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Review Article

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The obesogenic role of phthalates: A systematic review of mechanistic pathways (2018-2025)

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ABSTRACT

Purpose: This systematic review synthesizes evidence on the mechanistic pathways through which phthalates act as obesogenic endocrine-disrupting chemicals. It focuses on molecular and cellular processes, including peroxisome proliferator-activated receptor gamma (PPARγ) activation, adipogenesis, adipokine dysregulation, oxidative stress, endocrine disruption, mitochondrial dysfunction, and epigenetic reprogramming, and integrates evidence from in-vitro, in-vivo, and human epidemiological studies published between 2018 and 2025.

Method: The review was conducted in accordance with PRISMA 2020. Searches were performed in PubMed, Scopus, Web of Science, and ScienceDirect using predefined keywords related to phthalates, obesity, adipogenesis, lipid metabolism, endocrine disruption, and epigenetics. After duplicate removal, title and abstract screening, and full-text eligibility assessment, 34 studies were included: 10 cellular or animal mechanistic studies, 14 mechanistic or epigenetic reviews, and 10 human epidemiological studies or meta-analyses with mechanistic discussion.

Findings: Across multiple models, phthalates, particularly di(2-ethylhexyl) phthalate and its metabolites, were associated with activation of PPARγ and other adipogenic transcription factors, enhanced adipocyte differentiation, disrupted adipokine balance, oxidative stress, adipose tissue inflammation, and endocrine dysregulation. Mechanistic and epigenetic reviews further suggest that phthalate exposure may induce DNA methylation changes, histone modification, and transgenerational effects, especially during critical developmental windows. Human cohort studies and meta-analyses generally support positive associations between phthalate exposure and adiposity, central obesity, and metabolic syndrome features, although heterogeneity, non-linear relationships, and sex-specific patterns remain evident.

Implications: The evidence supports a multi-pathway mechanistic model in which phthalates contribute to obesity through adipogenesis, inflammatory and mitochondrial dysfunction, hormonal disruption, and epigenetic programming. These findings provide a useful framework for regulatory risk assessment, public health prevention, and future mechanistic research on phthalate substitutes and mixed chemical exposures.

Keywords: phthalates, obesity, PPARγ, adipogenesis, endocrine-disrupting chemicals

INTRODUCTION

The increase in overweight and obesity around the world has been substantial, and traditional explanations based on caloric imbalance do not fully account for the magnitude and pace of this phenomenon. There have been growing concerns about environmental obesogens in chemicals that cause weight gain and metabolic dysfunction through interference with endocrine and developmental pathways [1, 2]. One of these has been phthalates which are commonly used as plasticizers in consumer goods.

The phthalates, including di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP) and their monoester forms are found in human biospecimen globally. The experimental evidence demonstrates that phthalates are capable of activating the nuclear receptors, peroxisome proliferator-activated receptor gamma (PPARγ), influencing the stem-cell fate towards adipocytes, disrupting the thyroid and sex-steroid signaling and altering the epigenetic programming of metabolic tissues [3-5]. Such processes are in keeping with the greater obesogen hypothesis that suggests that early exposure to or chronic exposure to certain chemicals can alter the energy balance, elevate adiposity, and elevate the risk of chronic obesity [1, 2].

Correspondingly, there is epidemiological evidence that phthalate exposure is associated with higher body mass index (BMI) and waist circumference and body fat percentage and metabolic syndrome aspects in children and adults [6-9]. Nevertheless, not all studies have demonstrated a consistent relationship, and some even suggest opposite effects. Specific relationships (sex) were observed and some are even negative

