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Article Review

A Review of Di-(2-ethylhexyl) Phthalate (DEHP) Exposure and Metabolic Syndrome in Adults

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ABSTRACT

The sources of DEHP exposure are very wide because it is used as a plasticizer and additive in cosmetics and personal care products. Epidemiological studies have shown that DEHP and its metabolites can increase the risk of metabolic syndrome. However, this observation is still debated. Therefore, we conducted a systematic review aimed to investigate the relationship between DEHP exposure and metabolic syndrome in adults. This study used three databases, namely Pubmed, Scopus, and ScienceDirect, with English-language publications from 2019 to 2024. Seven cross-sectional and cohort studies from South Korea, the United States, Mexico, and Taiwan met the inclusion criteria selected through the PRISMA stages They were assessed for quality using the JBI Critical Appraisal Tool. The findings showed that only studies conducted in the United States and South Korea showed a significant association between DEHP and its metabolites (MEHP, MECPP, MCMHP, MEHHP, and MEOHP) with metabolic syndrome. However, these findings were limited to men, white men, premenopausal women, and postmenopausal women. In conclusion, DEHP and its metabolites showed inconsistent results on metabolic syndrome in adults. Recommendations are that further studies are needed with more robust designs in the future in various countries to clearly describe the relationship between DEHP and metabolic syndrome and strong regulation of phthalate use to minimize exposure.

INTRODUCTION

DEHP is a colorless liquid chemical with a faint smell. Another name for DEHP is bis(2-ethylhexyl) phthalate. DEHP is used as an additive to make plastics more flexible.[1] DEHP is in a wide range of products, including blood storage bags, medical tubes, raincoats, floor tiles, wall coverings, and upholstery.[2] In addition, DEHP can also be found in cosmetics and personal care items like sunscreen, body soap, facial cream, hand cream, nail polish, hair spray, skin cleanser, lotion, and body soap.[3–5] Human exposure to DEHP is high and ongoing because it is present in plastics, cosmetics, and personal care products.

Phthalate chemicals can enter the body through the skin, food, or respiration. [6] Eating accounts for around 95% of the total exposure to DEHP for adults, teenagers, kids, and toddlers. [7] It is through the migration of DEHP from packaging into food. DEHP was found in 70% of the 64 tested food samples, including cheese pizza, chicken nuggets, hamburgers, chicken burritos, and

French fries.[8] Phthalates tend to move toward foods that are hot and high in fat. Food's phthalate concentration rises with temperature and length of storage.[9] Apart from that, acidic foods can also increase phthalate migration. At an acidic pH (pH=3), DEHP and DnBP migrated the most, with cumulative concentrations of 159.8 and 104.9 μg/L, respectively.[10] Specifically, food packed in PVC or plastic materials exposes people to DEHP.[10,11]

The Environmental Protection Agency (EPA) claims phthalate compounds harm people's health and environment.[12] DEHP exposure has been associated with MetS components such as hyperglycemia and hypertriglyceridemia, levels of central adiposity and hypertension[13], and Adult obesity.[14] This condition is an indicator of metabolic syndrome (MetS). Mechanisms of phthalate exposure with metabolic effects include activation of the transcription factor Peroxisome Proliferator-Activated Receptor Gamma (PPAR), adipose tissue dysfunction, disruption of thyroid hormone function, antiandrogenic effects, oxidative stress and inflammation, and epigenetic changes.[15,16]

The widespread use of DEHP has raised concerns due to its persistent human exposure and its effects on health. Epidemiological studies have linked DEHP and its metabolites to the development of metabolic syndrome. However, these observations are still debated. Therefore, given the growing body of evidence in this area and the lack of literature reviews specifically examining the association of DEHP with metabolic syndrome, we conducted a systematic review of the association of DEHP with metabolic syndrome in adults.

