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REVIEW

Obesity and obesity related disease in adulthood: the dark side of early life exposure to Environmental Chemical Disruptors

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Abstract

Purpose The present review aims to summarize and collect data in support of the obesogenic theory to broaden knowledge regarding the intriguing relationship between exposure to environmental chemical disruptors (EDCs), obesity and obesity related diseases.

Methods A comprehensive search of the literature from 1990 to 2024 was performed in Pubmed using the word endocrine disruptor chemicals or obesogens and: adipose tissue, metabolic diseases, weight gain, gut microbiota.

Results In the past, genetic factors, an unbalanced diet and a sedentary lifestyle were considered the only risk factors for obesity development. On the other hand, recent studies described the obesogenic theory, suggesting that an interaction between exposure to EDCs with obesogenic activity, especially during early life development, and the endocrine system can play a key role in the greater susceptibility to the onset of obesity, not even excluding the involvement of the gut microbiota and its alterations.

Conclusions Data collected show that there is a close link between environmental exposure to EDCs during early life of development and the onset of obesity and related dysmetabolic diseases that may occur later in life.

Keywords Obesity · Obesogens · EDCs · Adipose tissue · BAT

Introduction

Obesity is a significant global public health problem. It is a chronic, relapsing disease that acts as a trigger for a wide range of other non-communicable diseases, such as diabetes, cardiovascular disease, metabolic syndrome, cancer, and infertility. Commonly, obesity is defined by a body mass index greater than 30 kg/m^2 [1, 2]. However, using BMI as the unique parameter for diagnosing obesity does not reflect the full impact of excess fat on health, limiting our understanding of the disease's pathophysiology. In 2017, the American Association of Clinical Endocrinology introduced a new diagnostic term,"adiposity-based chronic disease"(ABCD), to better describe the chronic nature of obesity and the adiposity underlying its complications, which contribute to morbidity and mortality [3]. This condition, known as adiposopathy, predisposes individuals to obesity-related comorbidities. It is now well known that adipose tissue is not only composed of adipocytes but also contains endothelial cells, fibroblasts, pericytes, preadipocytes, and various immune cells. All these cell types contribute to the secretory function of adipose tissue, making it a true adipose organ with endocrine, autocrine and paracrine actions [4]. The main molecules secreted by adipose tissue are adipokines. These molecules play a key role in regulating inflammation, food intake, body weight, insulin sensitivity, redox balance, energy metabolism, immune responses, and the reproductive axis. Adipokines also influence the cardiovascular system and certain brain functions related to mood, the reward system and eating behaviour. Disruptions in these mechanisms are linked to the development of obesity-related diseases, including diabetes, hypertension, atherosclerosis, fatty liver disease, dementia, obstructive sleep apnea, and certain cancers. [5]

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As obesity is a multifactorial chronic disease, several studies support the"obesogenic theory". This theory suggests that the rapid increase in obesity prevalence worldwide is not solely due to genetic or lifestyle factors such as poor diet, aging, and sedentary behaviour, but also to exposure to synthetic chemicals with xenobiotic activity [6].

Among these xenobiotics, the so-called obesogens are Endocrine Disrupting Chemicals (EDCs). These are defined as "exogenous chemicals or mixtures of chemicals capable of altering the functions of the endocrine system, causing adverse health effects in an intact organism, offspring, or population"[7].

Methods

A thorough literature search was performed on PubMed (accessing the MEDLINE database) for articles in English, published between 1990 and 2024. The search incorporated a combination of Medical Subject Headings (MeSH) terms and relevant keywords. Using PubMed's search builder, the search was structured with the following MeSH terms: ("Endocrine Disruptor Chemicals"OR"Obesogens") AND ("Adipose Tissue") AND ("Metabolic Diseases") AND ("Weight Gain") AND ("Gut Microbiota"). The MeSH term "Endocrine Disruptor Chemicals" was not explored, meaning only the specific term was used without including broader categories. Other MeSH terms were explored to include subcategories and relevant studies. Additionally, the keywords "obesogens", "adipogenesis" and "metabolic dysfunction" were used to identify relevant studies.

Non-English articles, conference papers, abstracts, and publications that overlapped with others were excluded. Only original studies, including randomized and non-randomized clinical trials, prospective and retrospective cohort studies, case–control studies, and review articles that focused on the effects of endocrine disruptors, obesogens, and environmental chemicals on adiposity, metabolic diseases, and obesity were included in the review. Additional articles referenced within the selected studies were also reviewed to include critical research that may have been overlooked in the initial search.

Endocrine Disruptors Chemicals (EDCs)

EDCs include a wide variety of substances such as synthetic drugs, estrogens, phytoestrogens, herbicides, pesticides, phenols, dioxins, and phthalates. These compounds are commonly found in commercial products like plasticizers, food care items, and food packaging materials [8, 9].

These man-made chemicals can interfere with the endocrine system in several ways. They may act as receptor agonists or antagonists, or interfere with hormone synthesis, release, transport, metabolism, and excretion [10]. Due to the lipophilic nature of many EDCs, these compounds are able to diffuse across cell membranes and exert their activity by interacting with nuclear hormone receptors. However, not all EDCs are lipophilic. Depending on their chemical properties and solubility, some act through alternative pathways. For instance, they may bind to membrane receptors, non-steroid receptors, or orphan receptors [8, 11]. EDCs can influence gene expression through epigenetic mechanisms, explaining the link between exposure during development and adverse effects in adulthood [12, 13]. A notable example is the development of uterine fibroids (UFs), hormonally responsive tumors affecting many women during their reproductive years. Early-life exposure to EDCs like diethylstilbestrol (DES) and bisphenol A (BPA) can reprogram the epigenome of myometrial stem cells (MSCs), leading to long-term changes in gene expression. These include alterations in DNA methylation and histone marks at estrogen-responsive genes, creating a pro-fibroid molecular environment [12]. Similarly, in males, prenatal exposure to EDCs like phthalates, especially DEHP, has been linked to reproductive disorders such as cryptorchidism, hypospadias, and declining fertility. Animal studies show that DEHP disrupts testosterone synthesis and testicular structure by downregulating connexin 43 (CX43), a key protein for steroidogenesis and cell communication. Additionally, DEHP may exert epigenetic effects on developing testicular cells, modifying DNA methylation and histone marks in genes regulating cell integrity and hormone production. These epigenetic changes during sensitive developmental windows could lead to long-term dysfunction and reduced fertility, paralleling mechanisms observed in female reproductive disorders. This underscores the importance of incorporating epigenetic endpoints into risk assessment strategies for EDCs [13].

