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Lifestyle interventions to reduce endocrine-disrupting phthalate and phenol exposures among reproductive age men and women: A review and future steps

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Abstract

Non-persistent endocrine-disrupting chemicals (EDCs), including phthalates and phenols, are ubiquitous in both the environment and human body. A growing body of epidemiologic studies have identified concerning links between EDCs and adverse reproductive and developmental health effects. Despite consistent evidence, risk assessments and policy interventions often arrive late. This presents an urgent need to identify evidence-based interventions for implementation at both clinical and community levels to reduce EDC exposure, especially in susceptible populations. The reproductive life cycle (menarche to menopause for females and after pubertal onset for males) includes some of the most vulnerable periods to environmental exposures, such as the preconception and perinatal stages, representing a key window of opportunity to intervene and prevent unfavorable health outcomes. This review aims to synthesize and assess behavioral, dietary, and residential EDC-driven interventions to develop recommendations for subsequent, larger-scale studies that address knowledge-gaps in current interventions during the reproductive life cycle. We selected 21 primary interventions for evaluation, in addition to four supplemental interventions. Among these, accessible (web-based) educational resources, targeted replacement of (known) toxic products, and personalization of the intervention through meetings and support groups, were the most promising strategies for reducing EDC concentrations. However, we document a paucity of interventions to prevent phthalate and phenol exposures during the reproductive years, especially among men. Accordingly, we recommend additional, larger clinical and community-based intervention studies to reduce EDC exposure. Specifically,

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*Phthalate and phenol abbreviations can also be found in Table 1.

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future intervention studies should focus on short-term, mid-, and long-term exposure reduction to phthalates and phenols. The latter, especially, is required for the development of clinical and public health guidelines to promote reproductive and developmental health globally.

Keywords

Endocrine-disrupting chemicals; Phthalates; Phenols; Interventions; Reproductive health

1. Introduction

Exposure to EDCs has become concerningly ubiquitous during the 21st century, representing a challenge for traditional risk assessment and society (Weschler, 2009; Schug et al., 2016). Today, EDCs hide in many everyday products such as: cosmetics, packaged and canned food, cleaning supplies, herbicides, pharmaceuticals, and more. First described in 1958 by endocrinologist Dr. Roy Hertz, EDCs are defined as exogenous chemical compounds, or their mixtures, that can interfere with any aspect of hormone action (Schug et al., 2016; Zoeller et al., 2012). Physiologic or metabolic changes to these systems following exposure to EDCs can occur through a variety of mechanisms, including, but not limited to, the interference of protein synthesis, secretion, cellular transport, and receptor binding (Schug et al., 2016; Zoeller et al., 2012; De Coster and van Larebeke, 2012; Kiyama and Wada- Kiyama, 2015; Lauretta et al., 2019; La Merrill et al., 2020). EDCs' ability to elicit molecular alterations critical to the etiology and progression of many diseases has inspired growing interest in understanding their underlying mechanisms of action. The harmful effects of phthalates and phenols on reproductive health and birth outcomes has provoked particular attention.

Previously, researchers have employed clinical and community interventions to reduce exposure to phthalates and phenols, but few have assessed if exposure reductions prevent adverse health outcomes. Most studies targeted women and men during their reproductive years, which for the purpose of this review are defined as the period between menarche and menopause in women and from pubertal onset onwards in men (Thomas et al., 2001). Though clinical and community-based interventions can target different stages of the human lifecycle, there is substantial evidence, both nationally and internationally recognized, that environmental exposure to phthalates and phenols may substantially impact fetal and infant health and development, especially during the preconception and prenatal periods, and may influence multiple generations (Hill et al., 2020; Harper et al., 2021; Atrash et al., 2006; Jacob et al., 2020; Stephenson et al., 2018). Preconception health, as defined by the CDC, encompasses human health during the reproductive years and is especially important for planned and unplanned pregnancies (Johnson et al., 2006). Emerging evidence shows that phthalate and phenol exposure results in epigenetic mechanisms in oocytes and sperm that reduce fecundity and can lead to several adverse pregnancy outcomes, including pregnancy loss and poor-quality embryos (Harville et al., 2019; Jenkins and Carrell, 2011; Kumar et al., 2013; Chen et al., 2016; Braun et al., 2017; Robinson et al., 2012; Marcho et al., 2020; Oluwayiose et al., 2021; Eichenlaub-Ritter and Pacchierotti, 2015; Santangeli et al., 2017;

Zhang et al., 2018; Segal and Giudice, 2019; Cariati et al., 2020; Jiang et al., 2021; Hipwell et al., 2019).

Although phthalates and phenols are metabolized within hours and are designated as non-persistent chemicals, the ubiquitous presence of EDCs in consumer products and the environment has produced daily chronic and episodic exposure with special concern for the most susceptible populations. The preconception period, the three months prior to conception, is a critical exposure window during which many reproductive and developmental outcomes are programmed. Recent studies have shown the significance of phenol and phthalate exposure during this understudied period (Stephenson et al., 2018; Hipwell et al., 2019; Zhang et al., 2021; Mustieles et al., 2018; Smarr et al., 2015). This review presents published intervention studies that address phthalate and phenol exposure during reproductive years, thereby highlighting the opportunity to reduce environmental EDC exposure through interventional methods. Furthermore, it aims to inspire improved approaches for future interventions to reduce exposure to EDCs, with the goal of improving reproductive health globally.

2. Overview of EDCs: Phthalates and phenols

2.1. Routes of exposure and potential targets

Phthalates and phenols are derivatives of benzene that sneak into products all around us—from packaged foods and cosmetics, to the phone, tablet, and laptop being used to view, download, or print this article. Phthalates and phenols are often referred to as “plasticizers” since they increase the shape, flexibility, and durability of plastics. Although these chemicals are short-lived and rapidly metabolized by the body (e.g., the phenol derivative bisphenol A has a half-life of around 6 h, phthalate monoesters have a half-life of around 12 h), their environmental ubiquity results in chronic exposure (Hoppin et al., 2002; Calafat et al., 2010; Liebelt et al., 2007; Völkel et al., 2002). Additionally, some derivatives of phenols, such as triclosan (TCS) and triclocarban (TCC), are more lipophilic and have longer half-lives (e.g., TCS has been observed to have half-life of about 21 h) (Smarr et al., 2017). Exposure to these chemicals can occur in our natural and built environments and may be influenced by our social environment—making them nearly inescapable in everyday life.

