Review

# Associations of Phthalate Metabolites and Obesity-Related Metabolic Factors

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**Diabetes and obesity have reached epidemic rates in most developed and developing countries. Over-nutrition and physical inactivity are established risk factors with key roles in the etiology of type 2 diabetes. However, these factors alone cannot fully account for either the rate or the magnitude with which diabetes has increased worldwide. Research on whether exposure to environmental endocrine disrupting chemicals (EDCs) may be a preventable risk factor for diabetes development has attracted considerable attention since the 1990s. Phthalates are a group of EDCs characterized by widespread human exposure; concerns about the adverse effects of exposure to phthalates on human health are increasing. Early studies regarding the toxicity of phthalates largely focused on reproductive health and development effects. More recent research has shifted towards possible metabolic effects that may increase the risk for obesity, insulin resistance, diabetes, and other related adverse health outcomes. Considering the ubiquity of phthalates in the environment, it is important to understand the potential hazards of these chemicals even at very low exposure levels; if those are confirmed, strategies must be developed to remove them from the environment or at least preclude widespread contamination. This review aimed to summarize current evidence on the potential hazards of phthalates with regard to metabolic disease and highlighted the importance of further investigation that will have high public health significance for both developed as well as developing countries, where the exposure may continue to be high for decades to come.**

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## INTRODUCTION

A growing number of environmental chemicals have been postulated to adversely affect the human endocrine system and ultimately lead to an array of metabolic disorders.[1,2] The US Environmental Protection Agency (EPA) defined an endocrine disrupting chemical (EDC) as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations".[3] EDCs interfere with the synthesis, secretion, transport, metabolism, binding, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development and/or behavior.[4] EDCs are highly heterogeneous and include a wide variety of man-made industrial chemicals and certain byproducts from their production and degradation processes.

Phthalates are a family of diester compounds of 1,2-benzenedicarboxylic acid (phthalic acid) widely used in manufacturing plasticizers, solvents and additives.[5] Phthalates are commonly found in cosmetics, food wrapping, medical devices and drugs, and a large number of other consumer products such as toothbrushes, tool handles and toys.[6,7] Due to widespread use of phthalates in industrialized countries, human exposure is ubiquitous. Phthalates enter the body by a variety of routes, mostly through ingestion, inhalation, and skin contact with consumer products. Following exposure, phthalates undergo step-wise metabolic transformation, which starts with hydrolytic breakup of diesters.[8] Depending on their molecular weight, the resulting monoesters are then either excreted in the urine or undergo additional transformation into glucuronide conjugates, some of which are then oxidized.[9] The free monoesters, the glucuronide conjugates, and oxidative metabolites of phthalates are all detectable in urine samples, and serve as useful markers of exposure to parent diester compounds.[10] As biomonitoring research increasingly recognizes the widespread human exposure to phthalates, with >75% of the US population having detectable phthalates in urine,[11] questions have been raised about the possible adverse effects of these chemicals on human health.[11,12] Earlier studies mainly examined the impact of phthalate exposure on cancer,[13] developmental outcomes,[14,15] thyroid function,[16] and reproductive problems.[17] More recent studies suggest that

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phthalates may also disrupt energy balance and homeostasis[18,19] and as a result cause obesity,[20] diabetes,[21] and atherosclerosis[22] in adults.

