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REVIEW

Protective effects of polyphenols against endocrine disrupting chemicals

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Abstract Endocrine disrupting chemicals (EDCs) are a heterogenous group of compounds dispersed throughout the environment that possess the ability to alter endocrine system function. While there are numerous routes of exposure to EDCs, the predominant source of many of these compounds is diet, largely due to their widespread use in food contact materials. In recent years, there has been a surge of research aimed at assessing exposure to EDCs, identifying their health implications, and developing approaches to minimize the risks they may entail. Due to their antioxidant and anti-inflammatory potential, polyphenols have been purported to confer protection against EDC-induced health detriments. This review discusses the evidence pertaining to dietary exposure to the two predominant EDCs, bisphenol A and phthalates, in the United States, their associations with diabetes, cancer, and cardiovascular disease outcomes, the potential for polyphenols to mitigate their disease-promoting effects, gaps in knowledge, and recommendations for future research.

Keywords Endocrine disrupting chemicals or EDCs · Bisphenol A or BPA · Phthalates · Polyphenols · Chronic disease

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Introduction

Recently, endocrine-disrupting chemicals (EDCs) have attracted the attention of public health organizations, prompting extensive study to determine how they impact human health. The term EDC refers to one of many environmental compounds that influence endocrine system function. The Environmental Protection Agency (EPA) defines an EDC as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones…responsible for homeostasis, reproduction, and developmental process" (Diamanti-Kandarakis et al., 2009). While there are numerous EDCs found in the environment, this review covers two of the most well-recognized and prevalent classes: bisphenol A (BPA) and phthalates (Filardi et al., 2020; Pacyga et al., 2019).

Aberrations in processes involving the endocrine system can increase the risk of cardiovascular disease (CVD), type 2 diabetes (T2D), cancer, and reproductive disorders. Therefore, EDCs may be implicated in their pathology and have been the focus of the aforementioned research (De Coster and van Larabeke, 2012; U.S. EPA, 2021b). Animal, cell culture, and human studies have indicated that chronic exposure to certain EDCs can promote chronic disease development and progression (Gore et al., 2015). However, many uncertainties remain about the effects of numerous EDCs and their influence on human health at current levels of exposure. Given the diseases they are implicated in are leading causes of death/disability (US Burden of Disease Collaborators, 2018), identifying sources of EDCs, quantifying exposure, elucidating risks they may entail, and minimizing exposure accordingly is crucial.

Exposure to EDCs, especially BPA and phthalates, occurs primarily through the diet, in addition to the environment.

EDCs are transferred to food via contact materials (especially plastic packaging), processing agents, pesticides, and herbicides (Bittner et al., 2014; Cao, 2010; Lauretta et al. 2019). Likewise, they bioaccumulate in frequently consumed mammals that graze on polluted pasture or are provided contaminated feed (Mantovani, 2016).

Many of the diseases EDCs are implicated in are deeply rooted in oxidative stress and inflammatory pathways (Nediani and Giovannelli, 2020). Inflammation and oxidative stress work in concert to diminish cellular antioxidant capacity, allowing for overproduction of free radicals. These free radicals then react with DNA and cell membranes, ultimately causing irreparable damage and producing toxic metabolites that propagate chronic disease progression (Khansari et al., 2009). Thus, by dampening inflammatory responses and neutralizing free radicals, diets rich in foods containing antioxidant/anti-inflammatory compounds may diminish some of the health risks attributed to EDCs. Polyphenols are a class of bioactive compounds prevalent in fresh fruits and vegetables with strong antioxidant and anti-inflammatory potential that have been investigated as beneficial phytochemicals in oxidative stress-related diseases (Cory et al., 2018; Forni et al., 2019; Sakaki et al., 2019). Currently, some evidence suggests these effects may confer polyphenols the ability to protect against the disease-promoting effects of EDCs, but research in humans is lacking, calling attention to a promising yet largely unexplored area of study (D'Angelo et al., 2019; Żwierełło et al., 2020).

In view of the importance of delineating the relationship between EDCs and human health and discovering approaches to combat the detriments they may cause, this review intends to summarize the evidence pertaining to dietary exposure to BPA and phthalates, how they influence disease risk, the basis for and available research on how polyphenols mitigate their adverse effects, gaps in knowledge, and suggestions for future research.

Endocrine-disrupting chemicals: types and characteristics

Bisphenol A (BPA)

Possibly the most well-known EDC, bisphenol A contains two phenolic rings linked by a methyl bridge and is formed via the condensation of two phenol groups and acetone in an acidic or basic medium (Almeida et al., 2018). It has long been produced in mass quantities to be used primarily in polycarbonate plastics and epoxy resins. Polycarbonate plastics have a wide variety of applications, commonly being used in infant and water bottles, safety equipment, medical devices, and compact discs. Similarly, epoxy resins have many purposes, ranging from their use in lacquers that coat metal products such as cans, water supply pipes, and bottle tops to serving as structural components of dental sealants and composites (Shelby, 2008). BPA can migrate from many of the aforementioned food-contact materials into food and liquids. This process is further augmented by heat, contact with acidic and alkaline substances, repeated use, and exposure to microwaves (Almeida et al., 2018).

Numerous studies conducted across various regions of the world have revealed that BPA exposure is remarkably widespread and that diet stands out as the predominant source (Filardi et al., 2020; Pacyga et al., 2019). Literature pertaining to diet-related BPA exposure in the U.S. will be covered in depth later, but generally, studies suggest exposure to BPA results mainly from the consumption of canned and pre-packaged foods/beverages, as well as the use of plastic cookware, utensils, and containers. Air, dust, and water also contribute to exposure, albeit to a much lesser extent (Bemrah et al., 2014; Cao et al., 2011; Careghini et al., 2015; Cooper et al., 2011; Rudel et al., 2011; Sakhi et al., 2014). There is substantial concern about this compound due to the fact that estimated intakes have repeatedly been found to be greatest on a per body weight basis in infants, children, and pregnant women, demographics in which it has been suggested there is a greater potential for adverse effects to manifest (Lakind and Naiman, 2011; Liao and Kannan, 2013; Muncke, 2011; Pacyga et al., 2019). Expectedly, BPA has garnered the attention of many consumer safety organizations and remained a consistent focus of research efforts aimed at identifying potential health detriments of EDCs. Furthermore, many precautionary actions have been taken to reduce exposure, including the exclusion of polycarbonate plastics/epoxy resins in food packaging and efforts to increase public awareness about which foods and materials are major sources of BPA.

Phthalates

Phthalates are another class of EDCs commonly encountered in modern day societies due to their use in hundreds of consumer products. Phthalates are diesters of orthophthalic acids that are categorized into two different classes based on their molecular weight, each used for a variety of purposes. Higher-molecular-weight (HMW) phthalates include di-2-ethylhexyl phthalate (DEHP), di-isononyl phthalate (DiNP), and di-isodecyl phthalate (DiDP)), and lower-molecular-weight (LMW) phthalates include diethyl phthalate (DEP), di-*n*-butyl phthalate (DBP), and butyl benzyl phthalate (BBP). HMW phthalates are mainly used as plasticizers in order to soften polyvinyl chloride (PVC) products employed in food packaging and manufacturing, and appear in water bottles, food containers, and wrappers. Conversely, LMW phthalates are used as solvents in many

personal care products and medications in order to retain color and scent (Cao, 2010).

As interest in phthalates has grown, many studies have been performed to identify major sources of exposure. On the whole, they have discovered that diet represents the main source of exposure to the HMW phthalates, followed by dust and air. In contrast, exposure to LMW phthalates occurs predominantly through the use of cosmetics and pharmaceuticals. HMW phthalates are abundant in certain high-fat dairy products, meats, and discretionary fat sources, and occasionally grain products (especially bread) and jarred/packaged fruits and vegetables. This is congruent with the fact that phthalates are lipophilic and that the processing/packaging of the abovementioned foods involves contact with materials containing them (PVC tubing, packing films, gaskets in lids of jars, coatings on cookware, and PVC gloves). Notably, the HMW phthalate content of these foods was susceptible to regional variation, likely a result of differences in the preparation, packaging, and transport methods employed (Fromme et al., 2007; Ji et al., 2010; Pacyga et al., 2019; Sathyanarayana et al., 2013; Serrano et al., 2014; Van Holderbeke et al., 2014). Reminiscent of BPA, groups purportedly most susceptible to harms of EDCs frequently have the greatest HMW phthalate exposure per unit of body mass, which sometimes surpass recommended daily limits established by the EPA (Serrano et al., 2014). Such observations, alongside uncertainties about their biological activities at current exposure levels, continue to motivate efforts to determine their implications for human health.

BPA and phthalates: major dietary sources of exposure in the United States

Dietary exposure to BPA

As shown in Table 1, several interventional, cross-sectional, and prospective studies have been carried out in the U.S. to identify dietary sources of exposure to BPA among various demographics. A large proportion of these studies were carried out using data from cycles of the National Health and Nutrition Examination Survey (NHANES). Urinary BPA concentration was the most common metric used to estimate dietary BPA exposure, though in a few instances serum and food samples were also utilized. Dietary habits were recorded using a variety of methods, including food frequency questionnaires (FFQs), 24-h dietary recalls, and other modified questionnaires.

The most consistent finding was that consumption of canned foods (fruits, vegetables, and soup) and beverages (mainly soda) was associated with greater urinary BPA concentrations, which is in line with the fact BPA is commonly used for epoxy resins found in can liners (Braun et al., 2011; Carwile et al., 2011; Hartle et al., 2016; LaKind and Naiman, 2011; Nomura et al., 2016; Quirós-Alcalá et al., 2013; Rudel et al., 2011; Teeguarden et al., 2011). Greater consumption of ultra-processed foods, foods comprised mainly of components isolated from their unprocessed counterparts (fats, added sugars, and starches) and include frozen meals, soft drinks, cold cuts, fast food, cakes, cookies, and pastries, was associated with greater concentrations of BPA (Buckley et al., 2019; Martinez Steele et al., 2020; Rudel et al., 2011; Teeguarden et al., 2011; Zota et al., 2016). In contrast, diets composed mainly of minimally processed foods or ranked high on healthy eating indices were associated with lower concentrations (Buckley et al., 2019; Martinez Steele et al., 2020; Rudel et al., 2011; van Woerden et al., 2021). In totality, these observations demonstrate that a diet rich in fresh, unprocessed fruits, vegetables, legumes, and whole grains with only moderate amounts of seafood, meat, and dairy products, would serve to lessen dietary exposure to BPA.