The classic toxicological principle "The dose makes the poison" formulated by Paracelsus, does not apply to EDCs. For these substances, it is often impossible to identify a clear threshold dose. EDCs can act like endogenous hormones, exhibiting non-linear and non-monotonic dose–response relationships [14]. In addition, EDCs show the so-called"cocktail effect"whereby combined exposure to different substances can cause additive, synergistic, or antagonistic effects [15]. EDCs are also persistent in the environment and tend to bioaccumulate and biomagnify through the food chain during production, use, and disposal [16]. The main exposure source in humans is diet, through the intake of contaminated water and food, even though exposure can also occur through air and particle inhalation

and transdermal absorption [17–19]. Details regarding classification, source of human exposure and bioaccumulation of EDCs, are shown in Table 1.

Exposure during fetal and neonatal periods, through the placenta or breast milk, can increase susceptibility to dysfunctions that may only appear in adulthood [11, 12, 32].

Several studies related to EDCs focused especially on the effects of these substances on males [13, 33–35] and females [36, 37] reproductive systems. However, EDCs can also disrupt other endocrine pathways, including the hypothalamic-pituitary-thyroid (HPT) axis [38, 39] and the hypothalamic–pituitary–adrenal gland (HPA) axis [40, 41].

An increasing number of studies suggest that various EDCs promote adipogenesis. They do so by enhancing lipid accumulation and altering energy balance. These substances may also disrupt hormonal control of the hunger-satiety circuit, promoting food conservation [42, 43]. Additionally, EDCs interfere with insulin sensitivity and glucose metabolism [43], contributing to the development of obesity and related diseases [44, 45] (Fig. 1).

Table 1 Classification, source of human exposure and bioaccumulation of EDCs

Chemical name	Restricted/Banned	Class of EDC	Sources of exposure	Bioaccumulation target	References
BPA	Restricted In the European Union, Canada and some states in the United States, restrictions have been implemented on the use of BPA in products for children, such as baby bottles and toys	Residential– Plasticizer	Industrial chemicals used for plastic and resin. BPA is used in the production of plastics intended to direct contact with food (plastic packaging, kitchenware and in inner coatings of cans and jar cap)	Tissues of several different aquatic species from marine and freshwater systems	[20] [21] [22]
DDT and its metabolites DDE	Banned	Synthetic agricultural Pesticide	Historic agricultural use, environmental contamination	Apex aquatic predator	[23]
Dioxins—TCDD	Restricted in food/environment	Synthetic industrial	Incineration of chemical manufacturing, pesticide manufacturing	Contaminated fish (tissues of predatory and bottom feeding species of fish)	[24]
DES	Restricted	Non-steroidal synthetic estrogen	Contaminated fish	Aquatic organisms and sediments	[25]
Parabens	Restricted Only the European Union (EU) has restricted the use of several parabens in cosmetics and food products	Cosmetics, food and pharmaceutical additive	Pharmaceuticals and personal care products	Tissues of marine and freshwater specimens	[26]
PFAS (PFOA and PFOS)	Restricted	Chemicals	Contaminated food and water, electrical wiring, lining of food wrappers	Tissues of seafood and other animal products	[27]
Phytoestrogens (Genistein and Daidzein)	Restricted in the European Union (EU)	Natural	Fish fed with soybean and its derivatives	Tissues of seafood and other animal products	[28]
PCBs	Banned	Synthetic industrial	Electrical and hydraulic equipment and construction materials	Fat tissues, meat, liver, milk and eggs of farm animals	[29] [30]
TBT	Banned	Agricultural pesticide– Organotin	Chemical used in antifouling paints for ship and boat hulls and as a wood preservative	In all aquatic taxa, especially in molluscs	[31]

Bisphenol A (BPA); Dichlorodiphenyltrichloroethane (DDT); Dichlorodiphenyldichloroethylene (DDE); 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD); Diethylstilbestrol (DES); Perfluoroalkyl substances (PFAS); Perfluorooctanoic acid (PFOA); Perfluorooctanesulfonates (PFOS); Polychlorinated biphenyls (PCBs); Tributyltin (TBT)

EDCs and adipogenesis

The endocrine system plays a central role in regulating fat, carbohydrate, and protein metabolism, ensuring energy balance. Any disruption in hormonal control can therefore promote fat accumulation and lead to obesity [43, 46].

EDCs with obesogenic activity alter lipid homeostasis and promote adipogenesis through various mechanisms. These include increasing the number and size of adipocytes and interfering with endocrine pathways that regulate adipose tissue development [43].

Exposure to endocrine-disrupting chemicals (EDCs) during early developmental stages either in utero or shortly after birth has been implicated in the increase of adipocyte numbers, a condition referred to as hyperplasia. In contrast, exposure during adulthood is more commonly associated with adipocyte hypertrophy, or an increase in cell size [47].

Recent evidence suggests that adipocyte numbers are established by late childhood and any increase in adipocyte numbers during early life becomes permanent and irreversible [47]. This supports the theory that exposure to EDCs or other environmental stressors during susceptibility window of development may lead to long-lasting alterations in adipose tissue architecture and function, thereby predisposing individuals to increased risk of obesity and related metabolic disorders in adulthood [48].

Prenatal exposure to persistent organic pollutants (POPs), such as the insecticide dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE) and to bisphenol A (BPA) has been associated with increased body weight in children. Notably, these effects appear to be more pronounced at lower doses, consistent with the non-monotonic dose–response relationships that characterize many EDCs [14, 49–51]. Furthermore, accumulating evidence suggests that the obesogenic effects of certain EDCs may extend across generations, even in the absence of continued exposure. For example, several studies showed that in utero exposure to EDCs with obesogenic activity such as TBT and the fungicide triflumizole can interfere with adipose cell recruitment and differentiation. In the offspring, mesenchymal stem cells (MSCs) are more likely to differentiate into adipocytes and exhibit epigenetic changes, particularly altered DNA methylation patterns in genes involved in adipogenesis [52, 53]. Besides, some transgenerational studies demonstrated that pregnant mice exposed to tributyltin (TBT) produce offspring with increased fat deposits. Remarkably, this phenotype can persist through at least the third generation (F3) in the absence of further exposure [54]. Similar data was also observed following exposure to BPA, phthalates, and DDT [55, 56].