METHODS

This study is a systematic literature review using 3 databases: Pubmed, Scopus, and ScienceDirect. Article screening using the PECO method as an inclusion criterion: (1) articles used by researchers are articles that discuss DEHP exposure with the occurrence of metabolic syndrome; (2) the population and samples are adults; (3) the results measured are metabolic syndrome.

The article selection process in this study follows the PRISMA stages which have 3 stages, namely the first stage focuses on searching for articles using keywords (("Phthalate" OR "Di-(2-ethylhexyl) Phthalate" OR "Bis(2-ethylhexyl) phthalate" OR "DEHP") AND ("metabolic syndrome") AND ("adults") so that 155 articles were obtained. In the second stage, data identification was carried out based on the year category, namely 2019 - 2024, and in English so 96 articles were obtained. In the third stage, filtering was carried out based on duplication, research articles, suitability with research objectives, and full text available so that 12 articles were obtained. In the fourth stage, the final data was determined based on the study of DEHP exposure with the incidence of metabolic syndrome focusing on adults, so seven JBI Critical Appraisal Tool articles were obtained. The seven selected articles had high study quality so that they could be further analyzed. The assessment of study quality using JBI can be seen in Table 1:

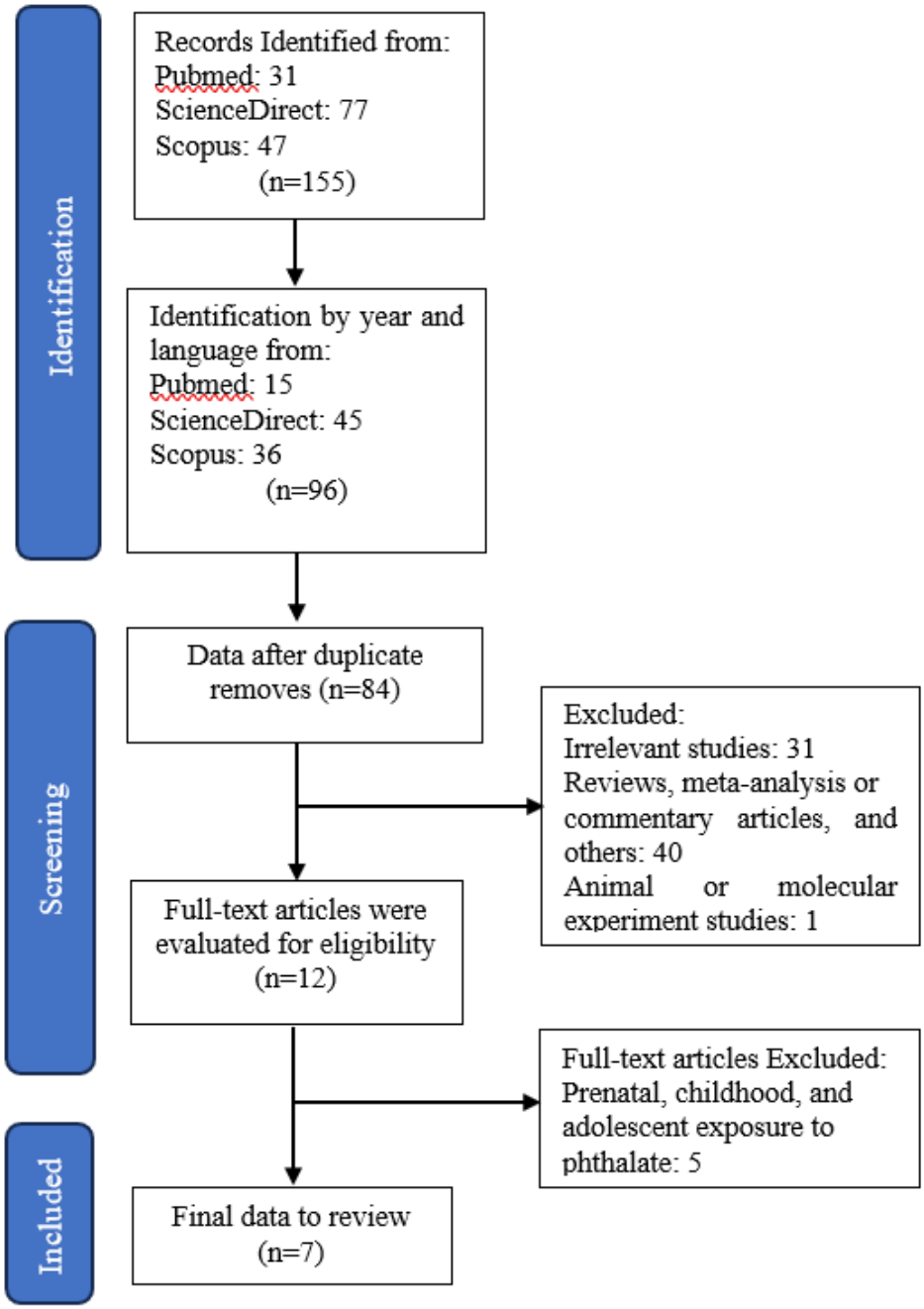

Fig. 1. PRISMA Stage

Table 1. Study Quality Assessment Using the JBI Critical Appraisal Tool

Author (Year)	JBI Critical Appraisal Tool											
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	% Yes
Shim et al., 2019	yes	yes	unclear	yes	yes	yes	yes	yes				87,5*
Ghos et al., 2021	yes	yes	unclear	yes	yes	yes	yes	yes				87,5*
Dubey et al., 2022	yes	yes	unclear	yes	yes	yes	unclear	yes				75*
Zamora et al., 2021	yes	yes	unclear	yes	unclear	yes	yes	yes	yes	yes	yes	81,8**