For food monitoring studies in which dietary exposure was calculated based on BPA concentrations of sampled foods, values obtained were appreciably lower than those reflected by urinary concentrations. This indicates that there may have been other non-dietary sources of exposure (Lorber et al., 2015; Morgan et al., 2018). In a follow-up of their 2018 analysis, Morgan and Clifton (2021) determined samples of bagel/bread-containing sandwiches from one participant contained the greatest concentrations of BPA. However, due to the fact similar food samples from other participants did not have markedly high BPA concentrations, and this particular individual reported using personal care products prior to assembling the meals in question, such observations were probably confounded. This observation, along with the disparities in BPA exposures obtained from calculations using food sample and urinary concentrations, emphasize that considerations for the contribution of other lifestyle habits to total exposure are vital. Lastly, although consumption of canned/packaged food in Teeguarden et al.'s (2011) interventional study increased urinary BPA concentrations, it did not affect serum concentrations, suggesting the use of serum BPA measures may be inadequate for classifying exposure, at least acutely.

Dietary exposure to phthalates

As reflected in Table 2, the majority of information about dietary phthalate exposure in the U.S. comes from cross-sectional analyses, most of which also utilized data from various NHANES cycles. While exposure to phthalates was assessed among a variety of demographics, there was a greater emphasis on groups of children and adolescents in comparison to the research on BPA exposure. Aside from food monitoring studies (which measured phthalate concentrations in food samples), all of the investigations used

Table 1 Studies investigating sources of dietary exposure to BPA in the US

Lead author/year	Study type	Sample demographic	Exposure assessment method	Sources of dietary exposure	Main findings
Buckley et al. (2019)	Cross-sectional	2212 NHANES participants aged 6 and older	24-h dietary recall paired with urinary BPA	Processed foods and beverages	Higher intake of ultra-processed food (specifically soft and fruit drinks) was associated with significantly greater BPA concentrations, whereas higher intake of minimally processed food was associated with a significantly lower concentration of BPA
Hartle et al. (2016)	Cross-sectional	7669 NHANES participants aged 6 and older	24-h dietary recall paired with urinary BPA	Canned foods and beverages	Higher intake of canned fruits/vegetables, pasta, and soup were associated with a significantly greater concentration of BPA, however the sample of canned soup consumers was very small
LaKind and Naiman (2011)	Cross-sectional	2548 NHANES participants aged 6 and older	FFQ and urinary BPA	Canned foods, canned/bottled beverages, and packaged foods	Greater consumption of soda, school lunches, and meals prepared away from home were associated with higher BPA concentrations
Martinez Steele et al. (2020)	Cross-sectional	9420 NHANES participants aged > 6	24-h dietary recall paired with urinary BPA	Ultra-processed foods	Higher consumption of ultra-processed and processed food was not significantly associated with greater BPA, although higher consumption of "ready-to-heat" ultra-processed foods was, and higher consumption of minimally processed food was inversely associated with BPA concentrations
Nomura et al. (2016)	Cross-sectional	68 healthy adults aged 20–59	3 24-h dietary recalls paired with 3 urinary BPA measurements	Canned foods, beverages, and pre-packaged or prepared meals	Higher canned food intake was associated with significantly greater concentrations of BPA

Table 1 (continued)

Lead author/year	Study type	Sample demographic	Exposure assessment method	Sources of dietary exposure	Main findings
van Woerden et al. (2021)	Cross-sectional	6418 NHANES participants aged > 18	2 24-h dietary recalls and urinary BPA	Dietary patterns	Higher dietary quality scores on four indices characterized by high fruit, vegetable, whole grain, dairy, seafood, and plant protein intakes and low refined grains, sodium, saturated fat, and added sugar intake were associated with significantly lower BPA concentrations. Increased consumption of fruit and whole grains were also independently associated with significantly lower concentrations
Zota et al. (2016)	Cross-sectional	8789 NHANES participants aged 6 and older	24-h dietary recall paired with urinary BPA	Fast foods	Higher intake of fast food meat was associated with significantly greater and grains were associated with significantly lower concentrations of BPA
Lorber et al. (2015)	Food monitoring study	Food samples from local supermarkets in Dallas, Texas	High Resolution Gas Chromatography/Low Resolution Mass Spectrometry	Supermarket foods	Canned food, especially meat and vegetables, had the highest concentration of BPA and accounted for 98% of calculated dietary BPA intake. Notably, these values were numerous orders of magnitude lower than intakes calculated from urinary BPA concentrations
Morgan and Clifton (2021)	Food monitoring study	188 food samples	Gas Chromatography/Low Resolution Mass Spectrometry	Solid food components of home-prepared meals	Of the sampled foods, prepared sandwiches (using bagels or bread) with tomato, cheese, eggs and ham contained the highest concentrations of BPA (possibly due to use following application of personal care products), followed by lasagna, tortilla soup, and chicken wraps

Table 1 (continued)

Lead author/year	Study type	Sample demographic	Exposure assessment method	Sources of dietary exposure	Main findings
Schecter et al. (2010)	Food monitoring study	Food samples from local supermarkets in Dallas, Texas	High resolution gas chromatography/low resolution mass spectrometry	Supermarket foods	The majority of canned food samples, including fruits, vegetables, meats, seafood, infant formula, cat/dog food, and soups, had detectable levels of BPA. Additionally, the few plastic wrapped samples also had detectable concentrations of BPA, although typically lower than those found in canned foods
Sathyanarayana et al. (2013)	Interventional trial	40 participants from ten families of parents and at least two 4–8 year old children	Pre-, intra-, and post Intervention urinary BPA	Fresh-food based intervention diet	Participants in the catered food arm providing fresh, local, and organic foods prepared/transported without plastic experienced a significant increase in BPA concentrations, whereas those in the written materials arm did not
Carwile et al. (2011)	Interventional trial	75 adults aged > 18	Two urinary BPA samples post-intervention	Canned and fresh soup	Consumption of canned soup for 5 days significantly increased urinary BPA concentrations, while the consumption of fresh soup decreased them
Rudel et al. (2011)	Interventional trial	20 parents and children who habitually consumed canned/bottled foods and drinks	Pre- and post-intervention urinary BPA	Fresh-food based intervention diet and habitual diets	The dietary intervention providing fresh and organic fruits, vegetables, grains, and meats prepared and stored in BPA free containers significantly reduced BPA concentrations. Researchers identified meals away from home, canned foods and soda, frozen dinners, water bottles, and microwaveable plastic as possible pre/post intervention sources of exposure

Table 1 (continued)

Lead author/year	Study type	Sample demographic	Exposure assessment method	Sources of dietary exposure	Main findings
Teeguarden et al. (2011)	Interventional trial	20 healthy adults aged 18–55	Pre- and hourly intra-intervention urinary and serum BPA	Canned foods	Total urine BPA concentrations increased significantly following ingestion of 3 meals containing canned fruits, vegetables, meats, and soup, as well as pudding cups, bottled water, and cream cheese packets, but serum BPA remained undetectable in virtually all samples
Mervish et al. (2014)	Prospective study	1101 girls aged 6–8	2–4 24-h dietary recalls and urinary BPA	Major and minor food groups and meals away from home	Greater consumption of grains, flour, and dry mixes, non-fresh vegetables, poultry, fats, total fish, and fried/fast-food fish was associated with greater concentrations of BPA
Morgan et al. (2018)	Prospective study	50 adults aged 19–50	3 sets of weekly food/water samples, food records, and urinary BPA samples (spot + 24 h)	Solid foods consumed in participants habitual diets	No data on specific foods was provided, but theoretical intakes calculated using BPA content of the food samples and reported intakes only explained around 20% of the total urinary BPA excretion
Polinski et al. (2018)	Prospective study	446 pregnant women aged > 16	Food Propensity Questionnaire and urinary BPA	Major food groups	None of the food groups were associated with significantly greater or lower concentrations of BPA following adjustment for sociodemographic characteristics
Braun et al. (2011)	Prospective study	389 pregnant women aged > 18	2 basic dietary recalls during pregnancy and 3 urinary BPA samples during pregnancy and after delivery	Fresh and packaged foods	Greater consumption of canned fruits was associated with significantly greater concentrations of urinary BPA
Quirós-Alcalá et al. (2013)	Prospective study	491 pregnant Mexican/Mexican American women aged > 18	FFQ and urinary BPA	Beverages, food groups, and meals away from home	Women who drank more than three sodas per day or ate three or more hamburgers per week had significantly greater concentrations of BPA

Table 2 Studies investigating sources of dietary exposure to phthalates in the U.S