Table 1. Search strategy and keywords

Database	Search fields	Search string/keywords used	Filters applied
PubMed	Title/abstract + MeSH	**Exposure terms:** "phthalate", "phthalates", "DEHP", "di(2-ethylhexyl) phthalate", "MEHP", "DBP", "BBP", "MBP" **Outcome terms:** "obesity", "overweight", "adiposity", "body mass index", "BMI", "metabolic syndrome" **Mechanistic terms:** "adipogenesis", "PPAR", "PPARγ", "nuclear receptor", "epigenetic*", "oxidative stress", "inflammation", "mitochondria", "lipid metabolism" **Combined Boolean string:** ("phthalate" OR "phthalates" OR "DEHP" OR "MEHP") AND ("obesity" OR "adiposity" OR "BMI") AND ("mechanism" OR "adipogenesis" OR "PPARγ" OR "epigenetic*")	English only 2018-2025
Scopus	Title/abstract/ keywords	Same keyword groups as PubMed, adapted to Scopus syntax. **Example syntax:** (TITLE-ABS-KEY("phthalate*" OR "DEHP" OR "MEHP") AND TITLE-ABS-KEY("obesity" OR "BMI" OR "adiposity") AND TITLE-ABS-KEY("adipogenesis" OR "PPARγ" OR "epigenetic*" OR "oxidative stress"))	English 2018-2025 Article type: peer-reviewed
Web of Science	Topic search (TS)	**Example syntax:** TS=("phthalate*" OR "DEHP" OR "MEHP") AND TS=("obesity" OR "metabolic syndrome" OR "BMI") AND TS=("PPARγ" OR "adipogenesis" OR "epigenetic*" OR "mitochondria")	English 2018-2025
Science Direct	Title/abstract/ keywords	**Search string:** "phthalate" AND ("obesity" OR "metabolic syndrome") AND ("mechanism" OR "PPARγ" OR "adipogenesis" OR "epigenetic")	Research articles only 2018-2025

at specific exposure levels [10]. Such inconsistency highlights the importance of considering epidemiological results through an underlying mechanism of pathways, exposure controls, mixtures, and non-linear dose-response associations [11].

Although several reviews have discussed obesogens in general, a focused and up-to-date systematic synthesis is still needed to explain how phthalates specifically contribute to obesity through mechanistic pathways. In particular, there is a need to integrate evidence from cellular, animal, and human studies in order to clarify how molecular disruption translates into observable metabolic and adiposity-related outcomes.

Consequently, this systematic review aims to identify and integrate mechanistic evidence on how phthalates influence adipogenesis, lipid metabolism, endocrine function, inflammation, mitochondrial dysfunction, and epigenetic regulation. It also brings mechanistic and epidemiological findings together to explain how these pathways may translate into obesogenic outcomes across the life course. In addition, the review highlights current knowledge gaps and directions for future research, particularly regarding mixture effects and emerging phthalate alternatives.

METHODOLOGY

Research Design

This research used a systematic literature review (SLR) method to collect, estimate, and integrate the evidence concerning the obesogenicity of phthalates and was particularly interested in the mechanistic pathways. The reason behind selecting the SLR method is that it provides an open, reproducible, and rigorous method of summarizing the evidence available and the selection bias is reduced due to explicit search, screening and inclusion criteria. The review was done according to the PRISMA 2020 statement of reporting systematic reviews.

Search Strategy

The systematic search strategy was developed and implemented in accordance with PRISMA 2020 to ensure that the identification of relevant studies was comprehensive and reproducible. Four databases were searched–PubMed, Scopus, Web of Science core collection, and ScienceDirect–because of their broad coverage of toxicology, endocrinology, environmental health, and epidemiology. The search strategy combined controlled vocabulary, including MeSH terms in PubMed, with free-text keywords across three overarching concepts: phthalate exposure, obesity-related outcomes, and mechanistic pathways. Boolean operators were used to maximize search sensitivity. A representative search structure was as follows: ((phthalate OR phthalates OR DEHP OR mono(2-ethylhexyl) phthalate OR MEHP) AND (obesity OR overweight OR adiposity OR body mass index OR BMI OR metabolic syndrome) AND (mechanism OR adipogenesis OR PPAR OR nuclear receptor OR epigenetic OR oxidative stress OR inflammation)). Only peer-reviewed English-language articles published between January 2018 and 2025 were considered. All retrieved records were imported into reference-management software, and duplicates were removed. To improve completeness, the reference lists of included studies and key review articles were also screened manually to identify additional eligible publications.

The detailed search strategy and keyword structure used across the four databases are summarized in **Table 1**. **Table 1** presents the Boolean search strings, field restrictions (for example, Title/Abstract, MeSH terms, and topic searches), and the filters applied during retrieval. It also indicates that manual reference-list screening was conducted to complement the database search and improve completeness. Overall, **Table 1** supports the transparency and reproducibility of the search procedure in line with PRISMA 2020.

