ASSOCIATION BETWEEN PHTHALATE EXPOSURE AND INSULIN RESISTANCE: A REVIEW

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Abstract. Insulin resistance refers to a state in which the target tissues have reduced biological sensitivity to insulin. Insulin resistance is considered the common pathophysiological basis of many chronic non-communicable diseases, including type 2 diabetes, non-alcoholic fatty liver, atherosclerosis and coronary heart disease. These diseases have become the major public health problems that seriously endanger human health and economic development nationwide, and the prevention and control of the occurrence of insulin resistance is a crucial issue. The occurrence of insulin resistance is a complex process influenced by genetics and environment. Genetic susceptibility, higher body mass index and less physical exercise are the main risk factors for insulin resistance. Besides, environmental endocrine disruptors such as phthalates may increase the incidence of metabolic disorders and explain a part of its increase. Therefore, this study reviews the epidemiological studies on the association between phthalate exposure and insulin resistance, and discusses the potential biological mechanisms. In conclusion, the majority of studies supported the hypothesis that phthalate exposure was significantly associated with the increased risk of insulin resistance. High oxidative stress, abnormal systemic inflammation and lipid metabolism were underlying mechanisms of insulin resistance induced by phthalates.

Keywords: *environmental endocrine disruptors, cardiovascular disease, oxidative stress, chronic inflammation, obesity*

Abbreviations

Phthalic acid diester		Phthalate metabolite	
Abbreviation	**Whole name**	**Abbreviation**	**Whole name**
DMP	Dimethyl phthalate	MMP	Monomethyl phthalate
DEP	Diethyl phthalate	MEP	Monoethyl phthalate
DiBP	Di-iso-butyl phthalate	MiBP	Mono-iso-butyl phthalate
BBzP	Butyl benzyl phthalate	MBzP	Monobenzyl phthalate
DEHP	Di(2-ethylhexyl) phthalate	MEHP	Mono(2-ethylhexyl) phthalate
		MEOHP	Mono(2-ethyl-5-oxyhexyl) phthalate
		MEHHP	Mono(2-ethyl-5-carboxyhexyl) phthalate
DiNP	Di-iso-nonyl phthalate	MiNP	Mono- iso-nonyl phthalate

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Introduction

Phthalates are a family of artificially synthesized chemicals since 1920s. They have been widely used as plasticizers in the production of polyvinyl chloride since 1950s (Kimber et al., 2010). For instance, high molecular weight phthalates including butyl benzyl phthalate (BBzP) and di(2-ethylhexyl) phthalate (DEHP), are commonly used in building materials, food packages, child toys, medical equipments, etc. Low molecular weight phthalates including diethyl phthalate (DEP) and dibutyl phthalate (DBP) are often used in personal care products. However, phthalates are not bonded to polymers with chemical bond. They are easily released into the surrounding environment, especially under high temperature or high fat conditions. Therefore, human is exposure to phthalates through digest, inhalation, dermal contact and medical treatment. A variety of phthalate metabolites can be detected in human urine, serum and other biological samples, and the detection frequency is almost 100%. It suggests that people have been generally exposed to phthalates. Therefore, it is very important to study the effects of phthalates on human health. In 2009, Grün and Blumberg reported that environmental endocrine disruptors are "obesogens" that can disrupt homeostasis and reward mechanisms, and increase individual sensitivity (change in weight set point) (Grün and Blumberg, 2009). In 2015, the Parma Consensus stated that the range of "obesogens" that increase obesity and metabolic syndrome susceptibility should be expanded and referred to as environmental "metabolic disruptors" (Heindel et al., 2015). At present, a large number of studies have conducted intense discussions on the obesity-causing effects of phthalates exposure. The increase in obesity is closely related to the development of insulin resistance, but insulin resistance can also occur independently of obesity.

The increasing prevalence of obesity and metabolic syndrome is a huge challenge in the field of public health. Insulin resistance is an important pathological feature of obesity and metabolic syndrome (Samuel and Shulman, 2012). Therefore, improving insulin sensitivity is an important strategy to prevent, delay or treat type 2 diabetes and metabolic syndrome. Although genetic susceptibility and lifestyle (such as diet, exercise, smoking, etc.) are considered as important causes of type 2 diabetes and metabolic syndrome, these reasons cannot fully explain the sharp increase in incidence of metabolic syndrome in recent decades. Studies have pointed out that exposure to environmental chemicals may be another important cause.

Therefore, this study aimed to review contemporary epidemiological literatures on the association between phthalate exposure and insulin resistance as well as its underlying mechanisms.