Animal studies have further implicated diethylstilbestrol (DES) exposure during prenatal or perinatal periods in long-term increases in body weight and fat mass. These effects are likely mediated through alterations in the genetic programming that regulates adipocyte development and distribution [57].

From a molecular perspective, obesogens can act by interfering with nuclear transcriptional regulators that control lipid flux and adipocyte proliferation/differentiation, such

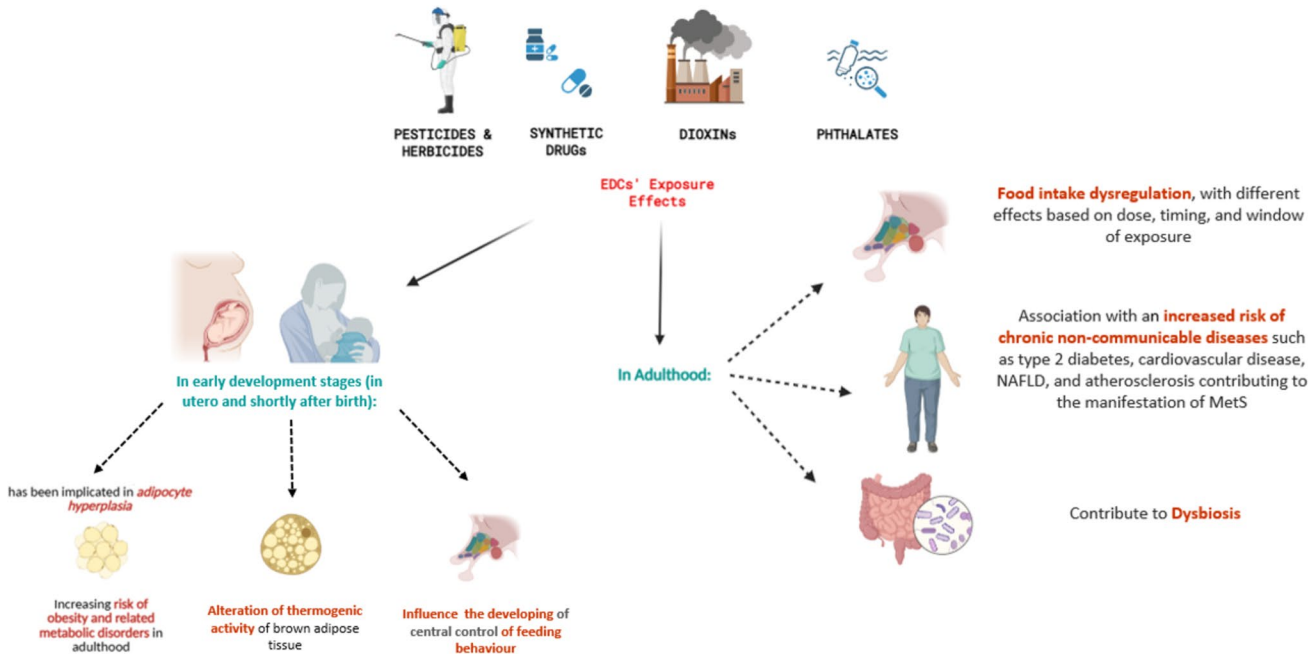

Fig. 1 Schematic overview of endpoints of obesity and obesity related diseases affected by Endocrine Disrupting Chemicals (EDCs). The picture has been created with Biorender

as peroxisomal proliferator-activated receptors (PPARα, PPAR-δ, and PPAR-γ) and steroid hormone receptors [45].

PPAR receptors dimerize with retinoic acid X receptor (RXR), and, activation of RXR-PPARγ can promote differentiation of adipocyte progenitors and preadipocytes in adipose tissue and regulate lipid biosynthesis and storage [58]. Conversely, the RXR–PPARα complex plays a role in fatty acid oxidation and lipid catabolism [59].

These receptors can bind a wide range of unsaturated fatty acids by acting as lipid sensors to regulate lipid homeostasis. PPARγ has been defined as the major regulator of adipose cell development for its regulatory activity on adipogenesis [60]; several EDCs alter adipogenesis through interference with PPARγ [48].

In vitro experiments using 3 T3-L1 fibroblasts have demonstrated that exposure to compounds such as TBT, BPA, nonylphenol, phthalates (especially their metabolites), and parabens can promote adipocyte differentiation via PPARγ activation [52, 53, 61–63]. Similarly, murine models have shown that phthalate metabolites enhance adipogenesis by upregulating PPARγ expression during critical windows of adipocyte differentiation [64].

Steroid hormones can also influence lipid storage and fat deposition and impact adipose tissue development [65]. For instance, estrogen replacement therapy has been associated with a protective effect against age-related adipose redistribution in postmenopausal women [66]. Likewise, phytoestrogens such as genistein and daidzein, found in soy, exert estrogen-like activity by modulating the estrogen receptor pathway [67].

Certain EDCs may stimulate endogenous estrogen synthesis. Notably, adipose tissue itself is an important site of estrogen production, as adipocytes express the aromatase enzyme responsible for converting testosterone into estrogen. Environmental obesogens that alter intracellular aromatase activity may consequently elevate estrogen levels within adipocytes, potentially promoting fat accumulation in both sexes [68, 69].

Moreover, EDCs may also interfere with the aryl hydrocarbon receptor (AhR), able to indirectly influence adipogenesis by altering PPARγ expression [70, 71]. Epidemiological studies have highlighted the obesogenic potential of polychlorinated biphenyls (PCBs), a group of persistent organic pollutants with dioxin-like activity, particularly when exposure occurs during fetal development. PCBs are also known to activate AhR, thereby mediating their effects on adipose tissue and neurodevelopment [49, 72, 73].

EDCs and brown adipose tissue

Adipose tissue represents the main site of accumulation of fat-soluble environmental pollutants [74] and, therefore, may be a target for various xenobiotic substances' action.

Several studies, indeed, investigated the potential influence of environmental pollutants on energy homeostasis and the development of obesity through the alteration of the thermogenic activity of brown adipose tissue (BAT) [75].