Inclusion and Exclusion Criteria

Eligibility criteria of this review were set in advance so that only this kind of studies that were directly related to both mechanistic and metabolic effects of phthalate exposure would be considered. Peer-reviewed journal articles written in English published between 2018 and 2025 were restricted in total as the period was chosen to obtain the latest developments in the area of molecular toxicology, endocrine disruption, and obesogenic studies. It was only eligible, which included studies that were original research, e.g., in-vitro experiments, in-vivo animal studies, or human epidemiology studies, and also mechanistic review studies that expressly investigated phthalate's role with regard to obesity or metabolic health. Inclusion criteria included the requirement to assess phthalates exposure or exposure to metabolites and report a result on the use of obesity or metabolic imbalance, including overweight status, adiposity, body fat distribution,

Table 2. Inclusion and exclusion criteria

Criteria type	Inclusion criteria	Exclusion criteria
Study characteristics	• Published between **2018-2025** • Peer-reviewed journal articles • English-language publications	• Non–peer reviewed sources (editorials, commentaries, letters, conference abstracts, theses) • Non-English publications • Full text not accessible
Study design	• Original *in-vitro* studies • *In-vivo* animal studies • Human epidemiological studies (cohort, cross-sectional, case-control) • Mechanistic reviews focused on phthalates and metabolic mechanisms	• Studies unrelated to metabolic or mechanistic endpoints (e.g., exposure-only studies) • High-dose industrial toxicology without environmental relevance
Exposure criteria	• Studies measuring phthalates or their metabolites (DEHP, MEHP, DBP, BBP, DINP, etc.) • Mixture studies where phthalate-specific effects are reported	• Studies examining only non-phthalate EDCs (e.g., BPA-only, PFAS-only) • Studies where phthalates are not the central exposure
Outcome criteria	• Obesity-related outcomes (obesity, overweight, BMI, adiposity, waist circumference) • Metabolic syndrome components (glucose, insulin, lipids) • Mechanistic endpoints: PPAR activation, adipogenesis, adipokines, oxidative stress, mitochondrial dysfunction, inflammation, hormonal disruption, epigenetic changes	• Studies evaluating outcomes unrelated to metabolism (e.g., reproductive toxicity only, neurotoxicity, carcinogenicity, ecotoxicology)
Relevance to review objective	• Explicit examination of phthalate-induced metabolic disruption or mechanistic pathways related to obesity	• Studies lacking metabolic outcomes or mechanistic relevance to adipogenesis or obesity

BMI, waist circumference, or metabolic syndrome items. Also, articles had to examine mechanistic outcomes that were directly related to phthalate-induced metabolic disruption, such as PPARα/PPARγ activation induction, adipogenesis induction, adipokine release, oxidative stress, mitochondrial damage, epigenetic alteration, inflammatory signaling, or hormonal imbalance. The inclusion criteria enabled the screening of literature that could provide information on a comprehensive picture of the phthalates as potential obesogens by giving emphasis on the literature that dealt with exposure and the mechanistic or metabolism outcomes. **Table 2** provides a summary of the exclusion and inclusion criteria that were applied specifically in this review by specifying the nature of the study, parameters of exposure, outcome parameters, and relevance criteria that were used in establishing eligibility.

Screening Process and PRISMA Flow

To ensure transparency, reproducibility, and methodological rigor, the screening process followed PRISMA 2020 standards. The searches conducted in PubMed, Scopus, Web of Science, and ScienceDirect yielded 1,330 records in total. After automated and manual duplicate removal, 972 unique records remained for title and abstract screening. At this stage, articles that were clearly unrelated to the review focus were excluded, including studies on non-phthalate endocrine-disrupting chemicals, studies focused only on cancer outcomes, and ecotoxicology or occupational safety studies without metabolic or mechanistic endpoints. After this initial screening step, 160 articles progressed to full-text assessment.

Articles of full-text were stringently evaluated based on the established inclusion and exclusion criteria. The causes of non-inclusion were systematically reported and categorized into no obesity or metabolic outcome, no mechanistic information related to metabolic disruption, use of non-phthalate, lack of exposure assessment or low quality of methodology. The total number of articles excluded because of the following reasons is 126.

Finally, 34 articles met all eligibility criteria and were included in the qualitative synthesis and mechanistic mapping, comprising 10 cellular or animal mechanistic studies providing molecular and physiological evidence for phthalate-induced adipogenesis and metabolic dysregulation, 14 review articles focusing on mechanistic, epigenetic, and obesogen-theory perspectives that comprehensively summarized endocrine-disrupting pathways and long-term metabolic programming, and 10 human epidemiological studies or meta-analyses reporting population-level associations with supporting mechanistic interpretations.

Data Extraction

A structured data-extraction strategy was used to ensure consistency, accuracy, and completeness in capturing all relevant information related to the mechanistic and metabolic focus of this review. A standardized extraction form was developed a priori on the basis of the review objectives and the major domains of mechanistic interest. Data from each included study were extracted independently by two reviewers, and any discrepancies were resolved through discussion and consensus or, where necessary, consultation with a third reviewer. This process strengthened methodological reliability and reduced the likelihood of subjective bias.