Shih et al., 2022	yes	yes	yes	yes	yes	unclear	unclear	yes				75*
Ko et al., 2019	yes	yes	yes	yes	yes	no	no	yes				75*
Ihenacho et al., 2023	yes	yes	unclear	yes	yes	yes	yes	yes	unclear	unclear	yes	72,7**

Ket: *JBI for Cross-Sectional Studies (8 Question); **JBI for Cohort Studies (11 Question)
JBI score classification: Studies with a score >70% (high quality), a score of 50%-70% (moderate quality), and a score <50% (low quality)

RESULTS

The articles reviewed come from Pubmed, Scopus, and ScienceDirect with English language publications from 2019 to 2024. They are original research using cross-sectional and cohort research methods. Table 2 below displays the journal summary results.

Table 2. Data Extraction Results

Author/ Year/ Country	Sample Characteristics		Study Design	Phthalate Detection & Mets Criteria	Number of case	Result	PECO Element
	Age	Sample Size					
Shim et al./2019/ Korea Selatan	>20 years	5.251	Cross-sectional Study	Urin; NCEP-ATP III	578 (11%)	1. MetS responders had considerably greater DEHP metabolites (MEHHP, MEOHP, and MECCP) than non-MetS respondents. 2. MetS and MEHHP levels were significantly correlated (OR=1.34; 95% CI= 1.001–1.808).	**Population:** The study using South Korean civilian population; **Exposure:** Heavy Metals, Bisphenol A, Volatile Organic Compounds and Phthalates; **Comparator:** Group not exposed to Heavy Metals, Bisphenol A, Volatile Organic Compounds and Phthalates; **Outcome:** Metabolic syndrome
Ghos et al./2021/ USA	≥ 18 years	10.017	Cross-sectional Study	Urin; NCEP-ATP III	Black men: 236 White men: 607	1. Increased probabilities of MetS prevalence were substantially correlated with higher MECPP levels. On the other hand, there was an	**Population:** The study used National Health and Nutrition Examination Survey (NHANES) data using specific subgroups of the non-institutionalized civilian population