White adipose tissue (WAT) characterized by unilocular white adipocytes represents a site of energy storage and contributes to the regulation of energy balance by releasing special adipokines [76]; on the other hand, BAT is characterized by multilocular brown adipocytes and is involved in the activation of thermogenesis due to the presence of uncoupling protein 1 (UCP1), localized in the mitochondria, important to increase energy expenditure [77, 78] and reducing lipid accumulation in the WAT, counteracting the development of obesity and dysmetabolic diseases [79–83].

The contribution of BAT on thermogenesis seems to decrease with age [84]; on the contrary, "beige" fat, also known as "brown-like inducible adipocytes", differs after birth from white adipocytes in response to environmental stimuli (e.g., temperature) and endocrine metabolic regulators such as thyroid hormones, adipokines, and cytokines. Although the two distinct types of thermogenic adipose tissue have different developmental origins, brown and beige adipocytes have important shared properties such as the expression of UCP1 [85].

The energy expenditure that results from thermogenesis in brown and beige cells can prevent hypothermia and metabolize excess lipids [86], therefore, both BAT and beige fat appear to have anti-obesity properties. Loss of BAT ("bleaching"), indeed, and reduced ability to induce aging are associated with aging, obesity, and poor overall metabolic responses [84].

Considering the role of BAT in thermoregulation, in which mitochondria participate extensively, several studies evaluated the involvement of different environmental factors on the metabolic pathways of mitochondrial biogenesis in which peroxisome proliferator gamma coactivator 1 (PGC1α) as well as the mechanisms of regulation of expression and activity of UCP1, are involved [84]. In particular, these pathways are highly regulated by several transcriptional factors, including PPAR and the receptor for thyroid hormones [87]; as EDCs are capable of interfering with altering hormone signaling even downstream of the secreting gland, they could mediate changes in brown fat lipid stores and utilization [88].

For example, prenatal exposure to DDT and its major metabolite DDE is associated with impaired BAT activity [89] due to reduced expression of factors involved in

thermogenesis, functional alteration of mitochondria, and downregulation of iodothyronine deiodinase type 2 (Dio2), which encodes for the enzyme that locally activates thyroid hormones through deiodination of T4 to T3, primarily involved in stimulating thermogenesis.

An in vivo study using Wistar rats showed that chronic exposure to DDE mimics most of the effects induced by a high-fat diet (HFD) on BAT and exacerbates the increase in lipid droplet size when administered together with an HFD. Considering the known role of oxidative stress in altering BAT function, it may underlie the ability of DDE and HFD to induce similar metabolic adaptations in BAT, resulting in reduced tissue thermogenesis, which may predispose to energy homeostasis disorders [90].

Furthermore, several studies have also demonstrated the bi-functional effect of these molecules at the subcellular level. In particular, DDT and DDE can negatively affect the functionality of mitochondrial transport chain complexes, resulting in reduced membrane potential and levels of ATP produced [91]. On the other hand, a recent study showed that DDT can induce adipogenic differentiation in vitro, through the activation of genes that can lead to the accumulation of lipids in adipose tissue, and on the other hand determine its protection from oxidation through increased levels of perilipin 1, promoting the obesogenic effect of the contaminant [92]. The effect of DDT/DDE and other obesogenic xenobiotics on BAT may also be mediated by the AhR receptor [93].

Shabalina et al. [94, 95], showed that treatment of mice with perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) results in a reduction in body weight and WAT mass due to upregulation of UCP1 protein and increased oxidative capacity of BAT mitochondria. These effects are probably due to the resulting acute increase in heat production, which would cause the rats to stop eating prematurely [94].

Furthermore, exposure to 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) belonging to the POPs family, seems to be associated with the development of a"wasting syndrome", probably similar to cachexia, which consists of a progressive loss of adipose tissue and reduction in body weight [96, 97]; similar results were also observed in several species exposed to dioxins [98].

The effects of other environmental contaminants such as phthalates and BPA on BAT, however, need to be investigated yet [99].

EDCs and hunger satiety circuit

The hypothalamus plays a crucial role in controlling food intake and energy status through two antagonistic neuronal populations of the hypothalamic arcuate nucleus (ARC): orexigenic (appetite-stimulating) neurons, characterized by co-expression of agouti-related peptide (AgRP) and neuropeptide Y (NPY), and anorexigenic (appetite-suppressor) neurons co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcription (CART) [100–103]. These ARC neurons project to several hypothalamic nuclei, including the ventromedial hypothalamic nucleus (VMH) and, most notably, the paraventricular nucleus (PVN) which behaves as a critical integrative hub for metabolic regulation. The PVN receives and processes both orexigenic and anorexigenic signals from the ARC and orchestrates the regulation of food intake and energy expenditure by modulating the outputs of neuroendocrine and autonomic nervous system pathways [104].

These systems are sensitive not only to peripheral peptide hormones like leptin, insulin and ghrelin [105], glucagon-like peptide-1 (GLP-1), peptide YY and glucagon [106, 107] but also to sexual and thyroid hormones as well as growth factors which can modulate hypothalamic circuits regulating appetite, satiety and metabolism [108].

Several studies have reported that environmental obesogens can alter food intake, with different effects based on dose, timing, and window of exposure [109–111] As a matter of fact, EDC exposure during early life is a critical window of exposure as the central control of feeding behaviour develops in utero and neonatally [112, 113].

Phytoestrogens as daidzein and genistein, represent an important source of EDCs and it has been reported that high phytoestrogen levels in male mice throughout embryonal and postnatal life decrease AgRP and increase the expression of genes coding for the appetite-modifying peptide as MCH and orexin A, but it has no effect on NPY, POMC, and CART expression [114].

Mice perinatally exposed to BPA from gestational day (GD) 0 to Post Natal Day (PND) 21 in combination with high-fat diet had a sexually dimorphic effect on hypothalamic circuits: in males, BPA impairs glucose tolerance, reduces POMC fiber innervation in the PVN and, in combination with HFD, increases NPY and AgRP expression in the ARC; instead in females, it induces weight gain and increase food intake, adiposity, and leptin blood levels, while in combination with HFD reduces POMC mRNA expression in the ARC [110].

Both phytoestrogens and BPA share a common xenoestrogenic activity, therefore it is possible that they may exert their action altering the estrogens' action on metabolism regulation [115, 116].