Bibliographic information for each included article, such as author, year of publication, and country, was recorded to contextualize temporal and geographical patterns in the evidence base. The extracted study-design information covered in-vitro cellular studies, in-vivo animal models, human observational studies, including cross-sectional, cohort, and case-control designs, and mechanistic review articles. Where relevant, additional details such as sample size, species or cell line, age group, and demographic characteristics were also documented to support cross-study comparison.

The extraction process also captured exposure-related characteristics, including the specific phthalate compound or metabolite under investigation, such as DEHP, MEHP, DBP, BBP, and DINP, the exposure level or dose, the duration and timing of exposure, and whether the study examined individual compounds or chemical mixtures. This level of detail was necessary for mapping dose-response patterns and for

distinguishing phthalate-specific effects from those driven by mixed exposures.

A central component of the review was the extraction of mechanistic outcomes, which were coded according to established pathways of metabolic disruption. These included nuclear receptor signaling, such as PPARα and PPARγ activation, adipogenic transcriptional changes, alterations in adipokine production, oxidative stress markers, mitochondrial dysfunction, inflammatory signaling pathways, hormonal perturbations, and epigenetic changes, including DNA methylation, histone modification, and microRNA regulation. This comprehensive mechanistic coding framework enabled a detailed synthesis of the converging biological pathways through which phthalates may exert obesogenic effects.

Obesity-related endpoints were also extracted in order to connect mechanistic findings with phenotypic outcomes. In cellular and animal studies, these outcomes included adipocyte differentiation, lipid accumulation, adipose-tissue hypertrophy, and related metabolic biomarkers. In human epidemiological studies, the extracted outcomes included BMI, waist circumference, body fat percentage, adiposity indices, and markers of metabolic syndrome such as glucose, insulin, triglycerides, and HDL-C. The combined extraction of mechanistic and phenotypic outcomes made it possible to synthesize evidence across models and link molecular alterations to observable metabolic effects.

Overall, this data-extraction approach enabled a robust and multidimensional characterization of the mechanistic pathways through which phthalate exposure may contribute to obesity and metabolic dysfunction.

Table 3 shows the final PRISMA data-extraction table for the 34 included studies.

Table 3. PRISMA extraction table of included studies (2018-2025)

No	Study	Study design	Population/model	Exposure (phthalates)	Key mechanistic findings
Cellular/animal mechanistic studies					
1	[12]	In-vitro	Human SGBS adipocytes	DEHP	↑ ROS, ↓ adiponectin, ↑ leptin; impaired lipid storage; adipocyte dysfunction
2	[13]	Human cohort + metabolomics	Children (China)	Urinary phthalates	Altered arginine–proline metabolism → metabolic dysregulation linked to obesity
3	[14]	Prospective birth cohort	Children (Greece)	Prenatal phthalates	Early-life endocrine disruption; changes in cardiometabolic markers
4	[15]	In-vitro adipogenesis assay	3T3-L1 adipocytes	Phthalates, BPA, parabens	↑ PPARγ, ↑ C/EBPα activation; enhanced adipogenesis without dexamethasone
5	[16]	Mechanistic review	-	Phthalates (general)	Phthalates promote adipocyte differentiation via PPARγ-mediated pathways
6	[17]	In-vivo subacute toxicity	Rats	Mixture: phthalates + BPA	↑ oxidative stress, adiposity, hormone disruption
7	[18]	In-vitro	Human SGBS adipocytes	DEHP	↑ NF-κB activation and inflammatory cytokines → adipose inflammation
8	[19]	In-vitro	Human adipose-derived stem cells	DEHP substitutes	Strong PPARγ agonism; accelerated human adipogenesis
9	[20]	Mechanistic review	-	Plasticizers incl. phthalates	Adipokine disruption; inflammation; adipose-mediated cardiometabolic risk
10	[21]	Toxicological mechanistic review	-	DEHP	Mitochondrial dysfunction, oxidative stress, apoptosis → lipid metabolism disorder
Mechanistic reviews–Hormones, epigenetics, PPAR, obesogen theory					
11	[1]	Review	-	Obesogens incl. phthalates	Obesogen framework; DOHaD; nuclear receptor disruption
12	[22]	Review	-	Phthalates	Thyroid, sex hormone disruption in early life
13	[3]	Mechanistic review	-	Phthalates	Direct activation of PPARα/γ, RXR; β-cell effects
14	[2]	Review	-	Obesogens	Stem-cell fate shift; microbiome; neuroendocrine disruption
15	[5]	Epigenetic review	-	Phthalates	DNA methylation, histone modifications, transgenerational programming
16	[23]	Mechanistic review	-	Obesogens	Adipogenesis models; nuclear receptor mechanisms
17	[4]	Review	-	Obesogens	PPARγ activation, energy balance, hypothalamus signaling
18	[24]	Review	Human health	Phthalates	Insulin resistance, metabolic disease pathways
19	[25]	Mechanistic review	Human	EDCs incl. phthalates	Oxidative stress, inflammation, receptor-mediated metabolic disruption
20	[26]	Scoping review	-	EDCs	Hormonal dysregulation, obesity prevention context
21	[27]	Review	-	Phthalates & BPA	Enhanced adipogenesis; adipokine disruption; metabolic interference
22	[28]	Experimental methods	Human PPAR assay	Phthalate monoesters	Confirms phthalate monoesters as strong PPARγ agonists
23	[29]	Epigenetic review	-	Phthalates	Organ-specific epigenetic alterations linked to metabolic outcomes
24	[30]	Review (pediatrics)	Children	EDCs incl. phthalates	Hormone disruption & epigenetic mechanisms → childhood obesity
Human epidemiology & meta-analyses with mechanistic discussion					
25	[6]	Systematic review & meta-analysis	Human	EDCs incl. phthalates	Links BMI/obesity with endocrine & adipogenic mechanisms
26	[31]	Review	Human (early-life)	Phthalates	Early-life endocrine/metabolic disruption → obesity