Exposure to non-persistent EDCs has been linked to an extensive list of poor health outcomes, including impaired reproductive health and adverse metabolic, immune, neurodevelopmental, and respiratory outcomes (Table 1) (Philippat et al., 2015; Paciência et al., 2019; Rogers et al., 2013 Apr; Ruiz et al., 2018; Lu et al., 2020 Nov; Costa et al., 2013/11/20. 2014 Oct 15.; Henley and Korach, 2006; Yilmaz et al., 2020; Jin et al., 2010; Chapin et al., 1997 Nov; Dobrzy ska, 2016). According to La Merrill et al. (La Merrill et al., 2020), EDCs lead to detrimental biological effects through a variety of mechanisms, including acting as an agonist, antagonist, or otherwise interacting with hormone receptors, disrupting hormone receptor expression, influencing signal transduction (leading to post-translational modifications), promoting epigenetic modifications in hormone-producing or hormone-responsive cells, changing hormone synthesis and transport, modifying hormone metabolism, changing the fate of hormone-producing or hormone-responsive cells, and changing the distribution of circulating hormone levels within the body—La Merrill et al.

(La Merrill et al., 2020) considers these to be the “key characteristics” of EDCs (La Merrill et al., 2020). While these actions broadly describe EDCs, researchers are still investigating the specific mechanisms of these chemicals. Nevertheless, the framework proposed by La Merrill et al. (La Merrill et al., 2020) may be useful when grouping EDCs for risk assessment, when determining which EDCs may pose the greatest threat, and, ultimately, when deciding which EDCs to prioritize during interventions.

It is important to note that although the term *endocrine disruptor* is now legally defined with implications for risk assessment and policy making, many EDCs show co-existing endocrine and non-endocrine actions (e.g., oxidative stress, inflammation), and are currently regarded as disruptors of homeostasis and physiology at multiple levels (Slama et al., 2016). Movement towards re-defining these exposures beyond their endocrine effects is needed to ensure a comprehensive understanding and response. Indeed, limiting their consideration as only “endocrine disrupting” misses the extensive range of impairments to human health. Regardless of their definition, their pervasiveness requires interventions to identify primary sources of phthalates and phenols exposure and to prioritize the items and consumer products contributing to higher internal EDC concentrations. Designing effective interventions to reduce exposure to EDCs poses a daunting task because individuals are exposed through inhalation, ingestion, and dermal contact (Casas et al., 2011). Some of the main sources of nonpersistent EDCs include dietary, behavioral, and residential/household exposures (Fig. 1). Interventions focus on one or multiple pathways to reduce participant exposure to EDCs; however, it is often hard to avoid all potential exposure sources. Additional studies should be conducted to further investigate exposure patterns and elucidate which exposure sources contribute most to internal concentrations of EDCs.

2.2. Phenols

The main concern with phenolic EDCs includes their impact on reproductive and endocrine outcomes, as supported by both toxicological and epidemiological studies, including changes in birth size, semen quality, and impaired reproductive capacity (Kahn et al., 2020; Rodprasert et al., 2021; Gore et al., 2015; Wang et al., 2019; Zhang et al., 2021; Mustieles et al., 2020; Messerlian et al., 2018; Joensen et al., 2018; Dodge et al., 2015). Phenols are often found in personal care products (PCPs) like sunscreen, cosmetics, fragrances, and toothpaste, in addition to manufactured plastics commonly used in food and beverage packaging, storage containers, can-linings and other everyday plastic items (Table 1) (Casas et al., 2011; Philippat et al., 2015; Khan et al., 2021; Vandenberg et al., 2007; Schecter et al., 2010; Mustieles et al., 2020; Ikhlas and Ahmad, 2020; Rosenmai et al., 2014; Ullah et al., 2018; Serra et al., 2019; Liao and Kannan, 2013; Michałowicz and Duda, 2007; Lv et al., 2019; Kahn et al., 2020). The specific chemical “phenol” is a known mutagen and possible carcinogen. “Phenol” is also considered a skin irritant that promotes oxidative stress to induce hepatotoxicity and hematotoxicity (Phenols, 2017). Bisphenols are derivatives of “phenol” that are used in or formed during the manufacturing of plastic products such as epoxy resins (Phenols, 2017). Bisphenol A (BPA) is one of the most common and well-studied bisphenols in recent years (Khan et al., 2021). This plasticizer is added during manufacturing to ensure durability of epoxy linings or hardening of polycarbonate plastics (Khan et al., 2021; Vandenberg et al., 2007; Schecter et al., 2010). BPA has been the

archival of the endocrine disruption field, providing strong evidence of multisystemic effects at low doses (Mustieles et al., 2020).

In addition to bisphenols, other derivatives such as TCS, TCC, and parabens (e.g., methylparaben [MP], ethylparaben [EP], propylparaben [PP], butylparaben [BuP]) are abundant in the environment impair reproductive health. For example, TCS and TCC are lipophilic, antimicrobial agents and preservatives added to soaps and dental hygiene products that are associated with decreased fecundity at elevated levels (TCS) and decreased gestational age at birth (TCC) (Vélez et al., 2015; Geer et al., 2017). More so, parabens are amphipathic preservatives that have been associated with diminished fecundability (MP and EP) in couple-based models (Smarr et al., 2017). Chlorophenols, catechol, nitrophenol, and aminophenol are phenolic chemical groups present in the natural environment but intervention studies have neglected researching them to the extent of BPA, parabens, TCS, and TCC (Michałowicz and Duda, 2007). These phenol compounds, like bisphenols, are used to manufacture plastics and can leach into soil and/or bioaccumulate in water (Lv et al., 2019).