In addition, exposure to BPA, both in vitro and in vivo, is associated with increased leptin levels [117, 118] and in a similar way mice neonatally exposed to methylparaben increase serum leptin levels while exposure to diethylhexyl phthalate increases leptin and decreases adiponectin levels [119, 120], as occurs during hyperplasia and hypertrophy of adipose tissue. It is still certainly not clear whether this effect on adipokines levels is directly determined or is a consequence of the obesogenic effect of these substances, through the mechanisms explained above. Either way, by interfering with adipokine secretion, obesogens may affect the hormonal control of hunger and satiety [121].

Furthermore, BPA exposure in early life in rats may also influence the function of the hypothalamus altering both presynaptic and postsynaptic signaling pathways, promoting addictive and compulsive behaviour resulting in overeating and subsequent obesity [122].

Similarly to the estrogenic ginestein and BPA, gender-specific effects have also been observed following chronic exposure of rats to the androgen agonist TBT; indeed, in females TBT exposure increased significantly NPY expression and food intake, while males showed a decrease of AgRP and CART and appetite [123].

EDCs and obesity related diseases

Exposure to EDCs is also associated with an increased risk of chronic non-communicable diseases such as type 2 diabetes, cardiovascular disease, non-alcoholic fatty liver (NAFLD), and atherosclerosis contributing to the manifestation of metabolic syndrome (MetS) [124].

Metabolic syndrome is characterized by abdominal obesity, glucose intolerance, dyslipidemia, increased triglycerides and reduced high-density lipoprotein (HDL) levels, hypertension, endothelial dysfunctions, and atherogenesis [125].

Low-grade chronic inflammation (LGCI) may be considered responsible for the establishment of the metabolic syndrome [126]; the increased levels of Tumor Necrosis Factor-α (TNF-α), indeed, occurring in obesity when combined with redoubt adiponectin expression, trigger the activation of nuclear factor kappa-light-chain-enhancer of activated B (NFκB) which in turn enhances reactive oxygen species (ROS) adhesion molecules and chemokines and cytokines expression resulting in excess glucose, free-fatty acids and disable insulin sensitivity [108].

Multiple molecular patterns are involved in EDCs interference with the onset of obesogenic and metabolic events.

DES-exposed mice during early life present alterations in glucose metabolism with a high prevalence of pancreatic beta cell hyperplasia and high levels of leptin and proinflammatory cytokines, suggesting that these could represent early markers of the development of metabolic syndrome and obesity-related diseases later in life [57].

Similarly, females perinatally exposed to phthalates such as diethyl hexyl phthalate or BPA exhibit hyperglycemia and increased inflammation of the pancreatic Langerhans islets and thus increased type 2 diabetes prevalence [127, 128].

BPA exposure is involved in the pathogenesis of various metabolic disorders such as insulin resistance, hepatotoxicity, disruption of pancreatic beta cells, and obesity [129].

In vitro studies on both 3T3-L1 and human adipose stromal cells treated with BPA, revealed an increased triglyceride content together with an increased release of proinflammatory cytokines by the activation of the NFκB pathway [130]; indeed, BPA treatment on rat hepatoma cell line increased triglyceride content and lipid accumulation [131].

A study conducted in Seveso, Italy, investigated the relationship between serum concentration of TCDD and the prevalence of diabetes, metabolic syndrome and obesity among women exposed during childhood following the 1976 industrial explosion. The results indicated a significant association between TCDD exposure and metabolic syndrome specifically among women who were 12 years old or younger at the time of explosion [132]. A subsequent study explored the impact of prenatal TCDD exposure on cardiometabolic risk in 611 offspring, aged 2 to 39 years, born to women affected by the same incident. The findings revealed sex-specific associations: a tenfold increase in maternal TCDD levels was significantly associated with a lower body mass index in daughters, while sons exhibited an increased risk of developing metabolic syndrome. These results suggest that prenatal TCDD exposure may have differential effects on cardiometabolic health outcomes based on sex [133]. In addition to dioxins, exposure to other persistent organic pollutants such as PCBs and Perfluoroalkyl substances (PFASs) are associated with the development of metabolic syndrome. Specifically, PCBs influence insulin-stimulated glucose uptake by an increase in both insulin receptor substrate-1 (IRS1) and glucose transporter type 4 (GLUT-4) and affect lipid metabolism due to their accumulation in adipose tissue [134]. Furthermore, a linear relationship between blood PCB concentration and waist circumference in non-diabetic adults with metabolic syndrome has been reported in a cross-sectional study [135, 136]. In addition, in utero exposure to PCBs can contribute to the development of metabolic syndrome, glucose intolerance, dyslipidemia and other obesity-related metabolic diseases in postnatal life [137]. Specifically, maternal exposure to PCBs was associated with childhood obesity with a more pronounced obesity in girls than in boys, indicating a clear gender difference [137]. Likewise, recent investigations

reported a close association between PFAS prenatally exposure and childhood obesity [138, 139]. Moreover, PFASs were associated with higher cholesterol in pregnant women which in turn is associated with a major risk of preeclampsia [140]. Two recent cross-sectional studies conducted in the Veneto Region of Italy investigated the health effects of PFAS in young adults aged 20–39 years who had been highly exposed to PFAS through contaminated drinking water prior to 2013. The first study assessed the association between serum PFAS levels and the prevalence of MetS. Among the 15,876 participants, 8.1% met the criteria for MetS, with specific PFAS positively associated with individual MetS components, particularly elevated blood pressure and triglyceride levels [141]. The second study focused on liver function, evaluating associations between PFAS serum concentration and hepatic biomarkers. Results indicated significant correlations between higher PFAS levels and altered liver function parameters, highlighting potential hepatotoxic effects of PFAS exposure in this population [142]. In addition to these findings, studies have shown that both PFOA and PFOS have been detected in thyroid tissue of patients undergoing thyroidectomy for various thyroid diseases [143]. Epidemiological research suggests an association between exposure to PFAS and alterations in thyroid function, including reduced circulating thyroid hormone levels, mainly due to an increase in the metabolic clearance rate of these hormones [144]. Furthermore, in vitro studies have shown that exposure of thyroid cells to high concentrations of PFOA and PFOS (up to 10^5 nM) can significantly inhibit cell proliferation, primarily due to increased cell death [145]. Collectively, these findings underscore the complexity of PFAS exposure outcomes, highlighting not only the impact on metabolic and liver functions but also potential disruptions in thyroid health. This further emphasizes the need for additional research to better understand the mechanisms by which these xenobiotics affect endocrine functions and to assess the potential long-term health risks associated with PFAS exposure.