Table 3 (Continued). PRISMA extraction table of included studies (2018-2025)

No	Study	Study design	Population/model	Exposure (phthalates)	Key mechanistic findings
27	[9]	Review	Human	Phthalates & BPA	PPARγ activation, estrogen disruption, adipocyte changes
28	[7]	Longitudinal cohort	Midlife women (USA)	Urinary phthalates	Faster adiposity gain; metabolic pathway disruption
29	[8]	National survey	Children (Korea)	Phthalates & BPA	↑ BMI, ↑ waist; adipogenesis & endocrine disruption pathways
30	[10]	Meta-analysis	Children	Prenatal phthalates	Critical window programming; non-linear dose-response
31	[32]	Cohort study	Multi-racial children	Phthalates + substitutes	Phthalate substitutes also linked to adiposity; PPARγ mechanism
32	[33]	Systematic review	Adults & children	Phthalates	Metabolic syndrome pathways: adipokines, insulin resistance
33	[34]	Cross-sectional	Adults (China)	Phthalates + metals	Mixture effects; oxidative stress, endocrine disruption
34	[35]	Review	Children	Phthalates & EDCs	Early-life hormone & epigenetic pathway disruption

FINDINGS

Overview of Mechanistic Evidence (Cellular, Animal, and Human Studies)

Across the 34 included studies, available mechanistic evidence suggests that phthalates, particularly DEHP and its primary metabolite MEHP, interfere with a variety of metabolic pathways that control adipogenesis, endocrine signaling, lipid metabolism, and epigenetic programming. Notably, consistent in vitro evidence indicates that phthalates activate PPARγ and increase the expression of adipogenic transcription factors such as C/EBPα, thereby promoting lipid accumulation in human and murine adipocyte models [15, 19]. Similar findings from animal studies indicate increased adiposity, oxidative stress, and metabolic imbalance [17]. These mechanistic observations are supported by findings from human epidemiological studies. A number of cohort studies revealed that there were significant relationships between the urinary phthalate metabolites and BMI, waist circumference and body fat percentage among children and adults [7, 8]. Even though the claims of mixed or sex-specific effects of prenatal exposure are noted in some studies [10], mechanistic analyses indicate that the differences can be caused by non-monotonic dose-response relationships, sensitivity at developmental stages, and hormonal compensation [1, 2].

PPARγ Activation and Promotion of Adipogenesis

Activation of PPARγ is one of the most consistently reported mechanisms through which phthalates promote adipogenesis. Experimental evidence indicates that DEHP, MEHP, and several related compounds can activate adipogenic transcriptional programs, enhance lipid accumulation, and facilitate the differentiation of preadipocytes into mature adipocytes.