Overview of epidemiological studies on the association between phthalate exposure and insulin resistance

A systematic literature search was used for MEDLINE database on March 17, 2021. The search strategy was TS= (phthalate OR "phthalic acid ester" OR "endocrine disruptor" OR "endocrine disrupting chemical") AND TS= ("insulin resistance" OR "insulin sensitivity" OR "pre-diabetic state" OR "hyperinsulinemia" OR "glucose intolerance" OR "diabetes" OR "metabolic syndrome"). Fifteen cross-sectional studies were found to have analyzed the association between phthalate exposure and insulin resistance (*Table 1*). The minimum age of the research subjects was 6 years old, but most of participants were teenagers, adults and the elderly people. The research

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publication year ranged from 2007 to 2020. The research sites included Asia [China (N= 4) and South Korea (N= 3)], America [the United States (N= 4) and Canada (N= 1)], and Europe [Sweden (N= 1), Belgium (N= 1) and Serbia (N= 1)], etc. The basic characteristics of each study were shown in *Table 1*.

Table 1. *The basic characteristics of studies analyzed the association between phthalate exposure and insulin resistance*

Reference	Publication year	Country	Study design	Sample size	Age of participants (year)
Stahlhut et al.	2007	United States	cross-sectional	1451	＞18
Lind et al.	2012	Sweden	cross-sectional	1016	70
Trasande et al.	2013	United States	cross-sectional	766	12～19
Kim et al.	2013	South Korea	cross-sectional	560	＞60
Dirinck et al.	2015	Belgium	cross-sectional	123	41±12.5
Attina &Tresande	2015	United States	cross-sectional	356	12～19
Lin et al.	2016	China	cross-sectional	793	12～30
Chen et al.	2017	China	cross-sectional	786	12～30
Dales et al.	2018	Canada	cross-sectional	4437	12～79
Dong et al.	2018	China	cross-sectional	300	＞50
Kim et al.	2018	South Korea	cross-sectional	137	6～13
Ko et al.	2019	China	cross-sectional	435	32.16±6.43
Li et al.	2019a	United States	cross-sectional	1605	12～85
Lee et al.	2019a	South Korea	cross-sectional	459	20～48
Milošević et al.	2020	Serbia	cross-sectional	305	18～50

Relationship between phthalate exposure and insulin resistance in children

Study only included girls aged 6～13 years as participants. It found that the percent of mono(2-ethyl-5-carboxyhexyl) phthalate (MEHHP%) of overweight girls was significantly higher than that of the control group. MEHHP% was positively correlated with girls' body mass index (BMI) percentile, body fat percentage, waist circumference and homeostasis model assessment-insulin resistance (HOMA-IR) (Kim et al., 2018).

Relationship between phthalate exposure and insulin resistance in teenagers

Among adolescents and young people, Lin et al. (2016) observed that there was a significant positive relationship of the urinary concentration of mono(2-ethylhexyl) phthalate (MEHP) with HOMA-IR and the particle level of vascular injury markers in circulation. Chen et al. (2017) performed more detailed analyses and obtained similar results in the total population and the youth population, but this phenomenon was not observed in the adolescent population. Trasande et al. (2013) found that for one logarithmic unit increase of concentrations of DEHP metabolites, HOMA-IR increased by 0.27 (0.14 to 0.40); Compared with the lowest quartile group of DEHP concentration (the incidence of insulin resistance, defined as HOMA-IR > two-fold standard deviations, was 14.5%), the incidence of insulin resistance was 21.6% in the third quartile concentration group (Trasande et al., 2013). To further verify the relationship of DEHP and its substitute di-iso-nonyl phthalate (DiNP) exposure with insulin resistance, another study found that for one logarithmic unit increase of DiNP, HOMA-IR

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increased by 0.08 (p value= 0.001); Compared with the lowest quartile group of DiNP and DEHP concentrations (the prevalence of insulin resistance was 23.4% and 20.5%, respectively), prevalence of the third quartile concentration groups was 34.4% and 37.7%, respectively (Attina and Trasande, 2015).