Lead author/year	Study type	Sample demographic	Exposure assessment method	Sources of dietary exposure	Main findings
Reeves et al. (2019a, b)	Case–control study	1257 postmenopausal women aged 50–79	FFQ and 2–3 Urinary Phthalate Samples	Dietary patterns	Higher scores on the healthy eating index were associated with significantly lower concentrations of DiBP and DEHP metabolites
Buckley et al. (2019)	Cross-sectional	2212 NHANES participants aged 6 and older	24-h dietary recall paired with urinary phthalates	Processed foods and beverages	Greater consumption of ultra-processed food was associated with significantly higher concentrations of MCPP, MCNP, and MCOP, whereas greater consumption of minimally processed foods was associated with significantly lower concentrations of these metabolites. Sandwiches/burgers, french fries, and ice cream appeared to contribute most to these associations
Colacino et al. (2010)	Cross-sectional	2374 NHANES participants aged > 6	24-h dietary recall paired with urinary phthalates	Common foods and beverages	Higher consumption of poultry was associated with greater DEHP metabolite concentrations, higher consumption of fruit with significantly lower DEHP metabolites but higher MnMP. Higher consumption of potato and tomato were associated with greater MEP, higher consumption of total vegetables with greater total/low molecular weight phthalates, higher consumption of meat with greater MEP and low molecular weight phthalates, and greater consumption of eggs and dairy with greater MEHP and MCPP, respectively
Martinez Steele et al. (2020)	Cross-sectional	9420 NHANES participants aged > 6	24-h dietary recall paired with urinary phthalates	Ultra-processed foods	Higher consumption of ultra-processed food, especially ready-to-heat food, was associated with significantly greater concentrations of the sum of DINP metabolites, MCNP, MCCP, and MBZP
Muñoz et al. (2018)	Cross-sectional	2196 children aged 6–11 and 2314 adolescents aged 12–19 from NHANES	24-h dietary recall and urinary phthalates	School lunches	Children who always consumed school lunch had significantly greater concentrations of DEHP metabolites, MNBP, and MCOP, but adolescents did not. No other positive or negative associations with school lunches, energy intake from cafeteria food, and fat intake from cafeteria food with any phthalate metabolites were observed

Table 2 (continued)

Lead author/year	Study type	Sample demographic	Exposure assessment method	Sources of dietary exposure	Main findings
Serrano et al. (2014)	Cross-sectional	656 pregnant women aged > 18	FFQ and urinary phthalates	Major food groups and culinary ingredients	Greater consumption of spices was associated with significantly lower concentrations of higher molecular weight phthalate metabolites, MnBP, and MiBP, and greater consumption of dairy was associated with a lower concentration of MiBP
Trasande et al. (2013a, b)	Cross-sectional	2743 NHANES participants aged 6–19	24-h dietary recall paired with urinary phthalates	Major food groups	Fruit intake was associated with significantly lower concentrations of MEP, MBzP, MEHP, MEHHP, and MEOHP, discretionary oil was associated with significantly lower concentrations of MIBP, grain intake with lower MEP, and soy intake with lower DEHP and the sum of high molecular weight phthalates. Meat/poultry/fish and total calorie intake was associated with greater concentrations of all four metabolites of DEHP, and the former also with MIBP
Tyrrell et al. (2013)	Cross-sectional	22,161 NHANES participants aged 18–74	Five 24-h dietary recalls paired with urinary phthalates	Major food groups	Total iron intake was associated with lower concentrations of MBP and MIBP in a few of the included cycles
Varshavsky et al. (2018)	Cross-sectional	10,253 NHANES participants aged > 6	24-h dietary recall paired with urinary phthalates	Meals and foods consumed at and away from home	Greater food and fat intake, especially of sandwiches, away from home (at a fast food restaurant, full-service restaurant, or cafeteria) was associated with significantly greater total phthalate concentrations across all age groups, driven by significant increases in DEHP and DINP concentrations. Greater energy intake and total fat were associated with greater phthalate concentrations in adults aged 20–59. Exposures in children were the greatest of all age groups
Zota et al. (2016)	Cross-sectional	8789 NHANES participants aged > 6	24-h dietary recall paired with urinary phthalates	Fast foods	Higher consumption of fast food and fast food derived fat was associated with greater concentrations of DINP and the sum of DEHP metabolites, grains were associated with significantly greater concentration of DEHP metabolites, and grains and meat were associated with greater DINP concentrations

Table 2 (continued)

Lead author/year	Study type	Sample demographic	Exposure assessment method	Sources of dietary exposure	Main findings
Schecter et al. (2013)	Food monitoring study	Food samples from local supermarkets	Gas chromatography/low resolution mass spectrometry	Supermarket foods	The most commonly detected phthalate was DEHP, which was found in the greatest concentrations in dairy, fish, pork, poultry, grains, and baby food
Sathyanarayana et al. (2013)	Interventional trial	40 participants from ten families of parents and at least two 4–8 year old children	Pre-, intra-, and post Intervention urinary phthalates	Fresh-food based intervention diet	Participants in the catered food arm providing fresh, local, and organic foods prepared/transported without plastic experienced a significant increase in DEHP metabolite concentrations, whereas those in the written materials arm did not. Food testing indicated that butter, cream, milk, cheese, ground cinnamon, cayenne, and coriander had high concentrations of DEHP
Rudel et al. (2011)	Interventional trial	20 parents and children from five families who habitually consumed canned/bottled foods and drinks	Pre- and post-intervention urinary phthalates	Fresh-food based intervention diet and habitual diets	The dietary intervention providing fresh and organic fruits, vegetables, grains, and meats prepared from fresh ingredients and stored in glass (not plastic) significantly reduced the concentration of DEHP metabolites. Researchers identified meals away from home, canned foods and soda, frozen dinners, water bottles, and microwaveable plastic as possible pre/post intervention sources of exposure
Mervish et al. (2014)	Prospective study	1101 girls aged 6–8	2–4 24-h dietary recalls and urinary phthalates	Major food groups and meals away from home	Greater consumption of grains, flour, and dry mixes (especially rice), full fat dairy, and fried fish/fast food were associated with higher concentrations of DEHP metabolites, and greater consumption of flour from mixed foods and fresh fruit were associated with greater and lower concentrations of MBZP, respectively
Polinski et al. (2018)	Prospective study	446 pregnant women aged > 16	Food propensity questionnaire and urinary phthalates	Major food groups	None of the food groups were associated with significantly greater or lower concentrations of high molecular weight phthalate or DEHP metabolites after adjustment for sociodemographic characteristics

Table 2 (continued)

Lead author/year	Study type	Sample demographic	Exposure assessment method	Sources of dietary exposure	Main findings
Watkins et al. (2014)	Prospective study	296 children aged 5	Simple food questionnaire and urinary phthalates	Packaged foods, beverages, and foods away from home	Consumption of fast food at least once per week was associated with a significantly greater MBZP concentration and a non-significantly greater MCOP concentration. MCOP was also non-significantly greater among children who consumed food stored in plastic more than once a week, and MCPP was significantly greater in children who consumed prepackaged beverages in the previous 24 h

DIBP Diisobutyl phthalate, *DEHP* Di(2- ethylhexyl) phthalate, *DINP* Diisononyl phthalate, *MCPP* Mono-(3-carboxypropyl)phthalate, *MCNP* Monocarboxy-isononly phthalate, *MCOP* Mono-carboxyoctyl phthalate, *MEP* Monoethyl phthalate, *MNMP*Mono-n-methyl phthalate, *MEHP* Mono-2-ethylhexyl phthalate, *MBZP* Monobenzyl phthalate, *MNBP* Mono-n-butylphthalate, *MIBP* mono-isobutyl phthalate, *MBP* Monobutyl phthalate, *MEHHP* Mono (2-ethyl-5-hydroxyhexyl) phthalate,*MEOHP* Mono-(2-ethyl-5-oxohexyl) phthalate

phthalate metabolite concentrations in urinary samples to quantify exposure. Finally, FFQs or 24-h dietary recalls were employed to characterize dietary habits.

Consistent with the notion that diet is the main source of exposure to the HMW phthalates (especially DEHP) due to their applications in food processing and packaging, associations between these compounds and foods/food groups were common and will be the focus of this section. Frequent consumption of ultra-processed and fast foods, especially those higher in fat, was associated with higher urinary concentrations of DEHP metabolites (Mervish et al., 2014; Watkins et al., 2014; Zota et al., 2016). Other studies provided more granularity, indicating that regular consumption of pre-packaged meals, refined grains, meat, fried fish, french fries, and ice cream was associated with greater urinary concentrations of HMW phthalates (Buckley et al., 2019; Martinez Steele et al., 2020; Rudel et al., 2011; Varshavsky et al., 2018). Aside from fast and ultra-processed foods, it was also revealed that greater consumption of grains, meat, high-fat dairy products, and select spices (ground cinnamon, cayenne, and coriander) coincided with increased concentrations of urinary DEHP metabolites. Additionally, greater consumption of fruits, minimally processed foods, and diets scoring higher on healthy eating indices coincided with significantly lower concentrations (Colacino et al., 2010; Mervish et al., 2014; Sathyanarayana et al., 2013; Transande et al., 2013a, 2013b). With regards to children and adolescents, school lunches were repeatedly shown to contribute to HMW phthalate exposure (Munoz et al., 2018; Varshavsky et al., 2018), although some discrepancies in findings across age groups were present, showcasing a need for additional studies in order to provide further clarification. In sum, this data indicates a dietary pattern similar to that which would reduce exposure to BPA would also be effective in curtailing HMW phthalate exposure, with moderation of high fat meat and dairy intake also being advisable.

Importantly, it must be acknowledged some studies had limitations that may have caused exposure misclassification and led to erroneous conclusions. First, a few did not record dietary habits close to when urinary samples were collected. Since urinary elimination of these compounds is rapid (Bastiaensen et al., 2020; Völkel et al., 2002), this could mean the food intake documented was not relevant to the concentrations of BPA/phthalate metabolites in the samples collected. While this may invalidate some findings due to an inability to assure food intake preceded increased urinary EDC concentrations, they can still provide useful information by reflecting general trends that warrant further study. Second, in multiple cases non-dietary behaviors likely contributed to exposure, which could confound some of the observed associations (Lorber et al., 2015; Morgan et al., 2018). Third, most studies included questionnaires that only captured intakes of heterogeneous food groups, prohibiting

precise identification of foods/ingredients that were major sources of exposure. Lastly, there was limited information pertaining to food processing and the type of packaging/containers used for storage or transportation, which may explain some of the variation across analyses. While the fact some findings remained consistent in higher quality studies does provide reassurance they were valid, these potential sources for error are worrisome and must be considered when interpreting the existing data, as well as in future investigations.

