabolites and cardiovascular disease (CVD) (Fu et al., 2020) as well as other cardiometabolic disorders (Giuliani et al., 2020), such as increased waist circumference (Stahlhut et al., 2007), obesity in male children (Zhang et al., 2014), insulin resistance (Shoshtari-Yeganeh et al., 2019), diabetes mellitus (Zhang et al., 2022), high blood pressure, and higher levels of total cholesterol in adults (Zhang, 2018). All these conditions belong to the cluster of cardiovascular risk factors included in the metabolic syndrome (MetS).

In recent literature, although some studies have analyzed the association of phthalate metabolites with individual components of the MetS (Piecha et al., 2016; Milošević et al., 2020; Medic Stojanoska et al., 2015; Trasande et al., 2013; Han et al., 2019), few of them have considered the MetS as a unique condition. Our hypothesis is that phthalate exposure is associated with a higher risk of the MetS in the general population. Therefore, our objective was to perform a systematic review and meta-analysis of the published literature on the association between phthalate metabolites and the MetS in children, adolescents, as well as in adults.

2. Materials and methods

This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Page et al., 2021). The protocol was registered on PROSPERO (CRD42023400806) (PROSPERO n, 2023).

2.1. Search strategy

The literature search was performed by two authors (DMM and PGC) using 4 different databases: Clarivate (Web of Science), Medline, PubMed, and Scopus, with no restrictions on the year of publication or languages. The last search was conducted on January 31st, 2023. We used the following keywords to identify the articles: ("phthalate" OR "phthalate metabolites" OR "urinary phthalate metabolites") AND "metabolic syndrome". Additionally, bibliographic references of the enrolled studies were retrieved.

2.2. Study selection

Two authors (DMM and PGC) performed the study selection. The following criteria were considered for the inclusion of the articles: (1) studies performed on humans; (2) analytical observational studies (including longitudinal cohort studies as well as analytical cross-sectional studies); (3) studies with quantitative measurements of urine phthalate metabolites; (4) to define the MetS, the criteria of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP/ATP-III) (Grundy et al., 2004) were used. The MetS was defined as having at least 3 of the following 5 criteria (waist circumference $\geq$102 cm in men or $\geq$ 88 cm in women; blood pressure (BP) $\geq$ 130/85 mmHg or treatment for hypertension; triglycerides $\geq$150 mg/dL; HDL-cholesterol $<$40 mg/dL in men or $<$ 50 mg/dL in women; and fasting blood glucose (FBG) $\geq$ 100 mg/dL or treatment for diabetes), regardless of some slight modifications of specific criteria based on the studied population; and (5) studies providing estimators of the association between phthalate exposure and the MetS along with their corresponding 95% confidence intervals.

Studies in animals, reviews, and commentaries not reporting primary data were excluded. In the case of duplicated original data, the article with more extensive original information was selected.

2.3. Data extraction

From the studies included, the following information was collected: first author, publication year, country and sample, study design, sample characteristics: size, percentage of men, age of the studied population; the technique used and the names of the phthalate metabolites analyzed, outcome assessment, the number of cases, the association estimates such as prevalence Odds Ratios (POR) and adjusted Odds Ratios (AOR); confounders, and the quality score of the article. Data extraction was performed by two independent authors (DMM and PGC).

2.4. Quality assessment

The quality of the studies included was assessed by using the Joanna Briggs Institute (JBI) critical appraisal tools for cross-sectional studies (Critical Appraisal Tools | JBI n, 2022; Stone et al., 2023), which evaluate eight bias domains. The overall quality of the study design was scored according to the number of criteria fulfilled and further classified as low, moderate, or high risk of bias. Discrepancies were solved by mutual agreement between the two co-authors (DMM and PGC).

2.5. Statistical analysis

From each study, we extracted information on central estimates (POR or AOR) and their 95% confidence intervals from the most saturated models, when comparing extreme categories of exposure. To assess the association between phthalate exposure and the MetS, pooled Odds Ratios (ORs) and their 95% confidence intervals were calculated by using the inverse-variance weighted method (The generic inverse variance outcome, 2023). Funnel plots were used to evaluate publication bias. Heterogeneity across studies was calculated by using the Inconsistency Index (I^2). Fixed effects models were used when I^2 was $<$30%; otherwise, random effects models were performed. When articles reported separate results for men and women, this information was considered independently. Analyses were conducted with Review Manager version 5.4.1.