2.3. Phthalates

Recent epidemiologic studies have found associations between environmental exposure to phthalates and adverse reproductive health outcomes, such as reduced fertility and disruptions in testicular development, mainly derived from their alteration of the hypothalamic-pituitary–gonadal axis. Phthalates' effect on peroxisome proliferator activated receptors (PPARs) and oxidative stress may also influence health outcomes (Hliseníková et al., 2020; Lottrup et al., 2006; Lyche et al., 2009; Heudorf et al., 2007; Hauser and Calafat, 2005; Baken et al., 2019; Benjamin et al., 2017). Phthalates are added to manufactured plastic products, such as vinyl flooring or food packaging, to improve flexibility and durability (Heudorf et al., 2007; Cadogan and Howick, 2012; Schettler, 2006). Phthalates are also found in PCPs, pharmaceuticals and medical devices, household furnishings, cleaning supplies, and others items (Table 2) (Heudorf et al., 2007; Cadogan and Howick, 2012; Schettler, 2006). Di(2-ethylhexyl) phthalate (DEHP) is a commonly used plasticizers and found in many of the items listed above, especially flexible plastics. DEHP is widely studied and observed to be toxic to endocrine and reproductive systems—contributing to decisions to regulate DEHP in Europe, Canada, and other countries (Rowdhwal and Chen, 2018).

Phthalates (*ortho*-phthalates) are generally divided into two categories: low-molecular weight (LMW) phthalates, which have three to six carbon-atoms in their backbone structure, and high-molecular weight (HMW) phthalates, which contain greater than six carbon-atoms in their backbone structure. (Segal and Giudice, 2019; Mustieles et al., 2020; Ikhlas and Ahmad, 2020) Individuals can experience LMW and HMW phthalate exposure simultaneously: food consumption is a primary source of HMW phthalate exposure and many LMW phthalates are found in PCPs. Robust epidemiologic evidence supports an association between exposure to both LMW and HMW phthalates and impaired reproductive health and development (Zhang et al., 2020; Yland et al., 2022; Kumar et al., 2015; Koch et al., 2013; Oh et al., 2006; Koniecki et al., 2011; Wolf et al., 1999; Jobling et al., 1995; Harley et al., 2019). DEHP, a HMW phthalate, has been detected at relatively

high concentrations in study populations representative of the United States (Meeker and Ferguson, 2011). Such findings highlight the substantial opportunity and potential impact that phthalate and or phenol intervention studies may have on safeguarding reproductive health.

2.4. Phenol and phthalate alternatives and replacements

The introduction of replacement products has made recognizing potential exposure routes and minimizing exposure increasingly complex. Based on limited studies, alternative chemicals in plastic products are anticipated to have similar endocrine disruption and developmental toxicity as their structural analogs, though the health effects of several alternatives remain unknown. Although researchers have critically investigated the health effects of BPA and spearheaded its regulation, there are surprisingly few studies addressing the multiple structural analogs to BPA (often used as alternatives) that may pose similar health risks, such as bisphenol S (BPS), bisphenol B (BPB), and bisphenol F (BPF), listed in Table 1. Some studies have examined the effects of BPA alternatives in mouse models and have observed that BPF, BPS, and BPB have similar androgenic/antiandrogenic and estrogenic/antiestrogenic activities as BPA (Ullah et al., 2018). Specific reproductive health outcomes following BPF, BPS, and BPB exposure may include decreased testosterone and toxic effects on spermatogenesis (Ullah et al., 2018). Additional rodent studies have found that BPB exposure decreased sperm counts and sperm quality in mice exposure (Ikhlas and Ahmad, 2020; Rochester and Bolden, 2015; Carvaillo et al., 2019). These budding observations highlight the importance of accounting for persistent routes of exposure if individuals are using BPA-free alternatives. While BPA-free products have been sought after in recent years, alternatives are typically manufactured with other bisphenols that may pose similar health risks. (Ikhlas and Ahmad, 2020; Rosenmai et al., 2014; Ullah et al., 2018; Serra et al., 2019; Liao and Kannan, 2013; Michałowicz and Duda, 2007; Lv et al., 2019).

Similar to BPA, several phthalates are regulated due to epidemiology and toxicology studies that report an association between phthalates and negative health outcomes. Plasticizers such as di-isononyl phthalate (DiNP), di-isopropyl heptyl phthalate (DHPH), and DEHP have been replaced with phthalate-free alternatives that have comparable structures such as di(isononyl)cyclohexane-1,2, -dicarboxylate (DINCH) and di-2-ethylhexyl terephthalate (DEHTP) (Mínguez-Alarcón et al., 2016). Similar to BPA-free alternatives, phthalate-free alternatives like DINCH may have similar negative health effects. Among females, exposure to DINCH, typically through cosmetics or polyvinyl chloride (PVC) materials, has been associated with decreased estradiol concentrations and retrieved oocyte counts (Mínguez-Alarcón et al., 2016). DINCH has also been observed to impact Leydig cell function and cause premature aging of the testes in mice models (Capioli et al., 2017). Unfortunately, currently there is no toxicity data on DEHTP in humans, though limited animal studies have observed DEHTP to have a minor effect on liver weight among rats when DEHTP comprised 1 % of their diet for 90 days (Barber and Topping, 1995). DEHTP exposure has also been reported to be widespread among populations in the United States (Silva et al., 2019; Silva et al., 2017). Like BPS, BFS, and BPB, studies exploring the potential health effects of DINCH and DEHTP are sparse or nonexistent. Plastic products that claim to be phthalate- and or phenol-free may still impact reproductive health—implying

that individuals should avoid or minimize plastic products during reproductive periods and interventions.

2.5. Reproduction health outcomes: The importance of paternal participation in interventions

Beyond adverse health impacts on mothers and women of child-bearing age, EDC exposures have been linked to long-term adverse health outcomes in their offspring, including, but not limited to childhood obesity and insulin resistance, delayed growth, cognitive and behavioral disorders, congenital abnormalities including heart defects, urogenital defects, and certain cancers (Wang et al., 2019; Park, 2020; Wang et al., 2018; Chatzi et al., 2019; Doherty et al., 2019; Tinkelman et al., 2020; Ren et al., 2018; Rankin et al., 2009; Fetita et al., 2006; Guo et al., 2021; Evans et al., 2019; Jacobson et al., 2018). During the preconception period, gametes are vulnerable to enduring, EDC-related epigenetic modifications that can be passed between generations (Stephenson et al., 2018; Marcho et al., 2020; Xin et al., 2015; Brehm and Flaws, 2019). As a result, optimizing gamete function during the preconception period is essential to preventing EDC-driven, multigenerational epigenetic inheritance (Marcho et al., 2020; Xin et al., 2015; Brehm and Flaws, 2019). Epidemiology studies have linked preconception exposure to phthalates and phenols among females *and* males to preterm birth and birth size (Zhang et al., 2021; Smarr et al., 2015; Frederiksen et al., 2014). Since women often carry the societal burden of pregnancy loss or adverse birth outcomes, paternal reproductive health is frequently overlooked.