Potential mechanisms of action and health impacts of BPA and phthalates

While most studies on BPA, phthalates, and other EDCs have revealed exposures are typically below maximum limits attained from toxicological research in animal models, the potential non-monotonicity, low-dose, and additive effects of many EDCs may mean these observations could lead to underestimation of the magnitude of their harms. Low-dose effects are those that occur at doses below what is traditionally used in toxicological studies, whereas non-monotonicity refers to a non-linear dose–response curve in which there is a point where the slope inverts. Additive effects are accentuated impacts that occur in the presence of two or more synergistic compounds. Since the existence of any of these indicate that EDCs may exert adverse effects at doses lower than currently established maximum intake limits, the possibility they can cause harm to human health at current levels of exposure cannot be ruled out (Vandenberg et al., 2012). However, the evidential basis for these characteristics is not particularly robust. Some research suggests that additive effects in EDCs are unlikely, that many low doses employed in animal studies are still high relative to typical human exposure, and that the mere presence of a measurable effect in cell cultures or animal models does not necessarily entail harm in humans (Kamrin, 2007; Nohynek et al., 2013). Outcome-based observational studies, which will be reviewed in this section, provide important information about the degree to which exposure to BPA and phthalates may adversely affect human health.

BPA mechanisms of action

Historically, detriments linked to greater BPA exposure have included hypertension, CVD, diabetes, cancer, obesity, altered reproductive function, and impaired growth and development of infants/children. These have been attributed to BPA's ability to bind and activate hormone receptors, regulate transcription factors, and prompt epigenetic changes, as demonstrated in numerous cell culture and animal studies. BPA has been hypothesized to affect the risk of cancer through interactions with estrogen receptors alpha and beta (ERa and ERb), estrogen-related receptor gamma (ERRy), G protein-coupled receptor 30 (GPR30), thyroid hormone receptors, and the androgen receptor. As for diabetes/insulin resistance, it is believed that BPA can increase risk through activation of the glucocorticoid receptor, peroxisome proliferator-activated receptors (PPARs), sterol regulatory element binding protein 1C (SREBP-1C), lipoprotein lipase (LPL), and fatty acid synthase (FAS). Lastly, it is thought to increase CVD risk through interactions with many of the previous nuclear receptors, in addition to vascular and intracellular adhesion molecules (VCAMs and ICAMs). While the stimulation of these receptors and their downstream effects on gene expression are involved in variety of cellular processes essential for life, excessive activation and altered cellular signaling contribute to disease progression (Acconcia et al., 2015; Cimmino et al., 2020). The large number of receptors affected by BPA and their involvement in disease pathophysiology across multiple organ systems offers an explanation as to why it is implicated in so many conditions.

BPA exposure and health outcomes

Detailed in Table 3 are studies assessing associations between BPA exposure and CVD, diabetes/insulin resistance, and cancer. There was substantial heterogeneity with respect to study design, location, exposure assessment methods, and demographics. Findings were similarly mixed, with greater exposure to BPA being associated with either a significantly greater or significantly lower prevalence or incidence of the three outcomes. The majority of studies were cross-sectional and only included single time point measurements of urinary/serum BPA post-diagnosis, though several prospective analyses were available.

For CVD, there was a fairly limited number of studies, most of which focused on outcomes related to atherosclerotic cardiovascular disease (ASCVD), including coronary artery/heart disease (CHD/CAD), myocardial infarction (MI), and peripheral artery disease (PAD) incidence or CVD mortality. While some cross-sectional studies found significant positive associations of BPA exposure with the prevalence of CVD, MI, and CHD, only one of the four prospective studies (on participants with type 2 diabetes) revealed that BPA was associated with a significantly increased incidence of MI (Hu et al., 2019). In addition to differences in the sample demographics, there are a number of potential explanations for this disparity, including the use of different exposure assessment methods (serum versus urinary BPA), a focus on different outcomes (mortality vs incidence/prevalence), and smaller sample sizes. Given that serum BPA has previously failed to quantify acute exposure (Teeguarden et al., 2011), that relationships with specific outcomes may vary, and that smaller

sample sizes may limit power to detect significant effects, it is important to carry out additional studies on the relationship between CVD and BPA exposure to address these issues and reduce existing ambiguity.

On the other hand, there were far more studies investigating potential associations between BPA exposure and T2D, gestational diabetes, or insulin resistance. Many of these found that greater exposure was associated with a higher prevalence or incidence of these conditions. That said, there was a similar tendency towards disagreement between cross-sectional studies and prospective cohort studies for some outcomes. A few of the latter used serum BPA (Shu et al., 2018; Yang et al., 2021), so results from these particular studies may need to be interpreted with caution. Also, despite concerns that pregnant women may be more susceptible to adverse effects of BPA, most studies investigating the incidence or prevalence of GDM found no significant associations with BPA. Although this seems to suggest BPA does not increase the risk of GDM, it may be possible that the use of single time point urinary measurements during pregnancy to assess exposure rather than multiple measurements prior to pregnancy prevented the studies from finding a relationship between the two. Accordingly, this should be something that future research efforts take into consideration. Notably, the two prospective cohort studies that used urinary BPA rather than serum BPA to measure exposure did find that greater BPA concentrations were associated with a significant increase in the risk of T2D (Ranciere et al., 2019; Sun et al., 2014). Sun et al. (2014) discovered that this relationship was only observed in premenopausal women, providing some support to the theory that younger individuals may be more susceptible to the detriments of BPA. Likewise, the only study concerning children (Menale et al., 2017) found that those with greater exposure to BPA had significantly greater HOMA-IR values. That said, the limited number of studies on these demographics highlight the exigency for further investigations before such a conclusion can be drawn.

There was only a small number of studies on BPA exposure and cancer, with variable designs, endpoints, and findings. On the aggregate, though a few studies observed positive associations between BPA exposure and the incidence of specific cancers, there was a dearth of distinguishable patterns. The most frequently studied outcome was breast cancer, and all but one study conducted by López-Carrillo et al. (2021) found greater BPA exposure was not associated with a significantly greater prevalence or incidence of this cancer. Once again, differences in exposure assessment methods, the ages of participants, study locations, and sample sizes could certainly explain the heterogeneity in results, and reflect how crucial it is for future studies to carefully consider these factors. On the other hand, BPA was positively associated with prostate cancer in both of the studies concerning this outcome (Salamanca-Fernández et al., 2021; Tse et al., 2017), indicating this may be an endpoint worth prioritizing in future research.

Phthalates mechanisms of action

As discussed earlier, the HMW phthalates, mainly DEHP, DINP, and BBP, are those whose main source of exposure is diet. Similar to BPA, these compounds have been hypothesized to increase risks of cancer, diabetes, and CVD, and impair sexual function and growth/development in light of their ability to bind to an array of hormone receptors, modify transcription factors, and induce epigenetic alterations. They have been suggested to modulate the risk of diabetes through interactions with PPARs, the thyroid receptor, and the liver-x-receptor, eliciting aberrations in lipid and glucose homeostasis. Conversely, they are thought to increase the risk of cancer through interactions with PPARα, estrogen receptors, and aryl hydrocarbon receptors, leading to the activation of cancer-promoting pathways. Finally, they are thought to increase the risk of CVD through interaction with many of the above receptors, along with androgen receptors, VCAMs, and ICAMs, which can induce oxidative stress, impair vascular function, and contribute to overweight/obesity and diabetes (Benjamin et al., 2017).

Phthalate exposure and health outcomes

Found in Table 4 are studies examining associations between phthalate exposure and CVD, cancer, and insulin resistance/diabetes, which were markedly heterogeneous with regard to location, sample size, demographics, and design. Conversely, exposure assessment methods were largely similar, and all except one study (Dong et al., 2018) used urinary concentrations of phthalate metabolites to quantify exposure.

Overall, studies investigating associations between HMW phthalate exposure and CVD prevalence/incidence or mortality were scarce. The primary outcomes considered were mostly related to ASCVD, namely CHD/CAD, stroke, or a composite of both. Findings generally suggested that although total exposure to HMW phthalates was not consistently associated with any CVD outcome, significant positive associations of the HMW phthalate metabolites MnBP and MEHP with stroke, CVD mortality, and CHD were found in multiple studies (Shiue 2013; Su et al., 2019; Trasande et al., 2021). Still, due to the limited number of studies, more data is required to firmly establish these or any other relationships between HMW phthalate exposure and CVD.

Conversely, there were many more studies examining the potential association between phthalate exposure and diabetes/insulin resistance. Upon review, it is evident that greater exposure to HMW phthalates was frequently positively associated with insulin resistance and diabetes in cross-sectional and prospective studies. However, a few

Table 3 Observational studies on BPA exposure and diabetes/insulin resistance, cancer, and CVD