The analyses were performed by classifying phthalates into LMW and HMW, according to their respective parent compound. We included four

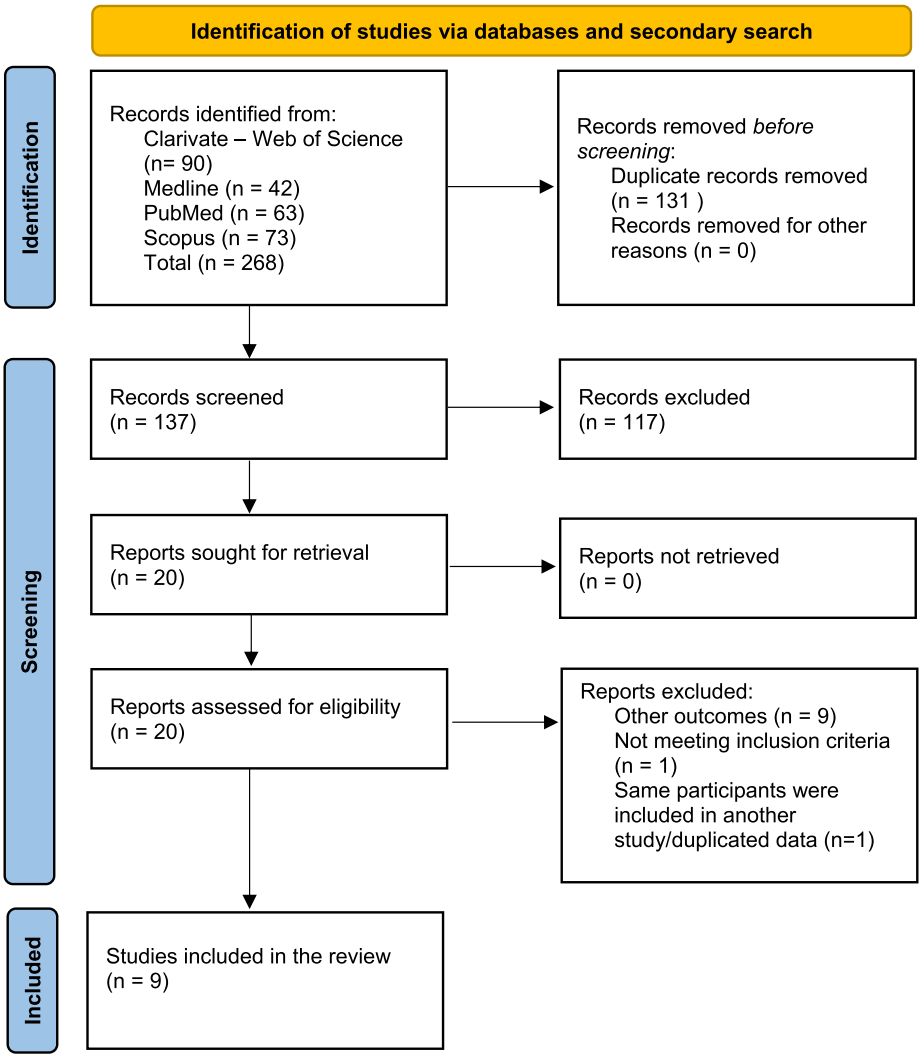

Fig. 1. PRISMA flow diagram of literature search and study selection.

LMW phthalate metabolites and six HMW phthalate metabolites, which are detailed in the supplementary material (Supplementary Table 1). A sensitivity analysis was performed by selecting studies with a low risk of bias based on the JBI checklist.

3. Results

3.1. Study selection

After a comprehensive search in four electronic databases, we found 268 studies that matched our search. After removing 131 duplicated records, we screened 137 studies, and 117 records were excluded after reading the title or the abstract. A total of 20 reports were sought for retrieval and assessed for eligibility. Of these, 11 were excluded for the following reasons: nine studies were excluded because other outcomes were evaluated (including polycystic ovary syndrome (Vagi et al., 2014; Akgül et al., 2019; Akın et al., 2020), or only individual parameters of the MetS were considered (Piecha et al., 2016; Milošević et al., 2020; Medic Stojanoska et al., 2015; Trasande et al., 2013; Han et al., 2019; Kim et al., 2013)), one did not meet the inclusion criteria (Gao et al., 2021), and another study (Nicolle-Mir, 2016) analyzed the same participants from James-Todd et al. (2016). Finally, nine studies were included in this review (Fig. 1).

4. Characteristics of the studies

Studies were conducted in the U.S.A (5), Taiwan (2), South Korea (1), and Mexico (1) (Table 1), and were published from 2013 to 2022. All the studies had a cross-sectional design, and no longitudinal studies were found. Sex-specific analyses were performed in five of the studies included (James-Todd et al., 2016; Gaston and Tulve, 2003–2014; Ghosh et al., 2021; Nagel, 2013; Shih et al., 2022), the overall population (men and women together) was analyzed in two (Ko et al., 2019; Shim et al., 2019), and two were performed exclusively among women (Dubey et al., 2022; Zamora et al., 2021). A total of 25,365 participants aged from 12 to 80 were enrolled, of which 41.2% were men.

In all the studies, phthalate metabolites were measured in spot urine samples. The exposure was categorized into quartiles in five studies included (James-Todd et al., 2016; Ghosh et al., 2021; Nagel, 2013; Shih et al., 2022; Shim et al., 2019), into tertiles in two studies (Gaston and Tulve, 2003–2014; Dubey et al., 2022), using the interquartile range in one study (Zamora et al., 2021), and in another, comparing the highest versus the lowest daily intake for phthalates based on urine measurements (Ko et al., 2019).