An apparent mechanistic theme in the studies reviewed is that phthalates, specifically, DEHP and its metabolite MEHP, can act as exogenous ligands of PPARγ, a master regulator of adipocyte differentiation. Both 3T3-L1 and human SGBS preadipocytes experiments in vitro regularly show that phthalate exposure promotes adipogenesis, lipid droplet deposition, and upregulation of adipogenic transcription factors, including PPARγ, C/EBPa, and SREBP-1c [15, 19]. These measurements are consistent with the theory of obesogen, due to which the cellular fate to adipocyte lineage commitment is re-directional with the use of environmental chemicals due to direct nuclear receptor activation [3]. Moreover, the phthalate alternatives (DEHT and DINCH) were demonstrated to activate PPARγ, which indicates that structural similarity between the plasticizer molecules might determine adipogenic similar potency [19]. Combined, all available evidence suggests that PPARγ-mediated adipogenic programming is a coordinated and repeatable process of phthalate-induced obesity.

Interference with Adipokine Release and Fatty Acid Storage

Beyond their role in promoting adipocyte differentiation, phthalates also influence adipokine secretion, thereby disrupting systemic energy homeostasis. It was shown that exposure to DEHP suppresses adiponectin, a key insulin-sensitizing hormone, while increasing leptin levels, a change that favors the development of leptin resistance associated with obesity [12]. These alterations in adipokine signaling contribute to metabolic inflexibility and impaired fatty acid storage, as DEHP-treated adipocytes exhibit abnormal triglyceride handling and increased lipolysis. Subsequent work by the same research group further reported DEHP-induced inflammatory signaling, including activation of NF-κB and enhanced cytokine release [18]. Such inflammatory responses not only compromise adipocyte function but also promote the spread of low-grade metabolic inflammation. All of these studies support the idea that, in combination with other factors, phthalates facilitate obesity by not only elevating the number of adipocytes but also reducing adipocyte endocrine capacity necessary to regulate the body to maintain metabolic homeostasis.

Oxidative Stress, Mitochondrial Impairment and Lipid Metabolism Disturbances

The other mechanistic theme relates to phthalate-induced oxidative stress and mitochondrial damage which in combination change the metabolic pathway of cells towards lipid accumulation. Rodent studies indicate that phthalates mixtures lead to the enhancement of reactive oxygen species, the establishment of lipid peroxidation, and the disruption of the mitochondrial membrane potential [17]. Such deficiencies diminish b-oxidation capability that stimulates lipid storage at the expense of fatty acid oxidation. Other reviews, including the one in [21] elaborate on how DEHP disrupts carnitine transportation, TCA cycles enzyme activity and part of the mitochondrial biogenesis, which leads to metabolic inefficiency. Transcriptionally speaking, redox-sensitive transcription factors are also triggered by oxidative stress and increase adipogenic gene expression, as oxidative imbalance is associated with increased adipocyte differentiation. This mechanistic model provides biologically plausible explanations for phthalate-induced lipid metabolism dysregulation and resultant obesity.

Hormonal Pathway Endocrine Disruption

Phthalates have far-ranging endocrine-disruptive impacts as well, affecting hormone signaling pathways with very

important roles in metabolic regulation. A number of those reviews note that phthalates disrupt thyroid hormones, glucocorticoids, estrogens, and androgens, all of which control energy expenditure, lipid storage, and glucose metabolism [2, 24]. As an example, phthalates may antagonize androgen receptors, disrupt signaling of thyroid hormones required to produce thermogenesis in the mitochondrion, and act in an estrogenic manner, which affects proliferation and fat localization of adipocytes. Also, the phthalates can trigger glucocorticoid receptor, increasing adipogenesis and central adiposity. The interactions between these multi-hormones help support the reason of non-monotonic dose-response relationships and sex-specific effects in phthalates, which are characteristics of endocrine-disrupting chemicals.

Epigenetic Remodeling and Developmental Resetting

Another emphasized mechanistic topic is epigenetic modifications caused by phthalate exposure especially in prenatal and early-life stages. As shown in [5, 29], phthalates have the ability to alter the pattern of DNA methylation, histone acetylation, and microRNA expression which are related to lipid metabolism, adipogenesis, and inflammatory processes. The changes still continue well beyond exposure and can also affect the risk of disease later in life, which is also in line with the developmental origins of health and disease (DOHaD) hypothesis. Gestational exposure to phthalates is associated with epidemiological evidence of decreased adiposity of children and changes in the methylation of metabolic genes [14]. The processes of epigenetic restructuring provide a strong argument to explain why childhood exposure results in permanent susceptibility to metabolic disorders and why they do not affect all sexes and stages.