**Experimental Studies of Phthalates, Glucose Metabolism and Insulin Sensitivity**

*In vitro and in vivo* experimental studies have shown that phthalates may interfere with glucose homeostasis and insulin sensitivity, increasing the risk of diabetes.[23] The phthalate metabolite diethylhexylphalate (DEHP) has been shown to have adverse effects on successive points in the insulin signal transduction cascade, including expression of the insulin receptor[24,25] and glucose transporter4 (GLU4) genes,[25] the phosphorylation of insulin receptor substrate,[26] and glucose uptake and oxidation.[24,25] **(Figure 1)** In animal models, DEHP reduced blood glucose utilization and hepatic glycogenesis and glycogenolysis,[27] reduced serum insulin and testosterone levels, while increased blood glucose, estradiol, and thyroxine levels.[28] DEHP-treated rats also showed deficiency in muscle glucose and lactate transport, reductions in muscle hexokinase,[23] impaired expression of insulin signaling molecules and decreased glucose uptake and oxidation in adipose tissue.[26] Developmental DEHP exposure disrupted the pancreas and altered whole-body glucose homeostasis.[29] In addition to their direct effects on insulin secretion and signaling, phthalates have also been demonstrated to bind to peroxisome proliferator-activated receptors (PPARs),[30,31] a family of nuclear receptors that control lipid storage and carbohydrate metabolism.[32] The potential insulin-sensitizing activity and anti-diabetic effects of PPAR-γ agonists have great therapeutic potential for the treatment of type 2 diabetes.[32] Binding of phthalates to PPAR-γ may modulate the effect of PPAR-γ and contribute to promotion of adipogenesis and dysregulation of glucose metabolism.[33,34] The effect of phthalate on PPAR-α is unclear.