All the studies defined the MetS using the NCEP/ATP-III criteria, although slight modifications were permitted. In one study, the criteria for waist circumference, blood pressure, and triglycerides were established according to age, sex, and height percentiles among adolescents (Gaston and Tulve, 2003–2014); another study used all the

Table 1
Characteristics of the studies included in the systematic review and meta-analysis assessing the association between phthalate exposure and the metabolic syndrome.

Author (year)	Country (sample)	Study design	Sample characteristics			Technique and phthalate metabolites analyzed	Outcome assessment	Number of cases	Association estimates	Confounders	Quality score according to the JBI checklist
			Sample size	Men (%)	Age						
Dubey et al. (2022) (Dubey et al., 2022)	U.S.A (NHANES, 2013 and 2016)	Cross-sectional	2004	0	≥15 y	HPLC-ESI-MS/MS Metabolites: MnBP, MEP, MiBP, MCNP, MCOP, MiNP, MCPP, MBzP, DEHP metabolites (MECPP, MEHHP, MEHP, MEOHP).	NCEP/ATP-III	965	POR (T3 vs T1)	Age, race/ethnicity, income, marital status, birth country, education, smoking, alcohol use, physical activity, and urinary creatinine	8/8
Gaston et al. (2018) (Gaston and Tulve, 2003–2014)	U.S.A (NHANES, 2003–2014)	Cross-sectional	918	501 (54.5)	12-19 y	SPE-HPLC-MS/MS Metabolites: MnBP, MEP, MiBP, MCPP, MBzP, ΣDEHP (MEHHP + MEHP + MEOHP).	NCEP/ATP-III for adolescents: waist circumference ≥90th percentile for age and sex; BP ≥ 90th percentile for age, sex, and height; triglycerides levels ≥110 mg/dL; HDL ≤40 mg/dL; FBG ≥110 mg/dL	Men: 31 Women: 14	POR (T3 vs T1)	Age, sex, race/ethnicity, physical activity, BMI, total caloric intake, total fat intake, economic adversity, and urinary creatinine	8/8
Ghosh et al. (2021) (Ghosh et al., 2021)	U.S.A (NHANES, 2005–2014)	Cross-sectional	10,017	5060 (49.6)	≥18 y	HPLC-ESI-MS/MS Metabolites: MnBP, MEP, MiBP, MCNP, MCOP, MCPP, MBzP, ΣDEHP (MECPP + MEHHP + MEHP + MEOHP).	NCEP/ATP-III	White men: 607 Black men: 236 Mexican/ Hispanic men: 304 White women: 595 Black women: 316 Mexican/ Hispanic women: 345	POR (Q4 vs Q1)	Age, education, smoking, total caloric intake, poverty, fasting status, and urinary creatinine	8/8
James -Todd et al. (2016) (James-Todd et al., 2016)	U.S.A (NHANES, 2001–2010)	Cross-sectional	2719	1388 (51.0)	20-80 y	SPE-HPLC-MS/MS Metabolites: MnBP, MEP, MiBP, MCPP, MBzP, ΣDEHP (MEHHP + MEHP + MEOHP).	NCEP/ATP-III	Men: 464 Women: 501	POR (Q4 vs Q1)	Age, sex, race/ethnicity, smoking, physical activity, total caloric intake, poverty, and urinary creatinine	8/8
Ko et al. (2019) (Ko et al., 2019)	Taiwan (military volunteers in Northern Taiwan, 2017)	Cross-sectional	435	388 (89.2)	Mean ± SD 32.16 ± 6.43 y	SPE-HPLC-MS/MS Metabolites: MnBP, MEP, MMP, MBzP, DEHP metabolites (MEHHP, MEHP, MEOHP).	NCEP/ATP-III slight modifications: waist circumference ≥90 cm (men) and ≥80 cm (women)	56	AOR (high vs low DI)	Sex, smoking, body weight, and urinary creatinine	7/8 Unclear exposure measurement
Saxena et al. (2013) (Nagel, 2013)	U.S.A (NHANES, 1999–2008)	Cross-sectional	2611	NA	20-80 y	Technique: NA Metabolites: MEP and MiBP	NA	NA	POR (Q4 vs Q1)	Age and urinary creatinine	NA
Shih et al. (2022) (Shih et al., 2022)	Taiwan (Taiwan Biobank Study, 2016–2020)	Cross-sectional	1337	693 (51.8)	30-70 y	HPLC-ESI-MS/MS Metabolites: MnBP, MEP, MiBP, MMP, MiNP, MBzP, ΣDEHP (MECPP + MEHHP +	NCEP/ATP-III slight modifications: waist circumference ≥90 cm (men) and ≥80 cm (women)	Men: 91 Women: 128	AOR (Q4 vs Q1)	Age, education, working status, and urinary creatinine	8/8