Unlike maternal exposures, early studies that investigated paternal exposures to phthalates and phenols mainly considered occupational exposures, birth defects, or cancer outcomes (Braun et al., 2017). Moving forward, intervention strategies should reflect the joint contribution of both progenitors to birth outcomes and human vulnerability to such chemicals because EDCs are widespread outside of occupational settings (Hipwell et al., 2019; Zhang et al., 2021). Paternal environmental exposures, specifically during the preconception period, contribute to adverse birth outcomes primarily through epigenetic modifications (DNA methylation, histone modification, altered microRNA) that influence sperm development and decrease sperm quality (Harville et al., 2019; Jenkins and Carrell, 2011; Kumar et al., 2013; Chen et al., 2016; Braun et al., 2017; Robinson et al., 2012; Marcho et al., 2020). These modifications to the epigenome may impair male fertility and embryonic development, increase the risk of adverse birth outcomes, and lead to multigenerational impairments or diseases (Stephenson et al., 2018). Including males and increasing paternal participation in interventions, especially during the preconception period, allows for the development of strategies to address couple-based pregnancy outcomes.

2.6. Measuring phenols and phthalates during intervention periods for comparison

Though phenols and phthalates are abundant in the environment, they have relatively short half-lives and are metabolized and excreted within hours (Hipwell et al., 2019; Casas et al., 2011; Oh et al., 2006; Koniecki et al., 2011). However, due to their omnipresence, >90 % of the general population experiences varying degrees of chronic exposure (Zhang et al., 2021; Frederiksen et al., 2014; Tschersich et al., 2021; Colorado-Yohar et al., 2021; CDC, 2015). Given their rapid metabolism there is significant variability in EDC concentrations

over a period of hours or a day, making it difficult to capture “true” EDC concentrations accurately and reliably. The growing evidence of phthalates and phenols association with adverse reproductive health outcomes necessitates the refinement and improvement of techniques to measure EDCs in intervention and epidemiological studies that explore potential associations. Establishing reliable methods for accurately measuring phthalate and phenol concentrations before, after, or throughout intervention periods is fundamental to determining whether changes in internal chemical concentrations are consequential. Currently, urine is commonly used to measure internal concentrations, though other samples such as colostrum/breast milk (dependent on the study population) are also employed. Conversely, residential intervention studies, among others, have investigated EDC exposure using indoor dust samples as a proxy for exposure (Rutkowska et al., 2020; Huang et al., 2021; Sears et al., 2020).

Detecting changes in phthalate and or phenol concentrations can be difficult and vulnerable to error due to the short biological half-life of phthalates and phenols (typically 12 h or less) and the variation in metabolism between different plasticizers (Calafat et al., 2010; Stahlhut et al., 2009). Ackerman et al. (Ackerman et al., 2014) explored temporal variability of phthalate metabolites and emphasized the importance of pooling urine samples and collecting multiple samples during each collection time to ensure measurements accurately capture internal concentrations of EDCs (Ackerman et al., 2014). Vernet et al. (Vernet et al., 2018) observed the greatest variation in phenol biomarkers throughout a single day and less variation of phenol biomarkers between days and weeks among pregnant women (Vernet et al., 2018). Additionally, an intervention led by Peng et al. (2018) demonstrated that BPA concentrations were the highest four hours after a meal, compared to two hours and six hours post-meal, and that the consistent timing of urine collection throughout the day is an important component for consideration when designing interventions (Peng et al., 2019). Most notably, Vernet et al. (Vernet et al., 2019) further investigated techniques to minimize within-person variability by comparing urine collection methods (Vernet et al., 2019). Vernet et al. (Vernet et al., 2019) found that pooling three samples per day (instead of pooling samples across days) yielded the greatest correlations (>0.80 , except for benzophenone-3 [BP-3] and TCS) and the most efficient estimates (Vernet et al., 2019). Cumulatively, these studies support that pooling urine from several timepoints scattered throughout the day is the best approach for accurately capturing the exposure.

3. Methods

3.1. Study population

Though phthalate and phenol exposure has been shown to result in poor health outcomes or physiologic changes throughout the human lifespan, this review will focus on reproductive years between menarche and menopause (and the comparative male reproductive years) consistent with increased interest in reducing phthalate and phenol exposure during preconception periods (Lauretta et al., 2019). The preconception period has been traditionally defined as the three months before conception; however, some recognize the preconception period as the entire oocyte maturation cycle (120 days or as a more fluid period longer than three months) before conception occurs, which accounts

for mistimed or unplanned pregnancies (Lancet, 2018). Regardless of the chosen definition, the period before conception is a critical window for fetal and infant health that provides an immense opportunity for clinical intervention to reduce toxic environmental exposures (Jacob et al., 2020; Stephenson et al., 2018). Due to the apparent lack of interventions conducted during the preconception period, this review will focus on interventions during reproductive years. Interventions that have participants in their reproductive years and report EDC concentrations (phthalates or phenols) following an intervention period are included in this study. Interventions that do not have any participants in their reproductive years or that do not report EDC concentrations (phthalates and or phenols) are excluded. Interventions that remain pertinent to the topic, but do not fit the inclusion criteria, are included as supplementary interventions. Although a systematic review was not conducted, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework was utilized to approach this topic and organize identified interventions (Page et al., 2021).