Relationship between phthalate exposure and insulin resistance in adults

Based on the data analyses of the National Health and Nutrition Survey of the United States in different years, Stahlhut et al. (2007) found that exposure to monoethyl phthalate (MEP) and monobenzyl phthalate (MBzP) was positively associated with the increase of waist circumference and insulin resistance in adult. In Canada, one study showed that DEHP metabolites were positively correlated with the increase of fasting blood glucose, fasting insulin, HOMA-IR and HOMA-β (the indicator of the islet β cell function). For one interquartile range increase of DEHP concentration, HOMA-IR increased by 0.15 (0.04～0.26), HOMA-β increased by 10.24% (3.71%～16.77%) (Dales et al., 2018). In 123 Belgium obese subjects without type 2 diabetes, phthalates exposure was associated with increased insulin resistance, decreased insulin sensitivity, and impaired pancreatic β-cell function (Dirinck et al., 2015). A total of 305 Serbians (18～50 years old) were divided into obesity group, type 2 diabetes group and healthy control group. Only in type 2 diabetes patients, serum insulin levels and HOMA-IR showed significantly difference in different MEP exposure groups (Milošević et al., 2020). To analyze the associations of phthalates exposure with the risks of insulin resistance and metabolic syndrome, the results revealed that dimethyl phthalate (DMP) exposure was associated with high HOMA-IR [odd ratio (OR) = 1.686, 95% confidence interval (CI) = 1.079～2.634) and risk of metabolic syndrome (OR = 2.329, 95%CI = 1.263～4.295). In addition, the role of HOMA-IR in mediating the effect of dimethyl phthalate exposure on metabolic syndrome was 43% (Ko et al., 2019). In the population of adult women, whether it was a single substance or a multi-pollutant model, several chemicals, including monomethyl phthalate (MMP), mono-iso-butyl phthalate (MiBP) and bisphenol S, had always been shown significantly positive associations with the concentrations of adipokines or the risk of insulin resistance (Lee et al., 2019a). Li et al. (2019a) found that serum antioxidant β-carotene had a protective effect on insulin resistance induced by DEHP.

Relationship between phthalate exposure and insulin resistance in elderly

In the elderly population (>50 years old), Dong et al. (2018) observed that the concentrations of most phthalate metabolites were positively correlated with HOMA-IR and the concentrations of 8-hydroxy-2'-deoxyguanosine (8-OHdG) and malondialdehyde, suggesting that phthalate exposure was related to insulin resistance and oxidative stress. A study in South Korea reported that the urinary concentrations of the secondary metabolites of DEHP, MEHHP and mono(2-ethyl-5-oxyhexyl) phthalate (MEOHP), were related to the risks of insulin resistance and diabetes (Kim et al., 2013). Besides, a Swedish study reported that high levels of MMP, MEP and MiBP were related to the increased prevalence of diabetes; MiBP was related to insufficient insulin secretion, and MMP and MEP were related to insulin resistance (Lind et al., 2012). The oxidative stress marker malondialdehyde was related to both DEHP and insulin resistance, suggesting that oxidative stress might play a role in mediating the effect of DEHP exposure on insulin resistance (Kim et al., 2013).

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Potential biological mechanisms

Most studies supported a positive correlation between phthalate exposure and risk of insulin resistance. It indicated that phthalates exposure might be related to glucose metabolic disorders, not only in obese and diabetic patients, but also in normal-weight non-diabetic individuals. The biological mechanisms of the relationship between phthalates and insulin resistance is still unclear. However, several biological mechanisms of insulin resistance occurring have been reported, including defects in the insulin signaling pathway, ectopic lipid accumulation, systemic inflammation, mitochondrial dysfunction, oxidative stress and endoplasmic reticulum stress.

Exposure to phthalates and oxidative stress

Studies have found that nutrient overload, insufficient physical activity, hypoxia, excessive psychological stress, and exposure to environmental pollutants could induce a series of responses including cellular stress, stress response and stress response disorders. These responses jointly inhibit the insulin signals in target cells, such as endothelial cells, liver cells, skeletal muscle cells, hypothalamic neurons, fat cells, etc. Therefore, the insulin resistance occurs (Onyango, 2018). Cellular stresses that induce insulin resistance include oxidative stress, nitrosative stress, carbonyl/electrophilic stress, genotoxic stress and endoplasmic reticulum stress. A large number of epidemiological studies have observed that phthalates exposure increases the level of oxidative stress in the body. Holland et al. (2016) reported that DEHP and the sum of high molecular weight phthalate metabolites were statistically associated with the level of isoprostaglandin, one of the oxidative stress markers, and this association exists throughout the whole period of pregnancy. Using urinary 8-isoprostaglandin F2α as a biomarker of oxidative stress, one study had found that the concentration of most phthalate metabolites were related to the increase of the concentration of 8-isoprostaglandin F2α (Van et al., 2019). In the population of children, some phthalate metabolites also showed positive relationships with malondialdehyde and 8-OHdG (Lee et al., 2019b). A male mouse experiment observed that DEHP inhibited miR-17 to disrupt the Keap1-Nrf2 redox system and activate the oxidative stress response Txnip in skeletal muscle; Oxidative stress upregulated miR-200a, which directly targeted the 3' untranslated sequence of Insr and Irs1, leading to obstruction of insulin signaling and impaired insulin-dependent glucose uptake in skeletal muscle, which ultimately promotes the development of insulin resistance (Wei et al., 2020). The role of oxidative stress in mediating DEHP and insulin resistance had also been confirmed in some cross-sectional studies (Kim et al., 2013; Dong et al., 2018), and serum antioxidant *β*-carotene was revealed a protective effect on insulin resistance induced by phthalates exposure (Li et al., 2019a). Li et al. (2019b) reported that the association between phthalates exposure and the risk of type 2 diabetes was mediated partlyby the oxidative stress induced by phthalates, especially by the biomarker of 8-OHdG.