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Country (sample)	Study design	Sample characteristics			Technique and phthalate metabolites analyzed	Outcome assessment	Number of cases	Association estimates	Confounders	Quality score according to the JBI checklist
			Sample size	Men (%)	Age						
						MEHP + MEOHP + MCMHP).					
Shim et al. (2019) (Shim et al., 2019)	Korea (KNEHS II, 2012–2014)	Cross-sectional	5251	2432 (46.3)	>20 y	UPLC-MS/MS Metabolites: MnBP, MBzP, DEHP metabolites (MECPP, MEHHP, MEOHP).	NCEP/ATP-III slight modifications: BMI ≥30 kg/m^2, blood pressure medication, anti-diabetic medication.	578	POR (Q4 vs Q1)	Age, sex, income, marital status, education, and urinary creatinine	8/8
Zamora et al. (2021) (Zamora et al., 2021)	Mexico (ELEMENT study 1994–2003)	Cross-sectional	73	0	Mean ± SD 46.6 ± 6.3 y	ID-LC-MS/MS Metabolites: MEP, MCOP, MCPP, MBzP, ΣDEHP (MECPP + MEHHP + MEHP + MEOHP).	NCEP/ATP-III	25	AOR per interquartile range	Age, physical activity, and urinary creatinine	6/8 Unclear exposure measurement and statical analysis

SD: Standard Deviation

HPLC-ESI-MS/MS: high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry.

SPE-HPLC-MS/MS: a combination of solid phase extraction, high-pressure liquid chromatography, and tandem mass spectrometry.

UPLC-MS/MS: ultra-performance liquid chromatography-tandem mass spectrometry.

ID-LC-MS/MS: dilution-liquid chromatography-tandem mass spectrometry.

Abbreviations of phthalate metabolites: Mono-n-butyl phthalate (MnBP); Mono-ethyl phthalate (MEP); Mono-isobutyl phthalate (MiBP); Mono-methyl phthalate (MMP); Mono-carboxynonyl phthalate (MCNP); Mono-carboxyoctyl phthalate (MCOP); Mono-isononyl phthalate (MiNP); Mono-(3-carboxypropyl) phthalate (MCPP); Mono-benzyl phthalate (MBzP); Molar sum of DEHP (ΣDEHP); Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP); Mono(2-ethylhexyl) phthalate (MEHP); Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP); Mono(2-carboxymethylhexyl) phthalate (MCMHP);

NCEP/ATP-III: National Cholesterol Education Program's Adult Treatment Panel III. NCEP/ATP-III criteria unless otherwise stated: waist circumference ≥102 cm (men) and ≥88 cm (women); blood pressure (BP) ≥ 130/85 mmHg or treatment for hypertension; triglycerides level ≥150 mg/dL; HDL <40 mg/dL (men) and <50 mg/dL (women); fasting blood glucose (FBG) ≥ 100 mg/dL or treatment for diabetes.

NA: Not available

BMI: Body Mass Index

POR: Prevalence adjusted Odds Ratio when representativeness at a country level.

AOR: Adjusted Odds Ratio for the sample.

DI: Daily intake. It was calculated by using the combined urinary phthalate metabolite concentrations and individual age, body height, body weight, creatinine concentration, and phthalate molecular weight.