3.2. Identifying and categorizing interventions

Over the Spring of 2022 a literature search was conducted and 855 articles were initially identified on PubMed (articles were restricted to 2010–2022 and the search algorithm was: *intervention study OR education intervention OR dietary intervention OR dietary modification intervention OR dietary trial OR behavioral intervention OR randomized intervention*) AND (*bisphenol OR paraben OR benzophenone-3 OR triclosan OR phthalate*) NOT (*dental OR bond strength OR dentin OR enamel OR adhesive OR sealant OR suture OR crowns OR resin*). From the PubMed search, 835 were excluded because they were not intervention studies and commonly investigated triclosan or other TCs for dental/orthodontic purposes. Four additional papers were excluded because they were duplicates. Additionally, four non-intervention epidemiological studies with pertinent outcomes were excluded, but identified for supplemental discussion. Overall, 25 published interventions on phthalate and or phenol exposure were identified; 15 of the 25 interventions were found using the PubMed algorithm. The remaining 10 interventions were identified using Google Scholar and keywords: *canned products or food interventions, endocrine disruptor, bisphenol a, polycarbonate containers, home or household interventions, fast food, educational intervention, plastics, preconception period trial, personal care product intervention*. Out of the 25 phthalate and or phenol interventions identified, 4 were excluded and reported as supplementary interventions since they did not report changes in EDC concentrations among participants in their reproductive years (i.e., interventions with mother-infant pairs were excluded if changes in parental metabolites were not reported). Ultimately, 21 interventions met our inclusion criteria (i.e., participants in their reproductive years with reported phthalate and or phenol concentrations following an intervention period) (Fig. 2).

Selected interventions were further categorized into dietary interventions, behavioral interventions, and residential interventions. Dietary interventions included any intervention that focused on dietary exposures (water, food, plastic food containers, canned food); 14 interventions fit this criterion (Sathyanarayana et al., 2013; El Ouazzani et al., 2021; Park and Chung, 2021; Galloway et al., 2018; Szybiak et al., 2017; Barrett et al., 2015; Carwile et al., 2011; Rudel et al., 2011; Peng et al., 2019; Kim et al., 2020; van der Meer et al., 2021; Jo et al., 2020; Chen et al., 2015; Christensen et al., 2012). Behavioral

interventions were defined as those that concentrated efforts towards personal care products or other exposures to phthalates and phenols through product use; six interventions fit this category (Ley et al., 2017; Hagobian et al., 2017; Harley et al., 2016; Hagobian et al., 2021). Lastly, interventions that were directed towards reducing exposure throughout the entire household or community and/or used residential dust samples instead of biologic concentrations of phthalates and/or phenols were categorized as residential interventions; one residential intervention was identified (Rutkowska et al., 2020). For the purposes of this review, interventions were exclusively classified based on their research aim and primary efforts. Once the interventions were categorized based on the above methods, information about each intervention was extracted, including study design, study population (gender and exact age range was reported if provided), intervention characteristics, exposure of interest, primary outcomes relating to phthalate and phenol concentrations, and some measure of percent change over the intervention period (Table 3 and Table 4).

Any information regarding participants not in their reproductive years was excluded from our main results when possible (i.e., if studies only provided one estimate that combined child–adult pairs, that was still reported, but if mother and child concentrations were reported separately, then only the mother’s concentrations were included). Given the lack of interventions investigating EDCs, exposures and outcomes of interest were broadly defined during the screening process. Exposures of interest included phthalates and or phenols (including parabens) during reproductive years. Outcomes of interest included estimated EDC concentrations post-intervention, comparisons between pre-intervention and post-intervention concentrations, and other useful intervention outcomes (i.e., adherence, feasibility, and attitudes); confidence measures were included when provided (i.e., 95 % CI). Ultimately, the risk of bias was assessed by evaluating the study design, sample size, and methods used to measure EDCs. For example, studies that pooled multiple urine samples per day were assumed to have the least amount of within-person variability (nondifferential misclassification bias), compared to studies that only took a single spot urine sample pre- and post-intervention (Vernet et al., 2018; Vernet et al., 2019). Poor adherence among participants was also reported when provided. Ultimately, due to the limited amount of published intervention studies on this topic, a broad approach was used to identify/review interventions.

4. Results

4.1. Brief overview of interventions

Following the literature search, a total of 21 interventions were identified that fit the inclusion criteria (Fig. 2). (Sathyanarayana et al., 2013; Park and Chung, 2021; Galloway et al., 2018; Szybiak et al., 2017; Barrett et al., 2015; Carwile et al., 2011; Rudel et al., 2011; Peng et al., 2019; Kim et al., 2020; Kim et al., 2021; Ley et al., 2017; Hagobian et al., 2017; Harley et al., 2016; Hagobian et al., 2021; Rutkowska et al., 2020; van der Meer et al., 2021; Jo et al., 2020; Chen et al., 2015; Christensen et al., 2012) Overall, five primary interventions and two supplementary interventions had participants outside their reproductive years (e.g., families, mother–child pairs); however, the majority ($n = 16$ primary) had a study population exclusively in their reproductive years. Commonalities

among several of these interventions included: 1) distribution of pre- and post- (and sometimes mid-) questionnaires to capture or predict potential sources of exposure, 2) urine samples to measure changes in phthalate and or phenol concentrations, though sometimes blood or household dust were also used, and 3) educational materials or discussion groups/ interviews to inform participants about EDCs and sources of exposure in their immediate environment (focus of these materials depended on the intervention type). Alternate PCPs or catered diets were occasionally provided in the primary interventions ($n = 11$). The most common intervention length was three days ($n = 4$), though there was heterogeneity in intervention lengths observed. Nine interventions of the 21 selected interventions included male and female participants; the remaining interventions were female exclusive. More so, some interventions exclusively investigated phenols ($n = 13$) or phthalates ($n = 2$), while others targeted both phthalates and phenols ($n = 6$). Four interventions did not fit the inclusion criteria but facilitated the cultivation of alternative intervention strategies and were therefore recorded as supplemental interventions (Table S1) (Jack et al., 2020; Priya et al., 2017; Butterfield et al., 2011; Sears et al., 2020).

Dietary interventions.