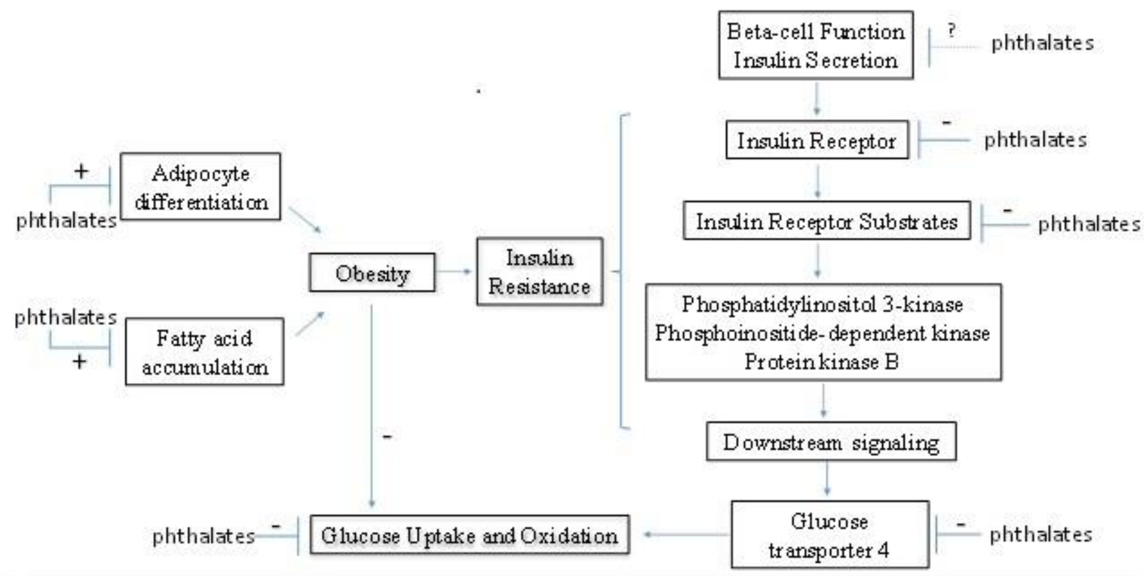


**Figure 1.** Effect of phthalate metabolites on glucose and insulin metabolism.

**Experimental Studies of Phthalates and Adiposity**

Phthalates have the capacity to promote the development of obesity through their action on adipocyte differentiation and fatty acid accumulation.[35] **(Figure 1)** Phthalates have been shown to promote adipocyte development from preadipocytes, mesenchymal stem cells, or both.[36] One mechanism by which phthalates are hypothesized to act as obesogens is the activation of PPARs, which are regulators of adipogenesis.[34,37] Several phthalates and phthalate metabolites act as PPAR activators, thyroid hormone axis antagonists or antiandrogens.[19] Exposure of mouse and human cultured cells to phthalates, especially mono-(2-ethylhexyl)-phthalate (MEHP) and monobenzyl-phthalate (MBzP), led to activation of PPAR-α and PPAR-γ, then to fatty acid oxidation and strong adipocyte differentiation.[31] Alternatively, dicyclohexyl phthalate (DCHP) has been shown to stimulate the glucocorticoid receptor, upregulate the expression of adipocytic proteins, and increase lipid accumulation in adipocytes,[36] also leading to development of obesity and dysregulation of lipid and glucose metabolism.

**Epidemiologic Evidence of Phthalate Metabolites and Glucose and Insulin Homeostasis**

An increasing number of epidemiologic studies have examined the association between human exposures to phthalates and glucose and insulin metabolism in adults, but the data is largely limited to cross-sectional studies from two population-based cohorts.**(Table 1)** A series of analyses using the National Health and Nutrition Examination Survey (NHANES) data, including 1999-2008 surveys, reported positive associations between urinary phthalate metabolites with fasting blood glucose (FBG), fasting insulin, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), or presence of diabetes;[38,40,42] though in a study by James-Todd et al, urinary mono-(3-carboxypropyl) phthalate (MCPP) was associated with lower level of HbA1c.[40] Another group of analyses were conducted using data from the Swedish Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study and found that higher levels of serum phthalate metabolites were associated with increased FBG, HOMA-IR and risk of diagnosed diabetes.[21,41] In contrast to these findings, in a study among 221 healthy Mexican women, only marginally significant positive associations with self-reported diabetes status were observed for mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) among a total of 9 urinary phthalate metabolites measured.[39]

**Table 1.** Epidemiologic Studies of Phthalate Metabolites and Glucose and Insulin Measurements.

| Author, year | Participants | | | | Sample | Design | Associations | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Age* | Gender | Population | | | FBG | Insulin | HOMA-IR | DM | HbA1c |
| Stahlhut, 2007[38] | 651 | >18 | M | NHANES 1999-2002 | Urine | Cross-sectional | | | ↑ | | |
| Svensson, 2011[39] | 221 | 54 | W | Mexican population | Urine | Cross-sectional | | | | NS | |
| James-Todd, 2012[40] | 2,350 | 20-79 | W | NHANES 2001-2008 | Urine | Cross-sectional | ↑ / ↓ | | ↑ | ↑ | ↓ |
| Olsen, 2012[41] | 1,016 | 70 | M&W | PIVUS | serum | Cross-sectional | ↑ | | | | |
| Lind, 2012[21] | 1,016 | 70 | M&W | PIVUS | serum | Cross-sectional | | ↑ / ↓ | ↑ | ↑ | |
| Huang, 2014[42] | 3,083 | 12-<80 | M&W | NHANES 2001-2008 | urine | Cross-sectional | ↑ | ↑ | ↑ | | |
| Sun, 2014[43] | 1,942 | 65.6 | W | NHS | urine | Nested case-control | | | | NS | |
| | | 45.6 | W | NHS II | urine | Nested case-control | | | | ↑ | |