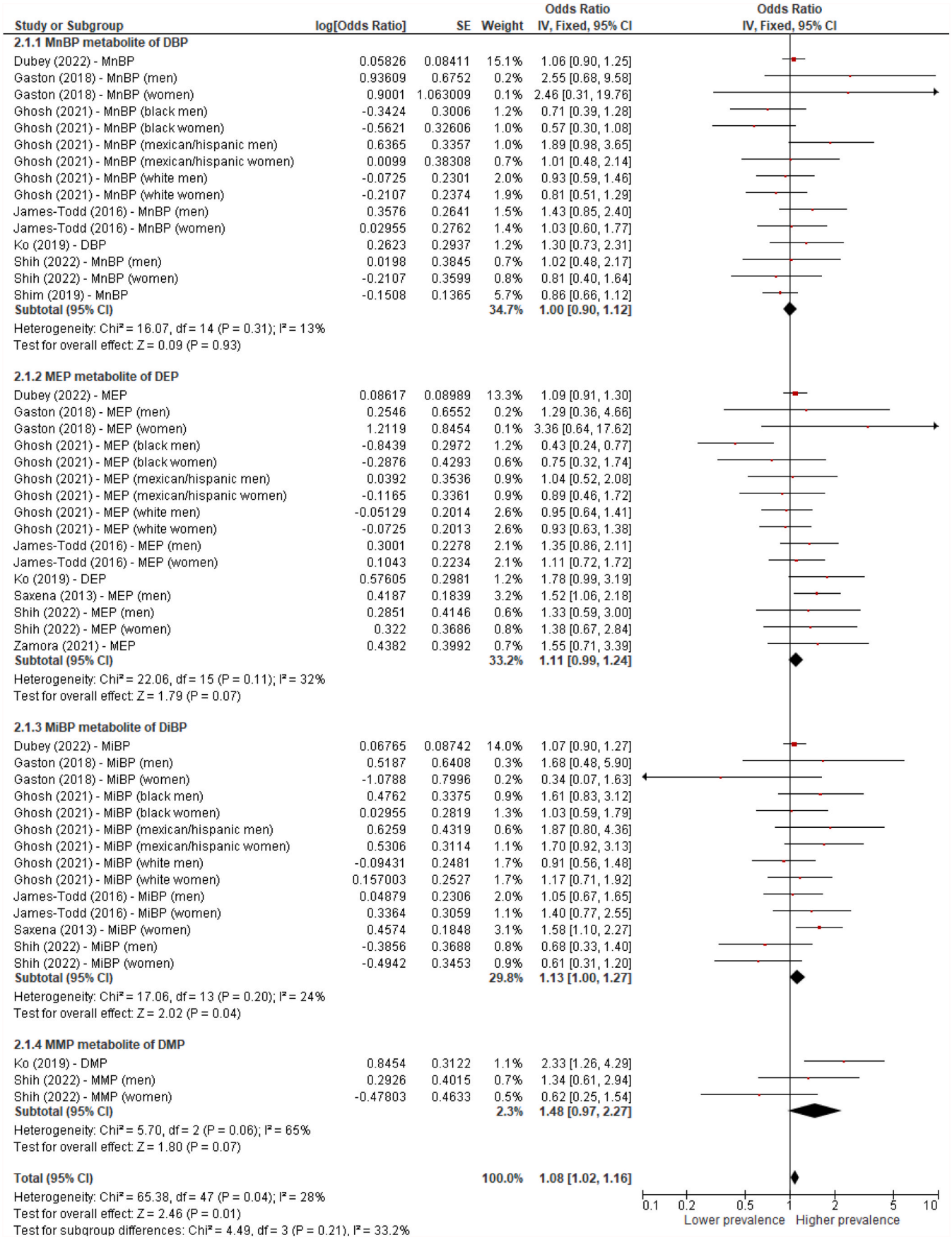

Fig. 2. Forest plot of the association between low molecular weight phthalates and the metabolic syndrome.

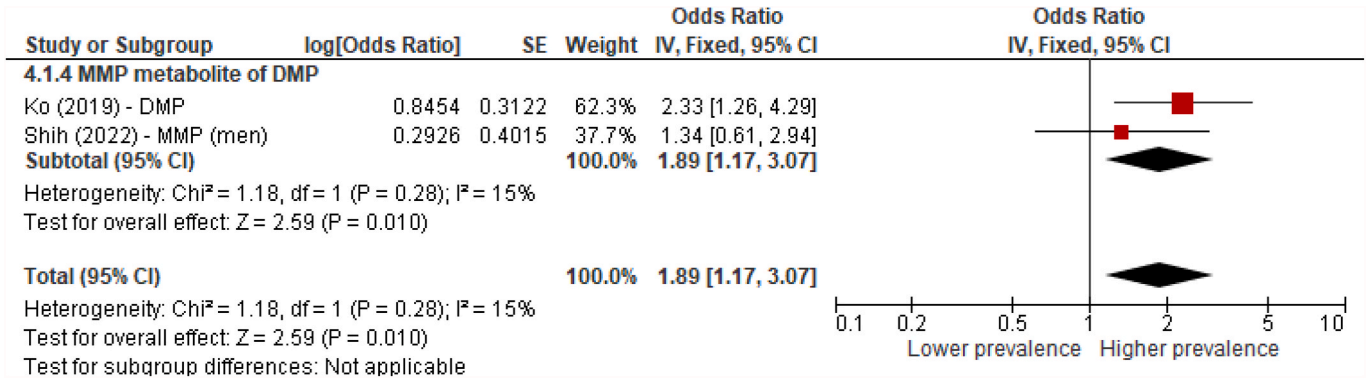

Fig. 3. Forest plot of the association between Mono-methyl phthalate (MMP) exposure and the metabolic syndrome in men.

NCEP/ATP-III criteria except the criterion for waist circumference which was modified for the Asian population (Ko et al., 2019); Finally, in Taiwan, Shih et al. (2022), modified criteria according to the guidelines of the Health Administration, Ministry of Health and Welfare were used. Thus, Shih et al. (2022) used an operational definition for the MetS based on BMI ≥30 kg/m^2, current BP medication in use, as well as current anti-diabetic medication in use, which is also accepted for the NCEP/ATP-III.

In total, there were 5256 cases of the MetS, although, in Saxena et al. (Nagel, 2013) the data on the number of events was not available. All the studies reported results adjusted for creatinine. In addition, adjustments for sociodemographic factors, lifestyles, fiber, as well as energy intake were also made.