Lead author/year	Country/study type	Sample demographic	Follow up	Exposure assessment method	Outcome	Main findings
Salamanca-Fernández et al. (2021)	10 European Countries/case-cohort	4812 adults aged 29–69	16.9 years	Serum BPA	Cancer	Breast Cancer: NS Prostate Cancer: + (T1 and T2)
Li et al. (2020)	China/cross-sectional	1230 adults	N/A	Urinary BPA	Cancer	Non-Small Cell Lung Cancer: +
Zhou et al. (2017)	China/cross-sectional	178 adults	N/A	Urinary BPA	Cancer	Thyroid Cancer: +
Tse et al. (2017)	Hong Kong/cross-sectional	833 men aged 35–84	N/A	Cumulative BPA Exposure Index	Cancer	Prostate Cancer: +
Marotta et al. (2019)	Italy/cross-sectional	55 participants > 18 with benign thyroid nodules/ thyroid cancer	N/A	Serum BPA	Cancer	Thyroid Cancer: NS
Hiroi et al. (2004)	Japan/cross-sectional	37 adult women	N/A	Serum BPA	Cancer	Endometrial Cancer: -
Yang et al. (2009)	Korea/cross-sectional	167 middle aged women	N/A	Serum BPA	Cancer	Breast Cancer: NS
López-Carrillo et al. (2021)	Mexico/cross-sectional	798 adult women	N/A	Urinary Free BPA	Cancer	Breast Cancer: +
Trabert et al. (2014)	Poland/cross-sectional	1150 postmenopausal women	N/A	Urinary BPA-Glucuronide	Cancer	Breast Cancer: NS (BPA-G)
Morgan et al. (2017)	USA/cross-sectional	3003 women aged > 20	N/A	Urinary BPA	Cancer	Breast Cancer: NS
Bao et al. (2020)	USA/prospective cohort	3883 adults aged > 20	9.6 years	Urinary BPA	Cancer	Cancer Mortality: NS
Wu et al. (2021a, b)	USA/prospective cohort	1062 postmenopausal women	11 years	Urinary BPA	Cancer	Breast Cancer: NS
Salamanca-Fernández et al. (2020a, b)	10 European Countries/case-cohort	4636 adults aged 29–69	16 years	Serum BPA	CVD	Ischemic Heart Disease: NS
Wang et al. (2015)	China/cross-sectional	3246 adults aged > 40	N/A	Urinary BPA	CVD	Peripheral Artery Disease: NS
Hu et al. (2019)	France and Germany/nested case–control (2 cohorts)	292 adults with T2D	~6–9 years	Urinary BPA and Chlorinated BPA	CVD	Myocardial Infarction: +
Melzer et al. (2012b)	UK/case–control	591 adults aged 30–95	N/A	Urinary BPA	CVD	Severe CAD: + Intermediate CAD: NS
Melzer et al. (2012a)	UK/nested case–control	1744 adults aged 40–74	10.8 years	Urinary BPA	CVD	Coronary Artery Disease: NS
Cai et al. (2020)	USA/cross-sectional	9139 adults aged > 20	N/A	Creatine adjusted urinary BPA	CVD	Coronary Heart Disease: + (Only males) Stroke: + (Only males)
Lang et al. (2008)	USA/cross-sectional	1455 adults aged 18–74	N/A	Urinary BPA	CVD	CVD: +
Melzer et al. (2010)	USA/cross-sectional	2948 adults aged 18–74	N/A	Urinary BPA	CVD	CHD: +
Moon et al. (2021)	USA/cross-sectional	9265 adults aged > 20	N/A	Creatine adjusted urinary BPA	CVD	CHD: +
Shankar et al. (2012)	USA/cross-sectional	745 adults aged > 40	N/A	Urinary BPA	CVD	Peripheral Artery Disease: +
Bao et al. (2020)	USA/prospective cohort	3883 adults aged > 20	9.6 years	Urinary BPA	CVD	CVD Mortality: NS
Salamanca-Fernández et al. (2020a, b)	10 European Countries/case-cohort	670 adults aged 29–69	23 years	Serum BPA	Diabetes/IR	Diabetes: NS

Table 3 (continued)

Lead author/year	Country/study type	Sample demographic	Follow up	Exposure assessment method	Outcome	Main findings
Tai and Chen (2016)	Canada/cross-sectional	1082 subjects aged 3–79	N/A	Urinary BPA	Diabetes/IR	Diabetes: + (Only males)
Shapiro et al. (2015)	Canada/prospective cohort	1274 pregnant women aged > 18	N/A	Urinary BPA	Diabetes/IR	GDM: NS
Duan et al. (2018)	China/case–control	502 adults	N/A	Urinary BPA	Diabetes/IR	Diabetes: + in Q2/Q3
Hou et al. (2021)	China/cross-sectional	390 pregnant women	N/A	Urinary BPA	Diabetes/IR	GDM: NS
Li et al. (2011)	China/cross-sectional	60 adult women with PCOS	N/A	Serum BPA	Diabetes/IR	Insulin Resistance: NS
Ning et al. (2011)	China/cross-sectional	3423 adults aged > 40	N/A	Urinary BPA	Diabetes/IR	Diabetes: NS
Bi et al. (2016)	China/prospective cohort	2209 middle aged adults	4 years	Urinary BPA	Diabetes/IR	Diabetes: NS
Shu et al. (2018)	China/prospective cohort	3510 adults aged 20–80	5 years	Serum BPA	Diabetes/IR	Diabetes: NS HOMA-IR: NS
Wang et al. (2017)	China/prospective cohort	620 pregnant women	Until birth	Urinary BPA	Diabetes/IR	GDM: -
Wang et al. (2019)	China/prospective cohort	2336 non-diabetic adults aged > 40	4 years	Urinary BPA	Diabetes/IR	Insulin Resistance: NS HOMA-IR: NS
Yang et al. (2021)	China/prospective cohort	535 pregnant women aged 20–40	Until birth	Serum BPA	Diabetes/IR	GDM: NS Insulin Resistance: + (middle term)
Zhang et al. (2019)	China/prospective cohort	1841 pregnant women	6 to 20 weeks	Urinary BPA	Diabetes/IR	GDM: NS
Andra et al. (2015)	Cyprus/cross-sectional	151 middle aged adults	N/A	Urinary BPA	Diabetes/IR	Diabetes: NS
Piecha et al. (2016)	Czech Republic/case–control	168 middle aged adults with metabolic syndrome	N/A	Urinary BPA	Diabetes/IR	Diabetes: NS
Ranciere et al. (2019)	France/case-cohort	755 non-diabetics aged 30–65	9 years	Urinary BPA-Glucuronide	Diabetes/IR	Diabetes: + in Q2/Q3
Turgut et al. (2016)	Germany/cross-sectional	47 chronic hemodialysis patients aged > 18	N/A	Serum BPA	Diabetes/IR	Diabetes: +
Jain et al. (2020)	India/case–control	300 adults	N/A	Serum BPA	Diabetes/IR	Diabetes: + HOMA-IR: NS
Ahmadkhaniha et al. (2014)	Iran/case–control	239 middle aged adults	N/A	Urinary BPA	Diabetes/IR	Diabetes: +
Menale et al. (2017)	Italy/cross-sectional	155 children with obesity aged 4–16	N/A	Urinary BPA	Diabetes/IR	HOMA-IR: +
Kim et al. (2013)	Korea/cross-sectional	1210 adults aged 40–69	N/A	Urinary BPA	Diabetes/IR	Diabetes: NS
Lee et al. (2021)	Korea/cross-sectional	3782 adults aged > 19	N/A	Urinary BPA	Diabetes/IR	Diabetes: + (Only males)
Mouneimne et al. (2017)	Lebanon/cross-sectional	501 adults aged > 18	N/A	Urinary BPA	Diabetes/IR	Diabetes: NS
Murphy et al. (2019)	Mexico/case–control	404 middle aged women	N/A	Urinary BPA	Diabetes/IR	Diabetes: NS
Ejaz Ul Haq et al. (2020)	Pakistan/cross-sectional	400 adults	N/A	Urinary BPA	Diabetes/IR	Diabetes: + HOMA-IR: +
Jing Li et al. (2018)	Saudi Arabia/case–control	101 adults aged 28–68	N/A	Urinary BPA	Diabetes/IR	Diabetes: +
Chang et al. (2018)	South Dakota/case–control	276 American Indian/Alaskan Native Adults	N/A	Urinary BPA	Diabetes/IR	Diabetes: NS

Table 3 (continued)

Lead author/year	Country/study type	Sample demographic	Follow up	Exposure assessment method	Outcome	Main findings
Aekplakorn et al. (2015)	Thailand/cross-sectional	2581 adults	N/A	Serum BPA	Diabetes/IR	Diabetes: +
Chailurkit et al. (2017)	Thailand/cross-sectional	250 adults aged > 50	N/A	Serum BPA	Diabetes/IR	Diabetes: NS HOMA-IR: + (in overweight)
Robledo et al. (2013)	USA/case–control	94 pregnant women aged > 18	N/A	Urinary BPA	Diabetes/IR	GDM: NS
Lang et al. (2008)	USA/cross-sectional	1455 adults aged 18–74	N/A	Urinary BPA	Diabetes/IR	Diabetes: +
Melzer et al. (2010)	USA/cross-sectional	2948 adults aged 18–74	N/A	Urinary BPA	Diabetes/IR	Diabetes: +
Sabanayagam et al. (2013)	USA/cross-sectional	3516 adults free of diabetes aged > 20	N/A	Urinary BPA	Diabetes/IR	Diabetes: +
Shankar and Teppala (2011)	USA/cross-sectional	3967 adults aged > 20	N/A	Urinary BPA	Diabetes/IR	Diabetes: +
Silver et al. (2011)	USA/cross-sectional	4389 adults aged > 20	N/A	Urinary BPA	Diabetes/IR	Diabetes: +
Sun et al. (2014)	USA/prospective cohort	1587 female nurses > 20	~ 7 years	Urinary BPA	Diabetes/IR	Diabetes: + (Only premenopausal women)

+ significant positive association, − significant negative association, *NS* non-significant, *IR* insulin resistance, *GDM* gestational diabetes mellitus, *HOMA-IR* homeostatic model assessment for insulin resistance

contradictory findings were also present, especially pertaining to gestational diabetes. As emphasized earlier, the use of single time point measurements after conception to determine exposure could limit the ability to detect any potential associations in this demographic. This suggests there is a possibility that these findings actually underestimate the effects of phthalates, underscoring the need for additional studies that take this into consideration. Lastly, some positive associations between lower molecular weight phthalate exposure and diabetes were also found in both types of studies. Alas, the majority of exposure to these compounds does not stem from dietary habits, so although they may have important implications, these results are not of particular relevance to this review.