**Table 2.** Summary of Epidemiologic Studies of Phthalate Metabolites and Obesity Measurements.

| Author, year | Participants | | | | Sample | Design | Associations | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Age[a] | Gender | Population | | | Weight or BMI | Waist or WHR | Body fat |
| Duty, 2005[47] | 295 | 36 | M | Andrology clinic patients | Urine | Cross-sectional | ↑ | | |
| Huang, 2007[51] | 75 | 26-43 | W | Pregnant women | Urine | Cross-sectional | ↑ / ↓ | | |
| Wirth, 2008[46] | 45 | 23-48 | M | Infertility patients | Urine | Cross-sectional | ↓ | | |
| Stahlhut, 2007[38] | 1451 | >18 | M | NHANES 1999-2002 | Urine | Cross-sectional | | ↑ | |
| Wolff, 2008[48] | 382 | 24 | W | Pregnant women | Urine | Cross-sectional | ↑ | | |
| Hatch, 2008[44] | 4,369 | 6-80 | M&W | NHANES 1999-2002 | Urine | Cross-sectional | ↑ / ↓ | ↑ / ↓ | |
| Whyatt, 2009[49] | 331 | 18-35 | W | Pregnant women | Urine | Cross-sectional | NS | | |
| Peck, 2010[53] | 45 | 19-51 | W | Hmong women | Urine | Cross-sectional | NS | | |
| Casas, 2011[50] | 120 | 17-34 | W | Pregnant women | Urine | Cross-sectional | NS | | |
| Svensson, 2011[39] | 221 | 54 | W | Mexican population | Urine | Cross-sectional | NS | ↑ | |
| Kasper-Sonnenberg, 2012[45] | 104 | 39.2 | W | Birth cohort in Germany | Urine | Cross-sectional | NS | | |
| James-Todd, 2012[40] | 2,350 | 20-79 | W | NHANES 2001-2008 | Urine | Cross-sectional | ↑ | ↑ | |
| Olsen, 2012[41] | 1,016 | 70 | M&W | PIVUS | Serum | Cross-sectional | ↑ | | |
| Lind, 2012[20] | 1,016 | 70 | M | PIVUS | Serum | 2 y apart | ↑ | ↑ | ↑ |
| | | | W | PIVUS | Serum | 2 y apart | ↑ | ↑ | ↑ |
| Meeker, 2012[8] | 269 | 21-45 | M&W | Infertility patients | Urine | Cross-sectional | ↑ | | |
| Huang, 2014[42] | 3,083 | 12-<80 | M&W | NHANES 2001-2008 | Urine | Cross-sectional | ↑ | ↑ | |
| Song, 2014[52] | 977 | 53.8 | W | NHS & NHS II | Urine | Prospective | ↑ | | |

↑: at least one phthalate metabolite showed significant positive association; ↓: at least one phthalate metabolite showed significant inverse association; NS: no significant association. A: Range or Mean.

Prospective studies, which address the critical temporality issue in making cause-effect inferences, are scarce. We identified only one nested case-control study that examined baseline phthalate exposure in association with incident type 2 diabetes. The study included 971 incident self-reported diabetes case-control pairs selected from Nurses' Health Study (NHS) & NHS II and measured 8 phthalate metabolites in baseline urine samples. The urinary concentrations of total phthalate metabolites and summed butyl phthalate metabolites were associated with increased risk of diabetes in the NHS II (odds ratio comparing extreme quartiles: 2.14 [95% CI: 1.19-3.85], p trend: 0.02 and 3.16 [95% CI: 1.68-5.95], p trend: 0.0001, respectively) but not in the NHS.

**Epidemiologic Evidence of Phthalate Metabolites and Measurements of Obesity**

Associations between phthalate metabolites and indices of obesity have been examined in a number of cross-sectional analyses among population-based cohorts in the US (NHANES[38,40,44]), Mexico,[39] Sweden,[20,41] Germany,[45] and hospital-based studies of men[8,46,47] and pregnant women.[48-51] Outcome parameters reported in these studies include body weight, body mass index (BMI), waist circumference, waist-to-hip ratio (WHR), and body fat measurements (**Table 2**). The majority of studies found a positive association between at least one phthalate metabolite and obesity measures, but inverse associations and null results were also reported. The study by Lind et al. is the only one that achieved objective assessment of body fat by magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DXA);[20]

significant positive associations were found for serum MiBP, MEP, and MMP with DXA-measured total fat, trunk fat, trunk/leg fat ratio, and MRI-measured subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) in both men and women. In this study, although the serum phthalate measurement at baseline preceded the obesity assessment by 2 years, the study results cannot be interpreted as prospective association because there was no baseline assessment of outcome variables. Prospective studies are scarce. We identified only one prospective study that examined phthalate exposure at baseline and subsequent body weight change. The study examined urinary concentrations of 9 phthalate metabolites and weight gain during 10-year follow-up among 977 NHS & NHS II participants and found that phthalic acid, MBzP and monobutyl phthalate, but no other phthalate metabolites, were associated with faster prospective weight gain in a dose-response fashion (p-trend < 0.01).[52]