Author/ Year/ Country	Sample Characteristics		Study Design	Phthalate Detection & Mets Criteria	Number of case	Result	PECO Element
	Age	Sample Size					
					Mexican/ Hispanic men: 304 White women: 595 Black women: 316 Mexican/ Hispanic women: 345	inverse relationship between the probabilities of MetS prevalence and higher MEHP levels 2. Gender stratification revealed a correlation between MetS and men's greater MECPP, MEHHP, and MEOHP levels. 3. The positive relationship between ∑DEHP and Mets is only among men 4. Only white men showed a correlation between ∑DEHP and an elevated risk of MetS when stratified by race and sex	of the United States, living in all 50 states and Washington D.C.; **Exposure:** 16 phthalate metabolites; **Comparator:** Group not exposed to 16 phthalate metabolites**; Outcome:** Metabolic syndrome
Dubey et al./2022/ USA	≥ 15 years	2.004	Cross-sectional Study	Urin; NCEP-ATP III	965 (48,15%)	1. A higher incidence of metabolic syndrome was linked to high-level MECPP, MEHHP, and MEOHP 2. In premenopausal women, concentrations of the metabolites MECPP, MEHPP, and MEOHP are linked to metabolic syndrome.	**Populasi:** The study used NHANES survey data with a population of reproductive-age and postmenopausal women aged 15 years or older by excluding female participants with extreme TT values, prepubertal women, and those without phthalate metabolites; **Exposure:** High exposure to 13 metabolites of High Molecular Weight (HMW) or Low Molecular Weight (LMW) phthalates; **Comparator:** Low exposure to 13 metabolites of High Molecular Weight (HMW) or Low Molecular Weight (LMW) phthalates; **Outcome:** Sex Hormones, Obesity, and Metabolic Syndrome
Zamora et al./2021/ Mexico	Average 46.6 years	73	Cohort Study	Urin; NCEP-ATP III	25 (34,25%)	1. DEHP metabolites (MECPP, MEHHP, MEOHP) were detected in 100 percent of samples. 2. MetS components were not associated with MEHP, MECPP, MEHHP, and MEOHP	**Population:** The study population included a sample of Mexican women; **Exposure:** Phenols, 16 Phthalate Metabolites, and Parabens; **Comparator:** Group not exposed to Phenols, 16 Phthalate Metabolites, and

Author/ Year/ Country	Sample Characteristics		Study Design	Phthalate Detection & Mets Criteria	Number of case	Result	PECO Element
	Age	Sample Size					
						3. ∑DEHP was inversely associated with hyperglycemia.	Parabens; **Outcome:** Development of Metabolic Syndrome
Shih et al./2022/ Taiwan	≥ 30 -70 years	1.337	Cross-sectional Study	Urin; Guidelines of the Health Administration, Ministry of Health and Welfar, Taiwan	219 (16,38%)	1. The highest quartile of MCMHP was positively correlated with hyperglycemia in the general population. Conversely, each MetS component was negatively associated with MEHP and MEHHP. 2. In older males, there was an inverse relationship between the likelihood of having MetS and greater concentrations of ΣDEHP. Increased waist circumference was positively correlated with higher MCMHP concentrations. 3. Higher MEOHP levels in women were inversely correlated with the odds of MetS in younger women and there was no statistical correlation in women >50 years of age. The odds of having MetS were only positively correlated with higher ΣDEHP concentrations 4. The risks of MetS were more than nine times greater for postmenopausal women with higher ∑DEHP concentrations than for those with lower ∑DEHP concentrations	**Population:** The study used data from the Taiwan Biobank (TWB) on cancer-free volunteers aged 30–70 years**; Exposure:** 11 phthalate metabolites**; Comparator:** Group not exposed to 11 phthalate metabolites**; Outcome:** Metabolic Syndrome
Ko et al./2019/ Taiwan	Average 32.16 years	435	Cross-sectional Study	Urin; NCEP-ATP III, except the criterion for waist circumference	56 (12,9%)	1. There is no discernible difference in the amounts of urinary phthalate metabolites in men and women. 2. Each phthalate Daily Index (DI) and Hazard Index (HI) for each MetS index indicated that the DI_{DEHP} group	**Population:** The study used participants who were performing voluntary military service in Northern Taiwan and underwent annual physical examinations at the Health Evaluation Center of Taoyuan Armed Forces General Hospital**; Exposure:** 7 phthalate