5. Study quality assessment

Six (James-Todd et al., 2016; Gaston and Tulve, 2003–2014; Ghosh et al., 2021; Shih et al., 2022; Shim et al., 2019; Dubey et al., 2022) out of nine of the studies included had a low risk of bias. However, not all quality criteria were displayed in two of the studies included. In Ko et al. (2019), the exposure measurement was performed in a non-standard way by using reverse dosimetry. And in Zamora et al. (2021), it was not specified if participants were free of the outcome at the beginning of the follow-up, and normative cut-off points of the exposure were not reported (Supplementary Table 2).

6. Meta-analysis

When all individual phthalates were considered, comparing extreme categories, the pooled OR for the MetS was 1.10 (95% CI, 1.07–1.14, I^2 = 17%) (Supplementary Fig. 1).

For LMW phthalates, the pooled OR for the MetS when comparing extreme categories of exposure was 1.08 (95% CI, 1.02–1.16, I^2 = 28%) (Fig. 2 and Supplementary Fig. 2). For individual phthalate metabolites, the pooled OR was 1.13 (95% CI, 1.00–1.27, I^2 = 24%) for MiBP (metabolite of DiBP) (Fig. 2); and the pooled OR for the MetS in men was 1.89 (95% CI, 1.17–3.07, I^2 = 15%) for MMP (metabolite of DMP) (Fig. 3).

For HMW phthalates, the pooled OR for the MetS when comparing extreme categories of exposure was 1.11 (95% CI, 1.07–1.16, I^2 = 7%). The pooled ORs that reached statistical significance for individual phthalate metabolites were: 1.12 (95% CI, 1.00–1.25, I^2 = 22%) for MCOP (metabolite of DiNP); 1.09 (95% CI, 0.99–1.20, I^2 = 0%) for MCPP (metabolite of DnOP); 1.16 (95% CI, 1.05–1.28, I^2 = 6%) for MBzP (metabolite of BzBP); and 1.16 (95% CI, 1.09–1.24, I^2 = 14%) for the ΣDEHP and its metabolites (Fig. 4).

Funnel plots for LMW and HMW did not suggest evidence of publication bias (Supplementary Fig. 3 and Supplementary Fig. 4).

7. Sensitivity analysis

When including the studies with a low risk of bias according to the JBIs critical appraisal tools, the pooled OR for LMW was 1.06 (95% CI, 0.99–1.13, I^2 = 22%) (Supplementary Fig. 5), and for HMW the pooled OR was 1.11 (95% CI, 1.07–1.15, I^2 = 10%) (Supplementary Fig. 6). An additional sensitivity analysis was conducted only considering adults, and the results remained similar.

8. Discussion

In this meta-analysis, conducted with nine studies and providing data from different cultures and lifestyles, the overall phthalate exposure was associated with a 10% higher prevalence of the MetS, when comparing extreme categories of exposure. The exposure to LMW phthalates was associated with an 8% higher prevalence of the MetS, with a light to moderate heterogeneity, when all studies were combined (I^2 = 28%). Four LMW phthalate metabolites were analyzed, of which MiBP was associated with a significantly higher prevalence of 13%; the parent compound of this phthalate (DiBP) is used in flooring, adhesives, lacquers, and lubricants (Diisobutyl phthalate – German Environmental Specimen Bank n, 1028). For MMP, another LMW metabolite, sex partially explained heterogeneity, and showed an 89% increased prevalence of the MetS among men. DMP (parent compound of MMP) is used in perfumes, aftershaves, shampoos, makeup, and nail care products, which are used differently by men and women (Wang et al., 2019).

On the other hand, exposure to HMW phthalate was associated with a significantly higher prevalence of the MetS of 11%, with a low heterogeneity across studies (I^2 = 7%). Four out of the six HMW phthalates analyzed (MCOP, MCPP, MBzP, and DEHP) were related to the MetS. Higher levels of exposure to MCOP, MCPP, as well as MBzP, showed a higher prevalence of 12%, 9%, and 16% respectively. The parent compounds of these metabolites have been used in the following products: DiNP (parent compounds of MCOP) in adhesives, inks, paints, and lacquers (Giuliani et al., 2020); DnOP (parent compounds of MCPP) in soap packaging (Tønning et al., 2009); and BzBP (parent compounds of MBzP) in car-care products, toys, food packaging, and personal care products (Giuliani et al., 2020). The HMW phthalate most widely studied, the DEHP (including ΣDEHP and its metabolites), showed a 16% higher prevalence of the MetS. Apart from food packaging, the DEHP has been used in perfumes, PVC plastics used in household products, and medical devices (Giuliani et al., 2020).

Finally, the funnel plot for both, LMW and HMW phthalates, had a symmetrical distribution, which suggests the non-existence of publication bias. Additionally, these findings along with the low heterogeneity found among studies support the validity of our results.