Epidemiological Evidence on the Support of Mechanisms on Human Side

The mechanistic results are confirmed on the basis of human cohort and meta-analytic evidence. The research reports consistently indicate a correlation between urinary phthalate metabolites and elevated BMI, waist circumference, body fat percentage, and metabolic syndrome elements [6-8]. Notably, results of the SWAN study in adult years indicate that women who were exposed to elevated levels of phthalates during midlife accumulate fat at a faster rate, which points to the possibility of phthalate-induced disruption of metabolism continuing into adulthood [7]. On the contrary, alternative prenatal exposure outcomes indicate reduced BMI [10], which upheld the existence of non-monotonic dose responses, timing-sensitive impacts, and compensatory alterations. The epidemiological and mechanistic findings are consistent, which strengthens the overall inference and supports the classification of phthalates as credible obesogenic contributors.

Integrative Mechanistic Model

By integrating cellular models, animal toxicology studies, mechanistic reviews, and human epidemiological evidence, a multi-layered model emerges to explain how phthalates may contribute to obesity and broader metabolic dysfunction. Across these lines of evidence, phthalates appear to act through interacting mechanisms at the molecular, cellular, endocrine, and population levels.

During the initiation phase, phthalates such as DEHP, MEHP, DBP, and BBP interact with nuclear receptors, especially PPARγ, but also PPARα, glucocorticoid receptors, and thyroid hormone receptors, thereby activating adipogenic transcriptional programs and promoting the differentiation of preadipocytes into mature adipocytes [3, 12, 15]. Evidence from 3T3-L1 cells and human SGBS adipocyte models further indicates that DEHP and some of its substitutes can directly trigger adipogenic processes even in the absence of standard adipogenic cocktails [16, 19].

Phthalates also disrupt adipokine signaling by increasing leptin levels and decreasing adiponectin levels, while at the same time promoting chronic low-grade inflammation, oxidative stress, and mitochondrial dysfunction [17, 18]. Together, these disturbances impair fatty-acid oxidation, increase lipid accumulation, and create a cellular environment that favors obesogenic change [20, 21].

At the systemic level, phthalates disrupt several endocrine axes, including thyroid signaling, glucocorticoid regulation, and reproductive hormone pathways. These hormonal disturbances may reduce metabolic efficiency, impair glucose-insulin homeostasis, alter lipid metabolism, and thereby increase susceptibility to weight gain and metabolic syndrome [2, 24, 27]. In this way, endocrine disruption connects molecular events to organism-level metabolic outcomes.

Epigenetic programming provides a plausible mechanism linking early-life phthalate exposure with long-term metabolic vulnerability in adulthood. Prenatal and childhood exposures have been associated with changes in DNA methylation, histone modification, and microRNA regulation in adipogenic and metabolic genes [5, 22, 29]. These epigenetic alterations may reset metabolic set points and persist into later life, consistent with the DOHaD framework [1, 30].

Finally, these mechanistic disruptions are reflected at the population level. Many epidemiological studies report associations between phthalate metabolites and higher BMI, waist circumference, adiposity, or more rapid body-fat gain in both children and adults [6, 8, 14, 32]. Meta-analyses likewise suggest generally positive associations between phthalate exposure and obesity-related indices across populations, although the strength and consistency of those associations vary [10, 33, 34].

Taken together, this integrative mechanistic model suggests that phthalates may contribute to obesity through a synchronized cascade involving

(1) nuclear receptor activation,

(2) adipokine and inflammatory dysregulation,

(3) systemic hormonal disruption,

(4) epigenetic programming, and

(5) population-level increases in adiposity.

These intersecting pathways support the view that phthalates are important environmental contributors to the global obesity burden.

DISCUSSION

This systematic review indicates that phthalates exert obesogenic effects through multiple biological pathways that interact to promote adiposity, insulin resistance, and broader metabolic dysfunction. At the cellular level, phthalates and their metabolites consistently upregulate adipogenic transcription factors and increase lipid accumulation,

providing a strong molecular basis for their obesogenic potential [15, 19]. In particular, activation of PPARγ and C/EBPα appears to be one of the principal pathways through which phthalates promote adipocyte differentiation.

Beyond adipogenesis, phthalates also alter adipokine release and contribute to insulin resistance and chronic low-grade inflammation. These findings suggest that phthalates not only increase adipocyte number but also impair adipocyte function, thereby promoting wider metabolic dysregulation [12, 20].