Furthermore, maternal exposure to environmental chemicals appears to be a significant pathogenic link in developmental renal disease and hypertension. Numerous studies have shown that renal disease and hypertension have a bidirectional relationship, where chronic kidney disease (CKD) being a complication of uncontrolled hypertension and hypertension is a frequent finding in renal disease [146, 147]; in addition, both renal disease and hypertension may have their origins in early childhood. Maternal insults including exposure to environmental chemicals such as dioxins, BPA, phthalates, and PFAS may induce renal programming, resulting in renal disease and hypertension in later life [147]. However, the long-term adverse effects on offspring from maternal exposure to environmental chemicals during pregnancy are still unclear, also because limited environmental chemicals have been evaluated in humans and animal models of renal disease and hypertension.

EDCs and microbiota

Intestinal eubiosis is essential for maintaining the integrity of the intestinal barrier, preventing intestinal permeability, a condition associated with the permeation of antigens, endotoxins, and pathogens and altered production of neurotransmitters and metabolites that induce chronic low-grade inflammation resulting in the development of several diseases. Maternal microbiota is essential in the development of healthy microbiota in the newborn, providing prevention towards non-communicable diseases (NCDs) [148].

Several studies have shown that the composition and diversity of the gut microbiota can be influenced by exposure to endocrine disruptors, which contribute to dysbiosis. Dysbiosis is associated with several disorders, including obesity, metabolic syndrome, acute and chronic kidney disease, and inflammatory bowel disease; in particular, dysbiosis induced by exposure to endocrine disruptors can contribute to increased intestinal permeability causing systemic inflammation and further endocrine imbalances [149, 150].

Javurek et al. studied changes in gut microbiota in parents and their pups in a model of California mice (*Peromyscus californicus*) exposed to BPA (50 mg/kg food weight) from periconceptional to weaning. Their data demonstrated that parental exposure to environmentally relevant BPA concentrations induced changes in the microbiota with an increase in *Akkermansia, Mollicutes, Prevotellaceae, Bacteroides, Erysipelotrichaceae, Methanobrevibacter, Sutterella* also in unexposed offspring [151]. Studies in the literature showed an association between these species and obesity and metabolic disorders [152].

Similarly, in a longitudinal study, it has been observed that perinatal exposure of C3H/HeN mice at 50 µg/kg bw/day BPA induced dysbiosis and immune system alteration postnatally resulting in glucose intolerance and reduction of *Bifidobacteria* in the feces [153].

In a non-obese diabetic (NOD) mouse model, Xu et al. evaluated the effects of BPA exposure on the development of type 1 diabetes and the involvement of the host immune system and gut microbiota. Specifically, male and female NOD mice were orally exposed to BPA, at previously evaluated environmentally relevant doses (30 or 300 µg/kg). Their data showed that BPA exposure in female mice induced a rapid onset of type 1 diabetes associated with an increase in *Bacteroidetes* and *Cyanobacteria* and a decrease

Table 2 Main prospective studies and meta-analyses included in the review (animal model studies)

First author, year of publication	Study type & design	Population	Results & major findings
Tang-Péronard et al., 2014 [49]	Cohort Study (from 1997 to 2000)	656 pregnant Faroese women 539 5–7 yo children	For 7-y-old girls who had OW mothers, PCB was associated with increased BMI and PCB and DDE were associated with an increased change in BMI from 5 to 7 y of age. PCB was associated with increased WC in girls with OW mothers and NM mothers. DDE was associated with increased WC only in girls with OW mothers
Vafeiadi et al., 2016 [51]	Cohort Study	500 mother–child pairs from the RHEA pregnancy cohort in Crete	Higher early childhood BPA was associated with excess child adiposity
Rönn et al., 2014 [117]	Prospective Study	890 70-year-old men and women studied for fat mass, fat distribution and serum adipokines levels	BPA associated positively with adiponectin and leptin, but negatively with ghrelin (better in women than in men) Serum concentrations of BPA were not related to adipose tissue measurements by DXA or MRI
Lignell et al., 2013 [73]	Cohort Study (POPUP cohort)	Breast milk from 413 first-time mothers analysed for di-ortho PCBs and tetra- to hexa- brominated PBDEs	PCB prenatal exposure was associated with ↑ birth weight and PBDE exposure with ↓ birth weight
Valvi et al., 2012 [137]	Cohort Study	344 children at 6.5 yrs from a Spanish birth cohort studied for prenatal OC concentrations (PCBs, DDE and DDT)	↑ RR of OW in the third tertile of PCB exposure and the second tertile of DDE exposure Associations between overweight and PCB and DDE concentrations were strongest in girls DDT was associated with overweight only in boys
Braun et al., 2016 [138]	Cohort study (HOME Study)	Children born to pregnant women from nine antenatal clinics associated with three hospitals in the Cincinnati, Ohio area from March 2003 to January 2006, studied up to 8 years of age for BMI, WC and BF according to maternal serum PFAS concentrations	Children born to women in the top two PFOA terciles had greater adiposity at 8 years than chil-dren in the 1 st tercile WC (cm) was ↑ among children in the 2nd and 3rd tercile compared to children in the 1 st tertile Children in the top two PFOA tertiles also had ↑ BMI gains from 2 to 8 years compared to children in the1 st tercile
Mora et al., 2017 [139]	Cohort Study (Project Viva)	Children studied for their adiposity in early childhood (median, 3.2 years) and in mid-childhood (median, 7.7 years) according to maternal serum PFAS concentrations	Prenatal exposure to PFASs was associated with small increases in adiposity measurements in mid-childhood, but only among girls
Stanaway et al., 2017 [155]	Observational study	Analysis of buccal microbiome of 65 adult farm workers and 52 adult non-farmworkers exposed to agricultural pesticide	An organophosphate pesticide exposure is correlated with significant alterations of the oral buccal microbiota composition Buccal bacterial analysis by azinphos-methyl blood detection has revealed a decrease of *Streptococcus*, *Micrococcineae*, *Gemella*, *Haemophilus*, *Halomonas*, *Actinomycineae*, and *Granulicatella*

Overweight (OW); Normal-weight (NM); organochlorine compound (OC); poly-chlorinated biphenyls (PCBs); dichlorodiphenyldichloroethylene (DDE); dichlorodiphenyl-trichloroethane (DDT); persistent organic pollutants (POPs); Waist Circumference (WC); Body Mass Index (BMI); Bisphenol A (BPA); Dual Energy X-ray Absorptiometry (DXA); Magnetic Resonance Imaging (MRI); polybrominated diphenyl ethers (PBDE); Perfluorooctanoic (PFOA); perfluoroalkyl substance (PFAS).

in *Firmicutes, Tenericutes,* and *Proteobacteria* resulting in a proinflammatory gut microbiota [154].