**Methodology Considerations in Phthalate Exposure Measurement**

Certain methodology issues in phthalate measurements must be considered when interpreting the results of existing studies. First, phthalates measured in plasma or serum are subject to rapid metabolism as well as contamination during sampling or processing.[53,54] Urine is the currently preferred biological matrix for assessment of human phthalate exposure.[55] Second, with the short physiologic half-lives of phthalate metabolites (several hours),[9] urinary levels likely reflect recent exposure. In most studies, the characterization of long-term exposure based on a single measure of phthalate is a potential source of misclassification. Previously reported intra-class correlation (ICC) obtained from repeated measurements within a short period of time ranged from 0.18 to 0.61 for MEP, 0.21 to 0.51 for MiBP, and 0.08 to 0.27 for MEHP,[56-60] with ICC < 0.40 considered poor, 0.40-0.75 fair, and > 0.75 excellent reproducibility, respectively. One study measured seven phthalate metabolites in two times urine samples 1-3 years apart among 40 NHS participants (mean age of 66, comparable to VITAL), ICCs ranged from 0.16 for MEHP to 0.46 for MEOHP and MECPP.[61] Of note, this study used a suboptimal analytical method for phthalates and the large variation may reflect measurement error or changes in exposure over time. Third, there is a large number of phthalate metabolites available for characterization. Some studies measured all common individual metabolites, while others examined only selected fraction, making it difficult to compare results across studies. Finally, in analyses of urinary phthalates, some correction for urine dilution (directly or indirectly), is warranted. It has been suggested that unadjusted concentrations of phthalate metabolites can be used in the statistical model, but urinary creatinine should then be included as a covariate.[62]

**Implications for Further Research and Conclusions**

Diabetes and obesity have reached epidemic rates in most developed and developing countries.[63,64] An estimated 342 million people have diabetes worldwide.[65] Over-nutrition and physical inactivity are established risk factors with key roles in the etiology of type 2 diabetes. However, these factors alone cannot fully account for either the rate or the magnitude with which diabetes has increased worldwide. Research on whether exposure to environmental EDCs may be a preventable risk factor for diabetes development has attracted considerable attention since the 1990s. Despite increasing concerns, current evidence on the potential hazards of phthalates with regard to metabolic disease remains limited and insufficient. Although epidemiologic studies have shown associations of some phthalate metabolites measured in urine or serum with various measures of dysglycemia, insulin resistance, metabolic syndrome, and diabetes, the results are inconsistent across studies. More importantly, the previous studies are predominantly cross-sectional, the interpretation of the data fall short of establishing causality due to the temporality issue. The only prospective study to our knowledge had assessed the outcome variables including incident diabetes and weight change based on self-report on questionnaires and the study only provided data for women. Furthermore, with the short physiologic half-lives of phthalate metabolites, a single measure of exposure may lead to misclassification of long-term exposure. Few studies have repeatedly measured urinary phthalates over time,[8,59] and no study has evaluated whether temporal changes in phthalate exposure are related to corresponding changes in metabolic and obesity-related parameters. Given these limitations of previous studies, future studies must further assess whether there is a causal relation between phthalate exposure and dysregulation of glucose and insulin metabolism and development of obesity, using prospective approach, with outcome variables characterized by accurate and objective methods and phthalate metabolites repeatedly measured using carefully validated assays. Such studies have high public health significance for both developed as well as developing countries, where the exposure may continue to be high for decades to come.

**CONFLICT OF INTEREST**

None.

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