Of the 21 identified studies, dietary intervention was the most popular approach to reducing EDC exposure. We identified 14 dietary intervention studies; most only focused on phenols ($n = 9$) (Table 3) (Sathyanarayana et al., 2013; El Ouazzani et al., 2021; Park and Chung, 2021; Galloway et al., 2018; Szybiak et al., 2017; Barrett et al., 2015; Carwile et al., 2011; Rudel et al., 2011; Peng et al., 2019; Kim et al., 2020; van der Meer et al., 2021; Jo et al., 2020; Chen et al., 2015; Christensen et al., 2012). Only two interventions exclusively investigated phthalate exposure (Barrett et al., 2015) and (Chen et al., 2015) and three focused on both phthalates and phenols (Sathyanarayana et al., 2013; Rudel et al., 2011; van der Meer et al., 2021; Barrett et al., 2015; Sathyanarayana et al., 2013; Rudel et al., 2011). Study populations included pregnant women, college students, families, teenagers, and women (not pregnant); five interventions had exclusively female populations (El Ouazzani et al., 2021; Park and Chung, 2021; Szybiak et al., 2017; Barrett et al., 2015; Chen et al., 2015). Most dietary interventions used spot urine samples to measure phthalate or phenol concentrations ($n = 13$), three of which pooled urine samples. Interventions typically involved two components: 1) educating participants about strategies to avoid dietary exposures and 2) providing replacement diets during the intervention period. Of the 14 dietary interventions, eight interventions supplied replacement diets to participants, while the remaining six did not provide alternative items. Even when catered diets were provided, investigators struggled to completely remove EDCs or trace all possible sources of exposure. This complication highlights the importance of proper consumer labeling/marketing and pre-testing alternative items provided during intervention periods.

Among the nine interventions that exclusively evaluated phenols, one study by Ouazzani et al., (2021) enrolled 268 women (~33 years old) for an intervention study, 230 of which participated in an additional three-arm randomized control trial (control group, $n = 78$; intervention group, $n = 152$) (El Ouazzani et al., 2021). After random assignment during the first trimester, intervention groups attended three workshops during the second and third trimesters on indoor air quality, nutrition, and personal care products. Spot urine

was collected pre-, mid-, and post-intervention and colostrum was collected at childbirth. Researchers did not observe a significant difference in dietary behavior or change in the percentage of participants with decreased BPA and paraben concentrations; however, there was a significant change in percentage of control (13 %) and intervention group (3 %) participants with BuP ($p = 0.03$) in their colostrum samples (El Ouazzani et al., 2021). There was also a significant increase in risk perception score (calculated using the perceived risk of and vulnerability to EDCs reported by participants) among intervention group participants (+15.73 control, +21.03 intervention, $p = 0.02$)—while the workshops/educational interventions did not significantly decrease dietary behaviors alone, they appeared to increase risk perception among participants (El Ouazzani et al., 2021).

In another randomized controlled trial, Syzbiak et al., (2017) evaluated BPA concentrations in women ($n = 20$, 10 control and 10 intervention, ages 22–25 years old) following a 7-day dietary exposure to canned items (Szybiak et al., 2017). Blood samples were collected at baseline, immediately post-intervention, and 7 days post-intervention. Following the intervention, mean serum BPA concentrations were significantly higher in the group that ate canned products ($p = 0.0008$) and BPA concentrations decreased significantly 7 days after the interventions completion ($p = 0.03$) (Szybiak et al., 2017). There was no statistically significant change observed in the control group ($p = 0.3$) (Szybiak et al., 2017). Canned food consumption was further explored in a randomized crossover design intervention conducted by Peng et al., (2018) (Peng et al., 2019). This intervention involved 20 college students ($n = 10$ male; $n = 10$ female, 21–32 years old), half of whom consumed canned food while the other half consumed fresh food. The intervention lasted 4 days with day 1 and day 3 as washout periods. Spot urine samples were collected before meals and 2, 4, and 6 h after eating on intervention days. Urinary BPA concentrations differed significantly following canned and fresh food consumption, and mean BPA concentrations were highest after meals, peaking at 4 h (2 h, $p = 0.001$, 152 % higher; 4 h, $p < 0.001$, 206 % higher; 6 h, $p < 0.001$, 79 % higher) (Peng et al., 2019). Together, these interventions highlight the importance of targeting known sources of EDC exposure, such as canned food, which typically contains BPA from epoxy linings, and consistently timing measurements (pre- and post-intervention) to avoid bias.

Carwile et al., (Carwile et al., 2011) also explored the impact of canned food, using a randomized 2×2 crossover trial (Carwile et al., 2011). Individuals ($n = 75$, ~27 years old) were split into two groups: one consumed fresh soup, while the other consumed canned soups. Spot urine samples were collected on day 4 and 5 of the intervention and pooled. Urinary BPA concentrations were significantly higher (22.5 ug/L, 95 % CI: 19.6–25.5 µg/L) than concentrations after fresh soup ($p < 0.001$) (Carwile et al., 2011). Kim et al., (Kim et al., 2020) also investigated canned food, but aimed to determine which foods contribute most to the total body burden of phenols. Over a 3-day period, 37 families (93 mother–child pairs, mothers ranging 30–50 years old) were asked to avoid canned, plastic-packaged, and fast/delivery foods (Kim et al., 2020). Participants were provided with educational materials and encouraged to keep diaries to track other potential exposure sources. Spot urine was collected pre-, mid-, and post-intervention. Researchers found a significant correlation between canned foods, take-out beverages, and fast food items and urinary BPA and BPS concentrations ($p < 0.05$); however, there was a nonsignificant decrease in urinary BPA (53.1

%, 95 % CI: 30.0–68.6; $p = 0.8669$) and BPS (63.9 %, 95 % CI: 37.1–79.3; $p = 0.0866$) among mothers after the intervention (Kim et al., 2020). This study further supports that canned food increases EDC exposure and that targeting canned items is a useful strategy for reducing phenol exposure.

Park & Chung (Park and Chung, 2021) conducted another intervention investigating urinary BPA concentrations in relation to menstrual pain (2021) (Park and Chung, 2021). Thirty female college students (~22.1 years old) were encouraged to reduce their processed food consumption through small-group education, monitoring and feedback, and peer support. Spot urine samples were collected pre-intervention and on the first morning after each menstrual cycle. Across the 4-week dietary intervention and ensuing 3 cycles (ranged from 4 to 6 weeks each) of post-intervention follow-up, researchers found a significant effect on BPA concentrations until the second menstrual cycle ($p = 0.000$) and that BPA levels significantly decreased ($p = 0.000$) irrespective of adherence level (Park and Chung, 2021). Galloway et al., (Galloway et al., 2018) also investigated BPA exposure and adherence with a 7-day intervention among 94 teenage students (17–19 years old) (Galloway et al., 2018). Uniquely, 108 students codesigned the intervention diet. Adherence was based on a “BPA risk score” (dietary items potentially containing BPA were given a 1). Spot urine samples were collected pre- and post-intervention. After 7 days, BPA remained in 86 % of the urine samples and no significant effect was observed ($p = 0.25$) (Galloway et al., 2018) There was also no relationship observed between urinary BPA concentrations and BPA risk score (beta coefficient 0.08, SE 0.07, $p = 0.55$) (Galloway et al., 2018) Results from both studies suggest that adherence may play a minimal role in interventions, but further investigation is needed.