In the small collection of studies available on cancer, the specific type of cancer studied and the direction of the findings varied greatly, prohibiting any inferences from being made. Breast cancer was the most frequently studied type of cancer, and most studies did not suggest phthalate exposure was associated with breast cancer. With that said, one case–control study found that greater exposure to the HMW phthalate DEHP was associated with a greater prevalence of breast cancer, and a prospective cohort study revealed HMW phthalate exposure was associated with breast cancer mortality, but not incidence. As with BPA, variance in the ages of the participants, sample sizes, and study location may represent potential sources of heterogeneity and warrant consideration in future investigations. In addition, greater HMW exposure was associated with a significantly greater incidence or prevalence of thyroid and prostate cancer in the small number of available studies (Chang et al., 2018; Chuang et al., 2020; Liu et al., 2020; Miao et al., 2020). These observations suggest that while further study of the associations between HMW phthalate exposure and all relevant cancers is essential, prioritizing the study of breast, thyroid, and prostate cancer would be wise.

All in all, there were multiple consistent positive associations between BPA and HMW phthalate exposure and some diabetes, cancer, and CVD outcomes, suggesting they may indeed be detrimental to human health at current levels of exposure. Even so, the limited number of prospective studies and occasionally disparate findings accentuate the need for additional well-designed investigations to further validate these results and to resolve prevailing quandaries.

Polyphenols: modifiers of EDC's associations with chronic disease?

As previously noted, due to how ubiquitous and pervasive many EDCs tend to be, it is probably naive to presume that exposure can be completely eradicated. Therefore, in addition to minimizing exposure, identifying behaviors that could modify associations between EDCs and adverse health outcomes is of particular importance. Given that BPA and phthalates are surmised to increase the risk of diabetes, cancer, and CVD largely due to their propensity to activate oxidative and inflammatory pathways involved

in these diseases (Gassman, 2017; Mariana and Cairrao, 2020), it has been proposed that dietary compounds with anti-inflammatory and antioxidant properties may attenuate their detrimental effects. Since polyphenols are some of the most well-established compounds with such properties, they have been studied for their ability to protect against the harmful effects of BPA and phthalates. Indeed, as seen in Table 5, preliminary in vivo and in vitro evidence has suggested that some polyphenolic compounds inhibit adverse cellular effects caused by exposure to BPA and phthalates. These compounds include resveratrol, curcumin, epigallocatechin gallate (EGCG), genistein, naringenin, and kaempferol. The following section will serve to explore the findings of this research and touch upon the potential implications for human health.

Resveratrol

Quite a few animal model and cell-culture studies have suggested that resveratrol, a natural stilbene found mainly in grapes and berries, may prevent carcinogenic and cardiotoxic effects due to BPA or phthalate exposure. Although one study carried out by Botelho et al. (2009) found that consumption of resveratrol did not confer beneficial effects to the offspring of pregnant female rats who were also treated with DEHP during gestation (and may have even increased oxidative stress), another from Ünal et al. (2016) found the opposite with regard to the LMW phthalate DBP. They demonstrated that co-administration of resveratrol with a low, but not high, dose of DBP prevented increases in apoptosis seen in the testis of male rats. This effect was hypothesized to be due to the ability of resveratrol to prevent DBP from lowering C-kit reactivity and by increasing angiotensin II receptor type 1 (AT-1) levels, and suggests it may protect against its testicular cancer-promoting effects. The contradictory findings in these studies underline the need to further investigate the possible interactions between resveratrol and different phthalates and their role in cancer incidence and progression.

Kang et al. (2013) conducted a study in human BG-1 ovarian cancer cells that showed the administration of resveratrol reversed the increase in cell proliferation induced by exposure to BPA by inhibiting cross-talk between ERa and IGF-1R signaling pathways. Consequently, they commented that resveratrol may prevent BPA from enhancing the progression of ovarian cancer. Finally, in a combination of in vitro and in vivo studies in human umbilical vein endothelial cells (HUVECs) and rats, respectively, Rameshrad et al. (2018) found that co-administration of resveratrol (as well as grape seed extract) with BPA prevented its ability to induce endothelial dysfunction, apoptosis, and other cardiotoxic effects. These benefits were attributed to resveratrol's ability to reduce lipid peroxidation and endothelial dysfunction, reflected by decreases in vascular cell adhesion molecule-1 (VCAM-1) and malondialdehyde (MDA) levels. These findings provide some support for the notion that resveratrol may mitigate some of the potentially atherogenic effects of BPA.

Curcumin

Curcumin is a bright-yellow diarylheptanoid found in turmeric root that has long been lauded for its supposed anti-inflammatory and antioxidant effects. Expectedly, there are a number of studies that have investigated the potential protective effects of this compound against BPA and phthalate-induced cellular damage. Li et al. (2014) and Dairkee et al. (2013) carried out studies using malignant and healthy human breast cells in which they determined the upregulation of cell-proliferation caused by exposure to BPA was prevented by co-administration of curcumin. The antagonistic effects of curcumin were ascribed to their ability to inhibit oncogenic microRNA expression, reduce ERa and mTOR pathway activation, and maintain proapoptotic negative regulators of the cell cycle. Altogether, these two studies indicate that curcumin may blunt the breast-cancer promoting effects of BPA.

Alongside possible anti-cancer effects, a few studies have shown that curcumin may prevent BPA-mediated insulin resistance. In studies using HepG2 and LO2 liver cell lines, one group of researchers discovered that the administration of curcumin alongside BPA abolished its ability to induce insulin resistance. These effects were presumably due to inhibition of JNK pathway activation, improved glucose uptake and shuttling into glycolytic pathways, and reduced oxidative stress and inflammation, indicated by decreases in MDA, TNFa, and Il-6 (Geng et al., 2017, 2018). As such, their findings insinuate that curcumin may protect against BPA-induced diabetes and insulin resistance.

Although the evidence is fairly scant, some studies have shown that curcumin may also prevent adverse health consequences of phthalates. Tsai et al. (2015) conducted a series of experiments that found while DEHP exposure increased the migration and invasion of cancerous liver cells in vitro and promoted tumor growth in vivo, these effects were suppressed by curcumin. Furthermore, it was found that this likely occurred due to the ability of curcumin to inhibit the AhR/ERK/SK1/S1PR3 signaling pathway that is activated by DEHP. Such observations highlight the possibility that curcumin might prevent DEHP-mediated carcinogenesis. Another study carried out by Wang and Dong (2012) revealed that pretreatment of HUVECs with curcumin diminished increases in ICAM-1 and IL-8 expression induced by DEHP through ERK and p38 MAPK signaling pathways. Though these authors were using these markers to study the possible role of DEHP in allergic inflammatory disorders, their results also underscore how curcumin may

Table 4 Observational studies on phthalate exposure and diabetes/insulin resistance, cancer, and CVD

Lead author/year	Country/study type	Sample demographic	Follow up	Exposure assessment method	Outcome	Significance of findings
Liu et al. (2020)	China/case–control	425 adults	N/A	Urinary phthalates	Cancer	Thyroid Cancer: + (MMP and MEHHP) - (MBP)
Miao et al. (2020)	China/case–control	222 adults	N/A	Urinary phthalates	Cancer	Thyroid Cancer: + (MEHP, MEOHP, MECPP, MEHHP, and sum DEHP)
López-Carrillo et al. (2010)	Mexico/case–control	454 women aged > 18	N/A	Urinary phthalates	Cancer	Breast Cancer: + (MEP) - (MBzP and MCPP)
Chang et al. (2018)	Taiwan/case–control	60 elderly men	N/A	Urinary phthalates	Cancer	Prostate Cancer: + (MiNP) NS (remaining metabolites)
Chou et al. (2021)	Taiwan/Cross-Sectional	496 middle aged chronic kidney disease patients	N/A	Urinary phthalates	Cancer	Urothelial Cancer: + (MEHHP)
Su et al. (2021)	Taiwan/Cross-Sectional	221 adults aged > 20	N/A	Urinary phthalates	Cancer	Colorectal Cancer: + (MEHP)
Chuang et al. (2020)	Taiwan/Prospective Cohort	240 men aged 30–65	8–9 years	Urinary phthalates	Cancer	Prostate Cancer: NS (All Metabolites) + (MBzP, DEHP, MECPP, MEOHP, MEHHP, and MCMHP in participants w/ obesity)
Holmes et al. (2014)	USA/case–control	170 women aged 30–88	N/A	Urinary phthalates	Cancer	Breast Cancer: + (MEHP)
Parada et al. (2018)	USA/case–control and Prospective Cohort	1308 adult women	17.6 years	Urinary phthalates	Cancer	Breast Cancer: NS (All Metabolites) Breast Cancer Mortality:— (MCPP and MCOP)
Morgan et al. (2017)	USA/Cross-Sectional	3003 women aged > 20	N/A	Urinary phthalates	Cancer	Breast Cancer: NS (All Metabolites)
Reeves et al. (2019a, b)	USA/Prospective Cohort	504 postmenopausal women aged 50–79	Up to 19 years	Urinary phthalates	Cancer	Breast Cancer: NS (All Metabolites)
Trasande et al. (2021)	USA/Prospective Cohort	5303 adults aged > 20	~ 10 years	Urinary phthalates	Cancer	Cancer Mortality: NS (All Metabolites)
Bai et al. (2017)	Australia/Cross-Sectional	1504 men aged 39–84	N/A	Urinary total phthalate	CVD	CVD: + (Total phthalates)
Dong et al. (2017)	China/Cross-Sectional	3082 middle aged adults	N/A	Urinary phthalates	CVD	CVD: NS (All Metabolites)
Su et al. (2019)	Taiwan/Cross-Sectional	696 adults aged < 60	N/A	Urinary phthalates	CVD	Coronary Heart Disease: + (MEHP, MnBP, and MiBP)
Shiue (2013)	USA/Cross-Sectional	5383 adults aged > 20	N/A	Urinary Phthalates	CVD	Stroke: + (MnBP) NS (Remaining Metabolites)
Sturgeon et al. (2016)	USA/Prospective Cohort	5080 adults aged > 40	7 years	Urinary phthalates	CVD	CVD: NS (All Metabolites)

Table 4 (continued)