Author/ Year/ Country	Sample Characteristics		Study Design	Phthalate Detection & Mets Criteria	Number of case	Result	PECO Element
	Age	Sample Size					
				modified by the Asian population (Health Promotion Administration, Ministry of Health and Welfare, 2007)		was not associated with MetS risk.	metabolites**; Comparator:** Group not exposed to 7 phthalate metabolites**; Outcome:** Insulin resistance and Metabolic Syndrome
Ihenacho et al./ 2023/ USA (Hawai and California)	45-75 years	1.728	ultiethnic Cohort Study	Urin; NCEP-ATP III	519 (30%)	MetS and phthalate metabolites (ΣDEHP: MEHP, MEHHP, MEOHP dan MECPP) did not have a statistically significant relationship	**Population:** The study used a population of men and women aged 45-75 years from 5 racial and ethnic groups (African Americans, Japanese Americans, Latinos, Native Hawaiians, and non-Hispanic Whites) living in Hawai'i and California enrolled from 1993 to 1996.; **Exposure:** BPA, triclosan, 5 parabens (methylparaben, ethylparaben, propylparaben, butylparaben, benzylparaben), phthalic acid, and 10 phthalate metabolites; **Comparator:** Group not exposed BPA, triclosan, 5 parabens (methylparaben, ethylparaben, propylparaben, butylparaben, benzylparaben), phthalic acid, and 10 phthalate metabolites; **Outcome:** Metabolic Syndrome

Journal summary data in Table 1 shows that the research, which was published between 2019 and 2024, was carried out in the United States (3), Taiwan (2), South Korea (1), and Mexico (1). There were five (5) cross-sectional studies and two (2) cohort study. The minimum age limit used is 15 years. Urine samples were used in each study to evaluate the metabolites of phthalates. Most studies defined MetS using the NCEP/ATP-III criteria (5), using the Health Administration guidelines, Ministry of Health and Welfare, Taiwan (1), and using 2 MetS criteria (NCEP/ATP-III criteria and Health Promotion Administration, Ministry of Health and Welfare, 2007) (1).

The difference in the MetS criteria used in the seven literatures did not cause a significant difference in the number of MetS findings. Where the two MetS criteria only have differences in the waist circumference limit, namely, according to the National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III), the waist circumference limit is ≥102 cm (male) or ≥88 cm (female).[17] While the criteria according to the Health Administration, Ministry of Health and Welfare, Taiwan guidelines, the waist circumference limit is ≥90 cm (male) or ≥80 cm (female).[18]

DEHP metabolites have varying relationships with MetS. Positive correlations between DEHP metabolites (MEHHP, MECPP, MEOHP) and ΣDEHP with MetS were only found in studies conducted in the United States and South Korea. However, this relationship was limited to men, white men, premenopausal and postmenopausal women. In addition, it was found that increased waist circumference and hyperglycemia in men were significantly associated with another DEHP metabolite, MCMHP.

DISCUSSION

Metabolic syndrome combines central obesity, elevated triglyceride levels, hypertension, decreased HDL, and elevated fasting blood glucose. [19]. Different health organizations, including the WHO, the International Diabetes Federation (IDF), the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), and the European Group for Study of Insulin Resistance (EGIR), have different definitions of MetS. [20] A person is considered to have metabolic syndrome if they satisfy three out of the five NCEP/ATP-III criteria, which are as follows: blood pressure ≥130/85 mm Hg or medication for hypertension, fasting blood glucose ≥ 110 mg/dl or treatment for diabetes, waist circumference ≥102 cm (men) or ≥88 cm (women), and fasting serum triglycerides ≥150 mg/dl.[17]