A pilot study led by Jo et al. (Jo et al., 2020) also yielded unexpected results following a dietary intervention. It enrolled 25 temple stay participants (13–64 years old) and served them a strict Buddhist vegetarian diet for five days to assess paraben exposure (Jo et al., 2020). Urine samples were collected pre- and post-intervention. While BuP concentrations significantly decreased among males ($p < 0.05$), urinary EtP significantly and unexpectedly increased ($p < 0.05$) following the five day intervention (Jo et al., 2020). The authors speculated that the increase in parabens was from seasoning and condiments. A similarly intense phenol-driven dietary intervention included a 48-hour intervention by Christensen et al., (Christensen et al., 2012). This study consisted of a fasting period and diaries to track personal activities (Christensen et al., 2012). Only 5 individuals (27–47 years old) participated in the 2-day fasting intervention. Urine was collected throughout the intervention, in addition to pre- and post-intervention samples (pooled). While there were no significant changes found, BPA concentrations declined ~ 66 % by the second day (Christensen et al., 2012). Investigators concluded that there was no correlation between PCPs and BPA concentrations. This study supports the need to pre-test dietary products and capture all routes of exposure.

Three dietary interventions (van der Meer et al., 2021; Sathyanarayana et al., 2013), and (Rudel et al., 2011) measured both phthalates and phenols (Sathyanarayana et al., 2013; Rudel et al., 2011; van der Meer et al., 2021). The dietary intervention by van der Meer et al. (2021), explored potential obesogenic properties of phthalates and phenols using a 3-month dietary intervention (van der Meer et al., 2021). Participants ($n = 218$, ~52 years old)

ate one of four caloric- restricted weight reduction diets. Urine was collected pre- and post-intervention, concurrently with weight loss parameters (waist circumference, BMI, and body fat percentage). After three months, there was a significant decrease in all HMW phthalates (FDR < 0.0001), except mono-n-hexyl phthalate (MnHP), and a significant association between mono-n-butyl phthalate (MnBP; $p = 0.031$), mono-benzyl phthalate (MBzP; $p = 0.005$), and waist circumference (van der Meer et al., 2021). Using a two-arm randomized dietary intervention over 16 days, Sathyanarayana et al., (Sathyanarayana et al., 2013) aimed to evaluate whether a 5-day dietary replacement was effective at reducing phthalate (HMW phthalates) and phenol (BPA) exposures among 10 families ($n = 21$ Arm 1; $n = 19$ Arm 2) (Sathyanarayana et al., 2013). Arm1 was provided with fresh and organic diets, while Arm 2 was only provided with educational handouts. Spot urine was collected pre-, mid-, and post-intervention. Following the intervention, DEHP ($p < 0.0001$) and BPA ($p < 0.05$) concentrations increased significantly among the intervention group (Sathyanarayana et al., 2013). Investigators posited that contamination by coriander and milk may have biased urinary phthalate concentrations. Both studies demonstrate the potential for within-person variability using urine samples and the possibility for only slight changes when new diets are introduced.

Rudel et al. (Rudel et al., 2011) conducted the third intervention study that investigated both phthalates and phenols (Rudel et al., 2011). To assess strategies for minimizing BPA and phthalate exposure, five families ($n = 20$) participated in a 3-day intervention. During the intervention, participants were provided with catered “fresh foods” (no canned or plastic-packaged foods) and other items to reduce their exposure (stainless steel water bottles and storage containers). Spot urine samples were collected over eight days, twice during pre-, mid-, and post-intervention (6 urine samples per person). At the end of the intervention, there was a significant decrease in both BPA ($p < 0.005$) and DEHP ($p < 0.05$) (Rudel et al., 2011). Additionally, the geometric means decreased significantly for BPA (by 66 %) and DEHP (by 53–56 %) (Rudel et al., 2011). This study supports that catered diets may provide a promising strategy to reduce both phthalates and phenol exposures. Overall, these studies illuminate the opportunity to reduce HMW phthalates, but suggest that LMW phthalates are more difficult to lower using a dietary intervention.

Two studies that did not record phenol concentrations and instead observed changes in phthalates only. Barrett et al. (Barrett et al., 2015) recruited 10 pregnant women (~26 years old) and provided them with a “mostly fresh” and organic low-phthalate foods for 3 days (Barrett et al., 2015). Participants completed daily food logs and interviews. The intervention period covered 8 days with days 1, 2, 6, 7, and 8 on a typical diet and days 3, 4, and 5 consuming the intervention diet. Urine samples were collected pre-, mid-, and post-intervention (days 1, 4, and 7). After the intervention, there was no significant change in phthalate concentrations ($p = 0.65$); however, interviews about dietary behaviors indicated that participants did not like the provided diets and experienced participation barriers (e.g., cultural, cost, and convenience) (Barrett et al., 2015). Chen et al. (Chen et al., 2015) also exclusively investigated phthalates and aimed to reduce phthalate exposure through seven specific intervention strategies (Chen et al., 2015). These strategies included, “handwashing, not using plastic containers, not eating food with plastic bag/plastic-wrap cover, not microwaving food, not taking nutrition supplements, and reducing use of cosmetics/personal

care products.” They were applied to a 7-day intervention period involving 30 girls (4–13 years old) (Chen et al., 2015). Participants were advised to record time-activity patterns. Urine was collected pre- and post-intervention. Following this intervention, a significant decrease in mono-butyl phthalate (MBP; $p = 0.009$) and mono-methyl phthalate (MMP; $p = 0.07$) among the high-frequency handwashing group was observed (Chen et al., 2015). Additionally, there was a significant decrease in mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP; $p = 0.038$) and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP; $p = 0.012$) among individuals who reported drinking from fewer plastic cups (Chen et al., 2015). Together, these studies demonstrate the difficulty of reducing phthalate concentrations using strictly dietary alterations and suggest an opportunity for behavioral interventions further reduce chemical exposure.