In a cohort of 65 agricultural workers and 52 non-agricultural workers, Stanaway et al. showed that exposure to agricultural pesticides can cause dysbiosis of the human buccal microbiota with a decrease in common genera present in the human microbiome (*Streptococcus, Micrococcineae, Gemella, Haemophilus, Halomonas, Actinomycineae and Granulicatella*), suggesting that the buccal microbiome could represent a novel biomarker to assess pesticide exposure in epidemiological studies [155].

Table 3 Main prospective studies and meta-analyses included in the review (animal model studies)

First author, year of publication	Study type & design	Population	Results & major findings
Chamorro-Garcia et al., 2013 [54]	Interventional study	12 C57BL/6 J female mice (F0) exposed to DMSO vehicle, the pharmaceutical obesogen ROSI, or TBT throughout pregnancy via the drinking water	Prenatal TBT exposure produced transgenerational effects on fat depots and induced a phenotype resembling NAFLD through at least the F3 generation
Manikkam et al., 2013 [55]	Interventional study	Harlan Sprague Dawley gestating female rats exposed to daily intraperitoneal injections of DMSO vehicle (control) or a mixture of plastic derived compounds (BPA, DEHP and DBP) during fetal days 8 to 14 of gestation	Significant ↑ in the incidence of total disease/abnormalities in F1 and F3 generation male and female animals from plastics lineages Pubertal abnormalities, testis disease, obesity, and ovarian disease (primary ovarian insufficiency and polycystic ovaries) were ↑ in the F3 generation animals
Skinner et al., 2013 [56]	Interventional study	Outbred gestating female rats (Hsd:Sprague Dawley®™SD®™ Harlan (Indianapolis, IN) transiently exposed to a vehicle control or DDT	Exposure to DDT can promote obesity and associated disease transgenerationally
Kirchner et al., 2010 [52]	Interventional study/ in vitro study	C57BL/6 J mice exposed to TBT, ROSI and CMC in utero	ADSCs from mice exposed to TBT in utero showed ↑ adipogenic capacity and ↓ osteogenic capacity with enhanced lipid accumulation in response to adipogenic induction ADSCs from animals exposed to TBT in utero showed ↑ expression of PPAR target genes such as the early adipogenic differentiation gene marker fatty acid-binding protein 4 and hypomethylation of the promoter/enhancer region of the fatty acid-binding protein 4 locus
Schmidt et al., 2012 [119]	Interventional study/ in vitro study	Female C3H/N mice studied for dietary DEHP exposure effects of on metabolism and fertility	Fertility was impaired in mice exposed to high doses of DEHP, and body weight and visceral fat deposits were ↑ in mice exposed to environmentally relevant doses Although F1 mice were exposed to DEHP only in utero and during lactation, metabolic changes in the offspring of diet-exposed females were observed
MacKay et al., 2017 [122]	Interventional study	Pregnant and lactating CD-1 mice exposed to low, environmentally relevant doses of either BPA or DES via their diet	Young adult offspring were resistant to leptin-induced suppression of food intake, body weight loss and hypothalamic pro-opiomelanocortin (POMC) upregulation. Both male and female BPA-exposed mice showed a reduced density of POMC projections into the paraventricular nucleus of the hypothalamus (PVN)
Arsenescu et al., 2008 [70]	Interventional study/ in vitro study	C57BL/6 wild-type (WT) or aryl hydrocarbon receptor (AhR)–/– mice treated with vehi-cle or PCB-77 (49 mg/kg, by intraperitoneal injection	PCB-77 may contribute to the development of obesity and obesity-associated atherosclerosis
Lin et al., 2011 [127]	Interventional study	Pregnant Wistar rats were administered DEHP or corn oil throughout gestation and lactation by oral gavage	At adulthood, female DEHP-exposed offspring exhibited elevated blood glucose, reduced serum insulin, impaired glucose tolerance and insulin secretion Male DEHP-exposed offspring had increased serum insulin, although there were no significant differences in blood glucose at fasting and during glucose tolerance test Both male and female DEHP-exposed offspring had significantly lower birth weight and maintained relatively lower body weight up to 27 wk of age
Bodin et al., 2014 [128]	RCT/ in vitro study	Offspring from female non obese diabetic NOD/ShiLtJ mice exposed to BPA via drinking water	Transmaternal BPA exposure, in utero and through lactation, accelerated the spontaneous diabetes development in NOD mice
La Merrill et al., 2014 [89]	Interventional study	C57BL/6 J mice were administered DDT from gestational day 11.5 to postnatal day 5 and assessed for their metabolic phenotype at different ages, up to nine months	Perinatal DDT exposure reduced core body temperature, impaired cold tolerance, decreased energy expenditure, and produced a transient early-life increase in body fat in female offspring When challenged with a HFD for 12 weeks in adulthood, female offspring perinatally exposed to DDT developed glucose intolerance, hyperinsulinemia, dyslipidemia, and altered bile acid metabolism
Migliaccio et al., 2024 [90]	RCT (?)	Male Wistar rats treated for 4 weeks with a standard diet, or a HFD alone, or together with DDE	An increase in paucilocular adipocytes and the lipid droplet size were observed in HFD-treated rats DDE administration mimics most of the effects induced by a HFD on BAT, and it aggravates the increase in the lipid droplet size when administered together with a HFD

Table 3 (continued)