Our results confirm the previously stated hypothesis that both types of phthalates are harmful, even though LMW phthalates showed a slightly lower risk than HMW phthalates (8% vs 11%). These results are

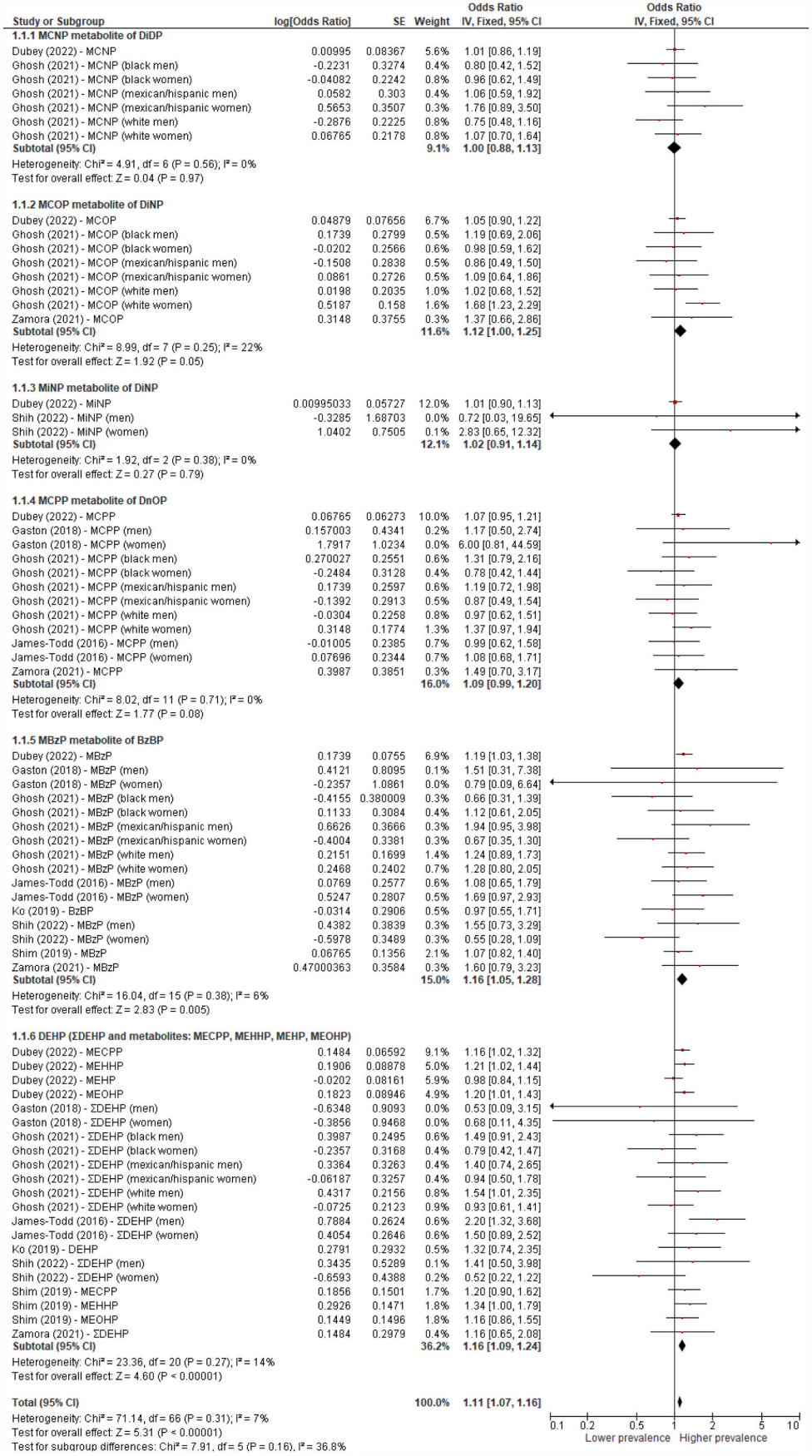

Fig. 4. Forest plot of the association between high molecular weight phthalates and the metabolic syndrome.

also in line with the published scientific evidence regarding phthalates and their association with cardiometabolic risk factors. Thus, a meta-analysis conducted in 2019 with 8 studies found that the exposure to two LMW phthalates (MnBP and MiBP), and six HMW phthalates (MCPP, MBzP, MECPP, MEHP, MEOHP, and ΣDEHP) showed a linear increased risk in insulin resistance (Shoshtari-Yeganeh et al., 2019). Similarly, another recent meta-analysis conducted with 7 studies showed that higher levels of three LMW phthalate metabolites (MnBP, MiBP, and MMP) and five HMW phthalate metabolites (MCPP, MEHHP, MEOHP, MECPP, and ΣDEHP) were positively associated with an increased risk of diabetes mellitus (Zhang et al., 2022). Overall, our results are consistent with those obtained for insulin resistance as well as for diabetes mellitus.