Lead author/year	Country/study type	Sample demographic	Follow up	Exposure assessment method	Outcome	Significance of findings
Trasande et al. (2021)	USA/Prospective Cohort	5303 adults aged > 20	~ 10 years	Urinary phthalates	CVD	CVD Mortality: + (MnBP, MEHHP, MEOHP, and MECPP) NS (Total HMW and DEHP metabolites)
Bai et al. (2017)	Australia/Cross-Sectional	1504 men aged 39–84	N/A	Urinary phthalates	Diabetes/IR	Diabetes: + (Total phthalate metabolites)
Dirinck et al. (2015)	Belgium/Cross-Sectional	123 adults aged > 18 with obesity and no history of diabetes	N/A	Urinary phthalates	Diabetes/IR	HOMA-IR: + (Only MEP)
Dales et al. (2018)	Canada/Cross-Sectional	2119 subjects aged > 12	N/A	Urinary phthalates	Diabetes/IR	HomA-IR: + (MEHHP, MEOHP, and sum of DEHP metabolites)
Shapiro et al. (2015)	Canada/Prospective Cohort	1274 pregnant women aged > 18	First Trimester until Delivery	Urinary phthalates	Diabetes/IR	GDM: NS (All metabolites)
Dong et al. (2017)	China/Cross-Sectional	3082 middle aged adults	N/A	Urinary phthalates	Diabetes/IR	Diabetes: + (MEHHP, MEOHP, MECPP, MCMHP, and sum of DEHP metabolites only in men)
Dong et al. (2018)	China/Cross-Sectional	300 adults aged > 50	N/A	Urinary and serum phthalates	Diabetes/IR	HomA-IR: + (MMP, MnBP, MBzP, MEHP, MEHHP, and MCMHP)
Duan et al. (2019)	China/cross-sectional	500 adults	N/A	Urinary phthalates	Diabetes/IR	Diabetes: + (MEOHP, MEHP, sum of DEHP metabolites, MMP, MiBP, and MCPP) - (MECPP and MCHP)
Li et al. (2011)	China/cross-sectional	60 adult women with PCOS	N/A	Urinary phthalates	Diabetes/IR	Insulin Resistance: NS (All Metabolites)
Piecha et al. (2016)	Czech Republic/cross-sectional	168 middle aged adults with metabolic syndrome	N/A	Urinary phthalates	Diabetes/IR	Diabetes: (MnBP, OH-MEHP, OXO-MEHP, and cx-MEHP)
Lee et al. (2021)	Korea/cross-sectional	3782 adults aged > 19	N/A	Urinary phthalates	Diabetes/IR	Diabetes: + (All metabolites, only using standard gravity adjusted model)
Kim et al. (2013)	Korea/prospective cohort	560 elderly adults aged > 60	2 years	Multiple urinary phthalate Measures	Diabetes/IR	HOMA-IR: + (Sum of DEHP metabolites)
Wu et al. (2021a, b)	Mexico/prospective cohort	618 pregnant women aged > 18	4–5 and 6–8 years	urinary phthalates	Diabetes/IR	HOMA-IR: + (Sum of all metabolites, MECPTP, and sum of DBP metabolites)

Table 4 (continued)

Lead author/year	Country/study type	Sample demographic	Follow up	Exposure assessment method	Outcome	Significance of findings
Li et al. (2019a)	Saudi Arabia/case–control	101 adults aged 28 to 68	N/A	Urinary phthalates	Diabetes/IR	Diabetes: + (All phthalate metabolites)
Lind et al. (2012)	Sweden/cross-sectional	1016 elderly adults	N/A	Urinary phthalates	Diabetes/IR	Diabetes: + (MiBP)
Chen et al. (2017)	Taiwan/cross-sectional	786 adolescents and young adults aged 12–30	N/A	Urinary phthalates	Diabetes/IR	HOMA-IR: + (MEHP only in young adults)
Huang et al. (2014)	USA/cross-sectional	3083 non-diabetic adults aged 12–80	N/A	Urinary phthalates	Diabetes/IR	HOMA-IR: + (All metabolites)
James-Todd et al. (2012)	USA/cross-sectional	2350 women aged 20–79	N/A	Urinary phthalates	Diabetes/IR	Diabetes: + (MBzP) HOMA-IR: + (MiBP and DEHP metabolites)
Stahlhut et al. (2007)	USA/cross-sectional	949 men aged > 18	N/A	Urinary phthalates	Diabetes/IR	HOMA-IR: + (MBP, MBzP, and MEP)
Transande et al. (2013b)	USA/cross-sectional	766 adolescents aged 12–19	N/A	Urinary phthalates	Diabetes/IR	HOMA-IR: + (sum of HMW and DEHP metabolites)
James-Todd et al. (2016)	USA/prospective cohort	350 pregnant women aged > 18	1st to 2nd trimester	Urinary phthalates	Diabetes/IR	Insulin Resistance: + (MEP) - (Sum of DEHP metabolites)
Li et al. (2019b)	USA/cross-sectional	1605 participants aged 12–85	N/A	Urinary phthalates	Diabetes/IR	HOMA-IR: + (sum of DEHP metabolites) - (MEP)
Shaffer et al. (2019)	USA/prospective cohort	705 pregnant women aged > 18	First trimester until Delivery	Urinary phthalates (T1 and T3)	Diabetes/IR	GDM: + (MEP)
Sun et al. (2014)	USA/prospective cohort	1587 female nurses > 20	~ 7 years	Urinary phthalates	Diabetes/IR	Diabetes: + (total phthalate, butyl phthalate, and DEHP metabolites in NHS II)
Zukin et al. (2021)	USA/prospective cohort	411 pregnant Latina women	First trimester until delivery	Urinary phthalates	Diabetes/IR	GDM: NS (all metabolites)

+ significant positive association, − significant negative association, *NS* non-significant

attenuate the atherogenicity of DEHP considering ICAM-1 and IL-8 have been implicated in CVD.

EGCG

EGCG, a catechin primarily found in green tea, has a considerable amount of evidence supporting its potential to confer protection against an array of chronic diseases. Unfortunately, research on its interactions with BPA and phthalates is sparse, but does suggest it exerts favorable effects. Mohsenzadeh et al. (2021a) demonstrated that in rat aortic cells and HUVECs, EGCG improved vascular responsiveness and attenuated increases in MDA, cleaved caspase-3, LC3A/B, bax/bcl2 ratio, and VCAM-1 elicited by BPA, respectively. Consequently, EGCG may prove useful in reducing BPA-induced impairments in vascular function and slow the progression of atherosclerosis. Continuing their work, these authors conducted another study in Wistar rats to investigate possible protective effects of EGCG against a broader range of metabolic derangements caused by BPA (Mohsenzadeh et al., 2021a, b). The addition of EGCG to BPA treatment markedly reduced its ability to promote increases in body weight, blood pressure, fasting plasma glucose, LDL-c, leptin, and inflammatory cytokines, and decreases in HDL-c, adiponectin, and GSH. The suppression of these adverse effects was largely attributed to EGCG-mediated increases in the phosphorylation of hepatic proteins (IRS-1, PI3K, and Akt) involved in the insulin signaling pathway. While further study is needed to verify these results, they allude to the possibility that EGCG may confer substantial protection against the multitude of metabolic detriments that appear to result from BPA exposure.

Genistein

Genistein is a naturally occurring phytoestrogen and isoflavone found in abundance in soybeans that has been extensively studied for its ability to protect against various cancers, CVD, and other common non-communicable diseases. A few interactions between this polyphenol and BPA have been investigated, specifically in relation to estrogen-sensitive cancer outcomes. In a study using rat sucklings, Wang et al. (2014) found that while BPA exposure during lactation encouraged proliferation of abnormal mammary gland cells later in life, co-exposure to genistein caused increases in normal proliferation and cell-differentiation of mammary gland structures earlier in life and significantly lowered abnormal proliferation later in life. Given that the differential responses seen with the addition of genistein can decrease mammary gland cell susceptibility to cancer, this compound may diminish the carcinogenicity of BPA. Similarly, multiple studies have suggested that genistein can protect against BPA-induced progression of ovarian cancer by reducing BG-1 ovarian cancer cell epithelial-mesenchymal transition, migration, and proliferation, and promoting apoptosis. These effects were hypothesized to result at least partially from genistein-mediated suppression of ERa and IGF-1R signaling pathways (Hwang et al., 2013a, 2013b; Kim et al., 2015).

Naringenin

Naringenin is a flavanone found almost exclusively in citrus fruits. Historically, research has suggested naringenin possesses a wide variety of biological activities and imparts numerous health benefits, leading some researchers to consider the possibility it could attenuate detrimental impacts of compounds such as EDCs. Of the compounds and outcomes considered in this review, it has only been studied in the context of inhibiting breast cancer-promoting effects of BPA. Using human estrogen-dependent breast cancer cell lines (MCF-7 and T47D), Bulzomi et al. (2012) found that naringenin was able to increase apoptosis by activating the p38 pathway and diminish the cell proliferation resulting from exposure to BPA by preventing its ability to interact with the ERa receptor and activate the Akt pathway. Thus, naringenin could possess the ability to prevent cancer-promoting capabilities of BPA.

Kaempferol

Kaempferol, a flavonol found in a number of fruits, teas, and ginkgo leaves, has been theorized to reduce the risk of common chronic diseases (especially cancer) through its ability to enhance antioxidant defenses against free radicals and modulate many other signaling pathways involved in disease pathology. In a study carried out using VM7Luc4E2 breast cancer cells, Lee et al. (2018) discovered that kaempferol was able to decrease breast cancer progression caused by exposure to BPA and triclosan through inhibition of their proliferative and anti-apoptotic effects. Administration of kaempferol in conjuction with BPA or triclosan exposure was found to upregulate the pro-apoptotic protein Bax, which was inhibited in the presence of either of these compounds alone. These initial results suggest there is a chance that kaempferol may inhibit the carcinogenicity of BPA, although additional research is needed to confirm their credibility.