Exposure to phthalates and systemic inflammation

A large number of animal experiments and epidemiological evidence demonstrate that phthalates exposure can cause an inflammatory cascade. An epidemiological study observed that higher concentrations of phthalates in urine were correlated with higher levels of high sensitive C reaction protein (hs-CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and were positively associated with the risk of

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cardiovascular disease, type 2 diabetes and hypertension (Bai et al., 2017). An animal experiment found that DEHP exposure induced the infiltration of macrophages in rat adipose tissue, promoted the secretion of interleukin-1β (IL-1β), TNF-α and the formation of inflammation, and interfered with normal lipid metabolism to result in the lipid metabolism disorders (Zhou et al., 2019). MEHP can regulated Sirtuinsgene expression in macrophages to further activate inflammasomes, leading to increased inflammation (Park et al., 2019). Nuclear factor kappa-B (NF-κB) is the most common signaling pathway related to inflammation. In vitro experiments had revealed that exposure to dibutyl phthalate during pregnancy could induce inflammation in the offspring's testicular cells, possibly by activating the lipid receptor CD68 and leading to intracellular P65 phosphorylation and transfermation to the nucleus, NF-κB was activated and then the cells synthesized TNF-α, IL-6, monocytes chemotactic protein-1 (MCP-1) and chemokine CXCL-10, NOD-like receptor protein 3 (NLRP3) inflammasomes accumulated. Pellino-dependent NLRP3 recruited Caspase precursors through the Caspase recruitment domain to release mature Caspase-1, and further recruited the precursor of IL-1 to release mature IL-1. Finally, the NF-κB/NLRP3 cascade signal resulted in the typical features of inflammation (Zhou et al, 2020). IL-1 directly inhibited the insulin signaling pathway and induced the occurrence of insulin resistance by reducing the phosphorylation of tyrosine of the insulin receptor substrate-1 and negatively regulating the gene expression of this substrate (Jager et al., 2007).

Exposure to phthalates and obesity and lipid metabolic disorder

Obesity is closely related to insulin resistance, especially the increase in lipid deposition and abnormal distribution patterns in insulin target organs. As mentioned above, phthalates have been classified as environmental "obesogens" and "metabolic disruptors", probably by increasing the number of fat cells, increasing the volume of fat cells, changing the basal metabolic rate, and regulating appetite and satiety, etc. (Muscogiuri et al., 2017). In vitro studies had shown that phthalates could bind to estrogen receptor alpha or androgen receptor, thus exhibited weak estrogenic activity and strong antiandrogenic activity (Gray et al., 2000; Takeuchi et al., 2005). The level of sex hormones in the body would affect the amount and distribution of fat. Phthalates were known as ligands to peroxisome proliferator-activated receptors (PPARs) (Hurst and Waxman, 2003; Bility et al., 2004). PPARs are a family of transcription factors with a key role in adipogenesis and lipid metabolism (Grun, 2009). PPARs mainly regulate adipocyte development, and promote adipocyte differentiation and maturation after activation (Evans et al., 2004). In addition, phthalates are known to interfere with thyroid function and may reduce the level of thyroxine in the circulatory system (Yao et al., 2016; Gao et al., 2017). Thyroid function plays a key role in maintaining basal metabolism and the regulation of energy balance. However, these biological mechanisms are complicated and potential interaction. For instance, in vitro experiment had observed that MEHP induced lipid accumulation by inhibiting the JAK2/STAT5 pathway, and damaged the liver parenchyma by aggravating oxidative stress and leaded to the occurrence of non-alcoholic fatty liver (Zhang et al., 2019).

Conclusions

Human exposure to phthalates is related to the risk of insulin resistance, which is consistent with our recent findings through an update of a systematic review and meta-

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analysis (Gao et al., 2021). These may be mediated by lipid metabolism disorders induced by chronic inflammation and oxidative stress. It is impossible to draw a causal relationship between phthalate and insulin resistance, because of lack of prospective cohort studies to date. Only one study population was girls aged 6 to 13, and the other study populations were adolescents and adults (including the elderly) aged over 12 years old. For young children, it is not clear whether phthalates exposure in early life is related to risk of insulin resistance. This is very important for whether moving or not the insulin resistance prevention window to early life. For the short biological half-life chemicals, phthalate metabolites were measured by one-time urine sample to evaluate exposure in the majority of studies. This might introduce exposure misclassification bias. Only three studies used Bayesian nuclear machine learning or hazard index models to evaluate the effect of co-exposure to multiple phthalate metabolites on insulin resistance. As phthalates are a class of chemicals with similar chemical structures and health effects, it is necessary to take the cumulative risk assessment of multiple phthalates combined exposure into consideration.

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