In our study, MMP (a metabolite of DMP) showed the strongest association with the MetS as well as the highest degree of heterogeneity out of all the phthalates studied. However, when we removed the estimate obtained in women by Shih et al. (2022), the heterogeneity decreased noticeably, and the prevalence was higher among men. Of note is that the most extreme result was obtained in the article by Ko et al. (2019), whose participants were performing voluntary military service. As previously mentioned, DMP is commonly used in cosmetics (Wang et al., 2019), but exposure can also occur via dermal and inhalation routes, resulting in occupational exposure and work-related hazards (Fréry et al., 2020) for example in phthalates manufacturing and workers in nail salons (Hines et al., 2009), as well as in cosmetics and perfume salesclerks (Huang et al., 2018). Apart from that, DMP is also present in products more commonly used by men in the workplace such as safety glasses, rubber coating agents, molding powders, pesticides, and insect repellants (Biomonitoring Summary | CDC n, 2023; Substance Information - ECHA n.d, 2023). However, the higher prevalence of the MetS among men needs to be confirmed due to the limited number of studies included in the MMP meta-analysis.

The positive association between phthalates and the MetS could be explained through several mechanisms. Phthalates influence pre-adipocyte differentiation into mature adipocytes, as well as intra-adipocyte lipid-storing through the activation of the peroxisome proliferator-activated receptor gamma (PPARγ), which is an important regulator of adipogenesis and is involved in adipose tissue functionality (Schaffert et al., 2022). There are also specific pathways for individual phthalates. For example, the exposure to DEHP has been shown to induce insulin resistance by promoting gluconeogenesis, and lipid accumulation in mice using the via of overexpression of the transcription factor forkhead box protein (FoxO1), which is the main target of insulin signaling (Wei et al., 2022). Thus, this transcription factor regulates glucose and insulin homeostasis in several tissues such as muscle, liver, the pancreas, as well as adipocyte tissues (Kousteni, 2012). Also, studies in mice have suggested that DEHP exposure could elevate blood pressure by the activation of the angiotensin-converting enzyme (ACE) and inhibiting the bradykinin-nitric oxide pathway (Deng et al., 2019).

In the Consumer Product Safety Improvement Act of 2008 (CPSIA), the Congress of the United States permanently prohibited children's toys and childcare articles that contained more than 0.1% of the following phthalates: DBP, DiBP, DiNP, BzBP, DEHP, and other phthalates (Phthalates Business Guidance & Small Entity Compliance Guide | CPSC, 2022). On the other hand, since July 2011, the European Union has prohibited the use of six phthalates (DBP, DiDP, DiNP, DnOP, BzBP, and DEHP) in toys (Phthalates, 2022). In July 2020, the European Union enacted new legislation, the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH), that mandatorily applies to chemical substances. The REACH regulations restricted four phthalates (DBP, DiBP, BzBP, and DEHP) from a wide variety of products, such as children's swimming aids, flooring, coated fabrics, paper, footwear, and office supplies. Finally, since November 2020 these phthalates have been restricted in clothing and related accessories, as well as in textiles that are in contact with human skin (Phthalates, 2022). It is of note that, phthalate exposure is still universal, and phthalate regulations were not operative at the inception of the studies included in our meta-analysis.

Our results showed that most phthalates that were significantly associated with a higher prevalence of the MetS have already been prohibited in plastic products in the European Union and in the USA, such as DiBP (parent compound of MiBP), DiNP (parent compound of MCOP), DnOP (parent compound of MCPP), BzBP (parent compound of MBzP), and DEHP. However, to our knowledge, the use of the DMP (parent compound of MMP) has not been restricted yet.

Our study has several strengths. It is the first systematic review and meta-analysis that assessed the association between phthalate exposure and the MetS in the general population. Also, our results could have practical implications as they could be of great impact on the regulation of some phthalates. In addition, central estimators were >1 in all the pooled ORs, indicating a high degree of consistency. Finally, this meta-analysis included a large number of participants from different countries and cultures.

This meta-analysis also has some limitations. First, we accepted slight modifications to the NCEP/ATP-III criteria to meet the characteristics of different biotypes and races. Second, moderate heterogeneity was observed in some subgroups, and random effects models were used in these cases. Third, no longitudinal studies were found, therefore, causality should be explored in the future. Finally, the results of this meta-analysis could vary due to recent regulations. Most of the studies included were performed in cohorts recruited from 1994 to 2020, when phthalate regulations had not come into force yet.

In conclusion, this systematic review and meta-analysis show that both, LMW as well as HMW phthalates are associated with a higher prevalence of the MetS when comparing extreme categories. Two specific LMW phthalate metabolites (MiBP and MMP) and four HMW phthalate metabolites (MCOP, MCPP, MBzP, and DEHP) are associated with a higher prevalence of the MetS.

Author contributions

Diana María Mérida: Methodology, Software, Formal Analysis, Investigation, Writing-original Draft, and Visualization. **Belén Moreno-Franco:** Writing-review&editing. **Montse Marquès:** Writing-review&editing. **Montserrat León-Latre:** Writing-review&editing. **Martín Laclaustra:** Writing-review&editing. **Pilar Guallar-Castillón:** Conceptualization, Methodology, Validation, Resources, Supervision, and Project administration.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2023.121957.

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