The occurrence of metabolic syndrome is frequently linked to variables including age, gender, genetics, ethnicity, way of life (including alcohol and tobacco use, physical activity, and food), and stress.[21–30] However, phthalates have also been found to disrupt the metabolic system. Phthalate metabolites of the DEHP type have been found in the US, Mexico, Korea, Japan, Taiwan, Vietnam, and Indonesia, among others, indicating that DEHP is still a commonly manufactured phthalate type.[18,31–35] Additionally, it was discovered that DEHP exposure has increased in China.[31,36]

This study's findings regarding the connection between DEHP and metabolic syndrome were inconsistent. Research conducted in Mexico, Taiwan, the American part of Hawaii, and California shows that DEHP and its metabolites do not have a significant relationship with metabolic syndrome.[35,37,38]. Meanwhile, research in the United States and South Korea shows that the metabolites MEHHP, MECPP, MEOHP, and ΣDEHP have a significant relationship with metabolic syndrome. However, this relationship was limited to men, white men, premenopause, and postmenopause women.[18,34,39,40] These results imply that phthalate metabolites and MetS have varied relationships depending on gender, age, and race/ethnicity. Additionally, it was found that elements of the metabolic syndrome were significantly connected with other DEHP metabolites, such as MCMHP, which was favorably correlated with men's increased waist circumference and hyperglycemia.[18]

The kind of metabolite determines the link between DEHP and metabolic syndrome. The differences in research results may be due to different and non-specific age limits based on age categories such as teenagers, adults, and the elderly. Some studies use age ranges too wide such as ≥15 years, ≥18 years, and >20 years. An age range that is too wide causes poor results because age is a risk factor for metabolic syndrome. Growing older can lead to changes in fat mass and

body composition, particularly in central obesity, which is one of the components of metabolic syndrome.

The possible reason for the correlation between phthalates and obesity is that they may interfere with adipose tissue function by interfering with PPAR-γ or PPAR-α, as well as with energy balance and endocrine steroid homeostasis. Phthalates may be associated with metabolic syndrome because they increase obesity by binding to PPAR-γ or PPAR-α, which alter the activity of endocrine hormones, or because they affect β-cell function. It is possible that in the female population, phthalate exposure is associated with metabolic disorders, such as obesity, via the sex hormone-binding globulin (SHBG) pathway.[40]

In several experiments on animals such as mice, it was found that a dose of 500 mg/kg/day was proven to cause toxicity, increase serum lipid levels, and change levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total cholesterol (TC).[41,42] The mechanism linking phthalates to hypertension is likely due to disruption of the renin-angiotensin-aldosterone system (RAAS). As peroxisome proliferator-activated receptor gamma (PPARγ) agonists, phthalates block the RAAS, a crucial hormone system that regulates blood pressure. [43] Experiments on mice given 0.1/1/10 mg/kg/day of DEHP for six weeks showed substantial increases in blood pressure.[44]

This study has limitations, namely that the studies included were mostly cross-sectional, small in number, and studies from only four countries, so the evidence obtained was inadequate. A more comprehensive explanation is still needed to link DEHP exposure to metabolic syndrome in adults. Therefore, further research is needed in various countries with certain age restrictions based on age groups through a more robust research method approach.

CONCLUSION

DEHP exposure has been widely found in the community, but the relationship between DEHP and metabolic syndrome in adults has inconsistent findings. Only studies conducted in the United States and South Korea showed significant associations and were limited to men, white men, premenopausal, and postmenopausal women. More studies with stronger designs are needed in the future to describe the relationship between DEHP and metabolic syndrome clearly. In addition, strict regulations on the use of phthalates are needed to minimize exposure.

Author's Contribution Statement:

Andi Daramusseng: Conceptualization, Methodology, and Data Collection. Sulistiyani: Investigation, and Data curation. Suhartono: Validation and Formal Analysis. Yusniar Hanani Darundiati: Writing- Reviewing and Editing.

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