One of the most important findings of this review is that several metabolic and endocrine pathways appear to be especially sensitive to early-life exposure, a pattern that is consistent with the DOHaD paradigm [1]. Epigenetic modifications induced during critical developmental windows may permanently alter metabolic trajectories and increase later-life vulnerability to obesity and related disorders [5, 29].

These findings are further supported by human cohort and cross-sectional evidence. Most studies report positive associations between urinary phthalate metabolites and adiposity-related measures [7, 8, 32]. At the same time, inconsistencies in some findings, particularly in prenatal exposure studies, highlight the complexity of exposure timing, sex-specific susceptibility, and the non-linear dose-response relationships often observed with endocrine-disrupting chemicals [10].

Overall, the convergence of mechanistic and epidemiological evidence strengthens the view of phthalates as environmental obesogens and supports continued regulatory efforts to reduce population exposure.

Practical and Population Health Ramifications

Through the accumulating mechanistic and epidemiological data on the obesogenicity of phthalates, there is escalating practical and public health consequences beyond the extensively studied reproductive toxicity. Risk assessment frameworks employed by regulatory agencies need to be enhanced with the expressions of risk factors by metabolic disruption, adipogenic activity, and endocrine-mediated processes since phthalates have been consistently demonstrated to trigger PPARγ, modify adipokine profiles, reduce mitochondrial activity, and trigger epigenetic alteration.

Particular attention should be given to vulnerable groups, especially pregnant women, infants, and children, because they are more susceptible to endocrine and epigenetic disruption during critical developmental stages, which may predispose them to metabolic disorders across the life course [30]. In addition, evidence that some common DEHP substitutes can produce adipogenic effects similar to those of DEHP through PPARγ-related pathways raises concern about regrettable substitution, whereby replacement chemicals may reproduce the metabolic toxicity of the compounds they are intended to replace [19, 28].

These findings support the need for a mechanism-informed chemical-substitution policy in which the metabolic and endocrine activity of alternative compounds is assessed before approval. From a clinical perspective, health professionals can also contribute to risk reduction by advising patients on practical ways to lower phthalate exposure, such as limiting the use of soft PVC products, reducing contact with plastic food packaging, choosing phthalate-free personal-care products, and avoiding the heating of food in plastic containers. Collectively, these regulatory, clinical, and public health strategies are important for reducing environmental contributions to obesity and metabolic disease at the population level.

Research Gaps

Although substantial progress has been made in understanding the obesogenic activity of phthalates, several important research gaps remain. First, most existing studies examine single phthalates, even though humans are exposed to complex mixtures of chemicals throughout life. Future research should therefore investigate combined exposures involving phthalates, metals, bisphenols, and other environmental pollutants in order to better capture real-world immunometabolic interactions.

Second, mechanistic biomarkers such as metabolomic, transcriptomic, and epigenomic signatures are still not commonly incorporated into human cohort studies, even though they are important for linking exposure to early biological change and downstream metabolic effects. Third, much mechanistic research continues to rely on comparatively high-dose exposure models, despite evidence of non-monotonic dose-response relationships for phthalates. This highlights the need for more studies using low-dose, chronic, and human-relevant exposure conditions.

Fourth, despite growing regulatory pressure and the increasing use of purportedly safer plasticizers, emerging evidence suggests that several replacements, such as DINCH and ATBC, may retain similar PPARγ-mediated adipogenic or endocrine-disrupting properties. Systematic mechanistic testing of substitute compounds therefore warrants priority attention.

Finally, more research is needed on sex-specific and developmental vulnerability. Experimental and epidemiological evidence suggests that hormonal regulation, critical exposure windows, and early-life epigenetic programming may lead to substantial variation in metabolic outcomes across sex and developmental stage. Addressing these gaps would strengthen mechanistic understanding and improve the accuracy of phthalate-related metabolic risk assessment.

CONCLUSION

This review synthesizes substantial evidence suggesting that phthalates may act as environmental obesogens through multiple convergent mechanisms, including PPARγ-mediated adipogenesis, endocrine disruption, persistent inflammation, mitochondrial impairment, and epigenetic programming. Evidence from cellular and animal studies is broadly consistent with human epidemiological findings showing associations with increased adiposity and metabolic dysfunction.

Given the widespread human exposure to phthalates, these findings underscore the need for mechanism-informed regulation, careful evaluation of substitute compounds, and strategies to reduce exposure at the population level. A clearer understanding of these pathways can help guide more effective responses to environmental contributors to the global obesity epidemic.

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