First author, year of publication	Study type & design	Population	Results & major findings
Xu et al., 2015 [93]	RCT (?)	Male wild type (WT), AhR null (AhR −/−) and AhR heterozygote (AhR +/−) mice fed a normal chow diet or a high-fat diet for up to 14 weeks	AhR deficiency protected against HFD-induced obesity, hepatic steatosis, insulin resistance and inflammation. These protective effects result from a higher energy expenditure in AhR deficient mice compared to WT Levels of transcript for both the thermogenic gene, uncoupling protein 1 (Ucp1), in brown adipose tissue and mitochondrial β-oxidation genes in muscle were significantly higher in AhR −/− and AhR +/− mice compared to WT
Angle et al., 2013 [109]	Interventional study	Pregnant female CD-1 mice (derived from three-month-old nulliparous mice) stratified in two groups: first group exposed to BPA doses (ranging from 5 to 50,000 µg/kg/day) and the other group exposed to DES	Prenatal exposure to low-dose BPA in male mice occurred in increased body weight and liver weight, abdominal adipocyte mass (number and volume), in insulin resistance, and in serum leptin and insulin levels and on the other hand, decrease in serum adiponectin levels. The higher exposure of BPA does not produce the same effects The exposure to 0.1-µg/kg/day dose of DES does not have all the effects that the low dose of BPA has produced
Bo et al., 2016 [111]	Interventional study	Three-month-old male and female C57BL/6 mice exposed to a dose of 0.025 mg/kg/day/body weight of TBT	Oral exposure to TBT reported increased feeding efficiency only in male mice and decreased leptin levels in both sexes, with the same weight gain Significative decrease in male mice of NPY expression
Cederroth et al., 2007 [114]	Interventional study	CD-1 male and female mice: HP group fed a high soy–containing diet [high phytoestrogen (HP)] and LP group fed a soy-free diet [low phytoestrogen (LP)]	Exposure to a diet rich in soy, from conception to adulthood occurred in reduced body weight, adiposity, increase in locomotor activity and resistance to cold In HP mice a decrease in AgRP and an up regulation of Orexin A and MCH were observed. No effect on NPY, POMC, and CART expression emerged
He et al., 2014 [123]	Interventional study	Female and male Sprague–Dawley rats exposed to TBT (0.5 µg/kg body weight) for 54 days	Exposure to TBT in male and in female rats resulted in significant increases in the hepatic total cholesterol and triglyceride concentration while an increase of body weight and fat mass was observed only in male TBT upregulates the expression of NPY in the female rats TBT downregulates POMC, AgRP and CART expression in the males
Javurek et al., 2016 [151]	Interventional study	Female and male mice (60–90 days of age—Peromyscus californicus) exposed to BPA (50 mg/kg feed weight) or EE (0.1 ppb) or control diet	BPA and EE administration increased *Bacteroides*, *Mollicutes*, *Prevotellaceae*, *Erysipelotrichaceae*, *Akkermansia*, *Methanobrevibacter*, *Sutterella* proportion in fecal samples of both female and male. These microbiota condition have been associated with inflammatory bowel disease, colorectal cancer and metabolic disorders
Malaise et al., 2017 [153]	Observational study	Female and male mice (strain not declared) exposed to BPA (50 µg/kg body weight/day)	Perinatal exposure to BPA in mice may contribute to several postnatally consequences: microbiota alteration and immune system imbalance. These conditions were correlated to glucose intolerance, a defect of IgA secretion in feces and a lower proportion of *Bifidobacteria* in the feces compared to the control group
Xu et al., 2019 [154]	Interventional study	Specific pathogen free (SPF) adult female and male non-obese diabetic (NOD) mice treated with BPA (30 o 300 µg/kg)	Oral administration of BPA seems to play a crucial role in rapid onset of type 1 diabetes and in a proinflammatory microbiota profile (↑*Cyanobacteria* and *Bacteroidetes*, ↓ *Proteobacteria*, *Firmicutes* and *Tenericutes*) only in female mice

BPA: Bisphenol A; Dichlorodiphenyltrichloroethane (DDT); aryl hydrocarbon receptor (AhR); tributyltin (TBT); rosiglitazone (ROSI); non-alcoholic fatty liver disease (NAFLD); bis(2-ethylhexyl)phthalate (DEHP); dibutyl phthalate (DBP); carboxymethyl cellulose (CMC); multipotent stromal stem cells (MSCs); Triflumizole (TFZ); Dimethyl sulphoxide (DMSO); diethylstilbestrol (DES); High-Fat Diet (HFD); Brown adipose tissue (BAT); dichlorodiphenyldichloroethylene (DDE); Tetrachloro-dibenzo-dioxin (TCDD); neuropeptide Y (NPY); melanocortin hormone (MCH); ethinyl estradiol (EE).

However, data regarding the effects of EDCs on the human gut microbiota are limited, therefore further studies also for the identification of the specific responses of the different species of the gut microbiome.

All the main prospective studies and meta-analyses included in the review are shown in Table 2 (human studies) and Table 3 (animal model studies).

Conclusions

Data above reported support a link between early environmental exposure to EDCs and the development of obesity and related dysmetabolic diseases that may occur later in life.

Adipocytes are endocrine cells that produce and receive endocrine signals from various tissues and, as such, are susceptible to EDCs especially, during critical developmental

windows. The obesogenic actions of EDCs should be considered as part of a very complex scenario resulting from multiple and bidirectional relationships between EDCs and genetic, epigenetic, and environmental factors, including parental diet/exposure, lifestyle, eating habits, gut microbiota, and others. In addition, it should be considered that obesogenic mechanisms operating in the early years of life may vary enormously over a lifetime due to chronic exposure to EDCs throughout the life span of exposed individuals.

The different effects of environmental pollutants, or mixtures of them, could be due to the different structure and chemical properties of the molecule, as well as to the different dose and time of exposure, so that further studies taking into account chronic and simultaneous exposure to different EDCs with agonist and antagonist mechanisms of action are needed to better understand their impact on adipogenesis and, more generally, on human health.

Lastly, understanding the mechanisms by which different environmental pollutants affect the functionality, organization, and structure of adipose tissue, and in particular, BAT, may be useful for shedding light on the various causes linked to the aetiopathogenesis of obesity, in which functional damage to cellular organelles has recently become increasingly evident. Furthermore, correcting EDC-induced changes in the gut microbiota appears to be a useful treatment to prevent obesity-associated metabolic diseases.

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Declarations

Conflict of Interest The authors declare no conflict of interest.

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