Paucity of evidence in humans: minimally traversed terrain

Despite the existence of conceivable mechanisms by which certain dietary polyphenols or other antioxidant/anti-inflammatory compounds could prevent certain cancer, diabetes/insulin resistance, and CVD-promoting effects of BPA or

Table 5 Studies investigating the ability of select polyphenols to inhibit cancer, CVD, and diabetes/insulin resistance-promoting effects of BPA and phthalates

Lead author/year	Study type	Endocrine disrupting chemical	Polyphenol	Related health outcome	Main findings
Botelho et al. (2009)	Animal model	DEHP	Resveratrol	Cancer	Co-administration of resveratrol with DEHP to rat dams did not protect against the deleterious effects induced by DEHP in their male offspring
Ünal et al. (2016)	Animal model	DBP	Resveratrol	Testicular cancer	Co-administration of resveratrol with a low, but not high, dose of DBP prevented dysregulation of apoptosis in the testis of male rats
Kang et al. (2013)	Cell culture	BPA	Resveratrol	Ovarian cancer	Co-administration of resveratrol with BPA inhibited its ability to increase cellular proliferation
Rameshrad et al. (2018)	Cell culture and animal model	BPA	Resveratrol	CVD	Resveratrol mitigated BPA-induced endothelial dysfunction, apoptosis, lipid peroxidation, and markers of vascular inflammation
Li et al. (2014)	Cell culture	BPA	Curcumin	Breast cancer	Co-administration of curcumin with BPA inhibited its ability to promote the proliferation of human breast cancer cells
Dairkee et al. (2013)	Cell culture	BPA	Curcumin	Breast cancer	Curcumin reduced BPA-induced proliferation of non-cancerous human breast epithelial cells, in addition to diminishing their ability to evade apoptosis
Geng et al. (2017)	Cell culture	BPA	Curcumin	Diabetes/insulin resistance	Co-treatment of HepG2 liver cells with curcumin prevented BPA from inducing insulin resistance
Geng et al. (2018)	Cell culture	BPA	Curcumin	Diabetes/insulin resistance	Curcumin alleviated BPA-induced insulin resistance in LO2 liver cells
Tsai et al. (2015)	Cell culture and animal model	DEHP	Curcumin	Liver cancer	Curcumin treatment suppressed the ability of BPA to increase migration and invasion of cancerous cells and promote tumor growth
Wang and Dong(2012)	Cell culture	DEHP	Curcumin	CVD	Pre-treatment of HUVECs with curcumin attenuated DEHP-induced increases in ICAM-1 and IL-8 expression
Mohsenzadeh et al. (2021a)	Cell culture and Animal Model	BPA	EGCG	CVD	In rat aortic cells and HUVECs, co-administration of EGCG with BPA improved vascular responsiveness and attenuated BPA-mediated increases in markers of vascular inflammation
Mohsenzadeh et al. (2021b)	Animal model	BPA	EGCG	Diabetes/insulin resistance and CVD	EGCG inhibited a range of metabolic aberrations observed in rats following exposure to BPA, including weight gain, insulin resistance, hyperlipidemia, and increases in inflammatory cytokines
Wang et al. (2014)	Animal model	BPA	Genistein	Breast cancer	In rat sucklings, genistein improved cell-differentiation of mammary glands early in life and reduced BPA-induced cell proliferation and impairment of apoptosis later in life
Hwang et al. (2013a)	Cell culture	BPA	Genistein	Ovarian cancer	Genistein suppressed BPA-induced proliferation of BG-1 ovarian cancer cells

Table 5 (continued)

Lead author/year	Study type	Endocrine disrupting chemical	Polyphenol	Related health outcome	Main findings
Hwang et al. (2013b)	Cell culture and animal model	BPA	Genistein	Ovarian cancer	Genistein inhibited BPA-induced BG-1 ovarian cancer cell proliferation by stimulating apoptosis and decreased tumor growth in mice
Kim et al. (2015)	Cell culture	BPA	Genistein	Ovarian cancer	Genistein decreased the migration capacity of BPA-treated BG-1 ovarian cancer cells
Bulzomi et al. (2012)	Cell culture	BPA	Naringenin	Breast cancer	Co-administration of naringenin with BPA increased apoptosis of MCF-7 and T47D breast cancer cells and decreased their proliferation
Lee et al. (2018)	Cell culture	BPA	Kaempferol	Breast cancer	Kaempferol inhibited BPA-induced VM7Luc4E2 breast cancer cell proliferation and enhanced apoptosis

phthalates, only a single observational studyendeavored to corroborate this possibility. In their investigation, Li et al. (2019b) did not consider specific polyphenols as protective against phthalate-associated insulin resistance, but instead the antioxidants vitamins A, E, C, and carotenoids. Regardless, they found that greater serum concentrations of beta carotene, reflective of greater dietary intake, attenuated the significant positive association between DEHP metabolites and HOMA-IR. While this particular study had some limitations, it still underscores there is likely value in exploring how intake of certain antioxidant/anti-inflammatory compounds could mollify health risks due to EDC exposure. Coupled together, Li et al.'s positive findings pertaining to beta carotene, a compound sharing the antioxidant and anti-inflammatory properties of polyphenols, and those from cell-culture/animal model studies on polyphenols interactions with BPA and phthalates, punctuate the fact this is an area of study rife with untapped potential. The latter indicate that future epidemiological studies should focus on considering the potential of genistein, naringenin, curcumin, and kaempferol to mitigate risks of breast or ovarian cancer due to BPA exposure, curcumin and EGCG to mitigate the risk of insulin resistance/diabetes due to BPA, resveratrol and EGCG to mitigate the risk of CVD due to BPA, and resveratrol and curcumin to mitigate risks of testicular cancer and CVD due to phthalate exposure. Furthermore, any other compounds that show promise in future cell culture and animal studies could also be considered in the same vein. If polyphenols are found to diminish the health detriments that result from EDC exposure, the consumption of a diet comprised mainly of fresh foods rich in these compounds would comprise a cost-effective and practical intervention capable of considerably improving public health without fully eliminating all sources of exposure, which will likely remain impracticable.

Discussion

Although studies characterizing sources of dietary exposure to BPA and HMW phthalates in the U.S. demonstrated that certain foods, food groups, and dietary patterns were consistently associated with greater exposure, a number of limitations were present and a couple major knowledge gaps remain. Limitations included the use of single spot urine sample collections, misalignment of urine sample and dietary record collection, and use of different adjustment methods for metabolite concentrations. Additionally, information pertaining to the contributions of specific subtypes of food groups to BPA/phthalate exposure, as well as on how packaging, storage, or processing methods may explain some of the variance in the observed associations, is scarce. Henceforth, while current evidence does provide useful information about general sources of dietary exposure,

future investigations are required in order to address these limitations and ambiguities.

Research on the associations between BPA/HMW phthalate exposure and cancer, CVD, and diabetes/insulin resistance was rather limited, and findings tended to be inconsistent, making it difficult to draw any firm conclusions. Many studies were cross-sectional or case–control, utilized a single urinary sample to classify exposure, and did not include known risk factors in adjustment models, all of which could invalidate the observed associations. There were a few prospective investigations, but unfortunately they still shared some of these limitations and their findings were similarly mixed. Nonetheless, BPA and HMW phthalate exposure were frequently associated with increased prevalence or incidence of some outcomes, highlighting the urgency for additional, well-designed studies to ascertain the magnitude of their influence on human health. At the very least, these studies should be prospective, include multiple extensive dietary records and urine sample collections, employ standardized urine dilution adjustment methods, and utilize strong multivariable models with adjustments for diet quality and other known disease risk factors. These practices will help establish temporality, reduce measurement error, and minimize the potential for residual confounding, in turn reducing uncertainty and allowing for stronger inferences to be made.

While an increased interest in identifying and characterizing EDCs and their possible impacts on human health has prompted a surge of research in recent years, many questions have yet to be appropriately answered. Since it would be impractical to discuss all of them, this review focused on two of the most commonly encountered and studied EDCs; BPA and phthalates. Literature concerning the main dietary sources of exposure to these compounds in the U.S. and their implications in three major chronic diseases; cancer, diabetes, and CVD, was reviewed and discussed. Finally, evidence supporting the possibility that certain polyphenols may attenuate adverse health effects associated with BPA and phthalate exposure was examined, and future research opportunities were identified.

Generally, studies on dietary exposure to BPA and phthalates in the U.S. demonstrated that canned foods and beverages, fast-food, and pre-packaged meals were the main sources of BPA, whereas high-fat dairy and meat, fried fish, fast and ultra-processed food, and grains were major sources of HMW phthalates. Although a few gaps in knowledge still need to be addressed, these findings suggest consuming a diet rich in fresh fruits, vegetables, whole grains, fish, low-fat dairy products, and legumes should minimize exposure to these compounds.

Current data concerning associations of BPA and HMW phthalate exposure with diabetes, cancer, and CVD does evince that typical levels of exposure may promote onset or progression of these diseases, but it is not unequivocal. Future investigations with robust methodology should be conducted to verify these observations, preferably emphasizing the outcomes currently deemed most likely to be affected by these compounds.

As discussed, though there are a host of in vitro and in vivo studies indicating polyphenols can inhibit detrimental cellular effects of BPA and phthalates, there is an absence of studies examining if they reduce the incidence of disease in humans. Henceforth, in addition to providing further clarification on the health implications of BPA and HMW phthalates, future investigations represent an opportunity to evaluate how the intake of various polyphenols may diminish the strength of their associations with disease outcomes. Findings from the available mechanistic studies offer useful information regarding which combinations of polyphenolic compounds, EDCs, and outcomes may be the most auspicious to study.

In closing, the many lingering questions and concerns surrounding the health impacts of EDCs strongly emphasize the urgent need for high-quality studies capable of providing more definitive answers. Moreover, inquiry into the attenuation of their possible health detriments by dietary antioxidant compounds such as polyphenols may prove especially fruitful and underscores an excellent research prospect for those involved in this area of study. Hopefully in the years to come there will be an abundance of well-coordinated research that will assist in unraveling current uncertainties.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

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