Small sample sizes, potential nondifferential misclassification bias from within-person variability using spot urine samples (especially when samples were not pooled), failure to measure and or capture all possible exposures (dietary and not, though food and behavior diaries were occasionally utilized), and potential misreporting of personal activities during the intervention period limited many of these studies. Additional barriers to dietary interventions included the participants’ inability to afford organic and fresh foods (when not provided), cultural preferences, and the general convenience of consuming foods and beverages without EDCs. Amid these potential limitations, common intervention strategies included intense education and communication with participants (online or in-person instruction, educational workshops, small group instruction, follow-up monitoring, peer support groups, interviews, guidelines/strategies, and questionnaires), diaries or risk scores to gauge all potential sources of exposure during the intervention, and replacement products (especially of known EDC sources) or catered diets.

4.2. Behavioral interventions

Six behavioral interventions were identified during the literature review: four were randomized controlled trials and two that were community-based interventions (Table 4) (Ley et al., 2017; Hagobian et al., 2017; Harley et al., 2016; Hagobian et al., 2021). All participants were female and included: mothers with young children, pregnant women, non-pregnant women, and adolescent females. Four of the interventions focused solely on phenols, while the other two studied both phthalates and phenols. Among the six behavioral interventions, one intervention relied exclusively on educational materials and utilized a web-based intervention approach to reduce phthalate and phenol exposure (Kim et al., 2021). The remaining five studies supplied participants with replacement products in addition to educational materials about routes of exposure, and one intervention supplied replacement products alone. Intervention periods ranged from 3 days to several months. All behavioral interventions collected urine samples and observed changes in EDC concentrations— five of these differences were significant. Harley et al. (Harley et al., 2016) was the only study to observe a nonsignificant change, though they still observed a decrease in some EDCs (Harley et al., 2016).

Four behavioral interventions only evaluated changes in phenols (Ley et al., 2017; Hagobian et al., 2017; Hagobian et al., 2021; Huang et al., 2021). Hagobian et al. (Hagobian et

al., 2017)'s pilot study followed 24 premenopausal, college-aged women (11 control; 13 intervention) over a 3-week period (Hagobian et al., 2017). In addition to entry questionnaires to gauge exposure, the intervention group met with counselors (weekly) who encouraged them to consume organic foods, fostered self-incentives, and provided feedback. The intervention group was given BPA-free cosmetics, PCPs, and storage containers. Spot urine samples were collected pre- and post-intervention. At the end of the 3-week intervention, the geometric mean creatinine-adjusted urinary BPA *decreased* significantly in the intervention group (-0.71 ng/m), while the geometric mean urinary BPA concentration *increased* significantly in the control group (0.32 ng/mL; $p = 0.04$) (Hagobian et al., 2017). The observed treatment \times time effect from study entry to 3 weeks was significant on urinary creatine concentrations ($p = 0.04$) (Hagobian et al., 2017). Hagobian et al. (Hagobian et al., 2021) conducted another behavioral intervention among college-aged women to evaluate the effectiveness of social cognitive theory to reduce bisphenols over a 3-week period among 30 premenopausal women (15 control; 15 intervention) (Hagobian et al., 2021). The intervention included weekly meetings with counselors who promoted self-regulation skills/positive reinforcement and provided feedback/encouragement. Participants were also provided with bisphenol-free alternatives. Spot urine samples were collected pre- and post-intervention. Following the intervention, a significant treatment \times time effect on creatinine-adjusted BPS (-1.42 ug/g creatinine intervention; -0.09 ug/g creatinine control) was observed; there were no significant changes in BPA and BPF (Hagobian et al., 2021). Although adherence decreased with time, the intervention was deemed feasible. Together, these two studies demonstrate the potential utilization of personalized educational interventions and frequent meetings/encouragement to reduce exposure to EDCs.

To further explore exposure pathways and evaluate the reliability of EDC biomarkers, Huang et al. (Huang et al., 2021) conducted a multi-pathway exposure assessment and double-blinded intervention study (Huang et al., 2021). Ten women ages 22–26 were provided with different PCPs over an 18-day period (6 control days, 6 intervention days, followed by another 6 control days). In addition to collecting urine samples to measure internal concentrations, external environmental samples were analyzed (dust, drinking water, and diet). Participants were provided with PCPs (facial cleanser, toner, and facial cream) that were paraben-free or had the lowest paraben concentrations. Urine samples were collected pre-, mid-, and post-intervention (4th, 10th, and 16th days) and three spot urine samples were collected each day ($n = 566$ total urine samples). Food ($n = 170$), indoor dust ($n = 6$), and drinking water ($n = 12$) samples were also collected. Huang et al. (Huang et al., 2021) concluded that exposure from PCPs contributed to $> 99\%$ of exposure to parabens and that urinary paraben concentrations were positively correlated with environmental exposures (Huang et al., 2021). Notably, urinary creatinine-adjusted parabens were significantly lower during the intervention period ($p < 0.05$) and were hypothesized to have similar routes of exposure (positive correlation between MP and PP, $r = 0.98$ and $p < 0.05$) (Huang et al., 2021). This study supports that PCPs contribute to exposure and are important to target during EDC interventions.

(Ley et al., 2017) also exclusively investigated phenols in their behavioral intervention (Ley et al., 2017). This study aimed to minimize exposure to TCS/TCC from wash products (e.g., toothpaste) among 154 pregnant women from 20 weeks' gestation (78 exposed;

76 not exposed). To assess the effects of these phenols, urine was collected pre- and post-intervention (36 weeks' gestation and/or post-delivery) and blood samples were also collected (50 participants provided one urine sample, 54 participants provided two urine samples, and 13 participants provided three urine samples). For the intervention, participants were either provided with products with or without TCS/TCC. At study completion, a 7-fold, significant difference ($p = 0.002$) between the exposed (post-intervention 19.0 pg/ul median [3.1–80.6 Q1-Q3]) and unexposed (post-intervention 2.7 pg/ul [0.3–10.9 Q1-Q3]) was observed; exposure to TCS/TCC was not found to affect thyroid function (Ley et al., 2017). While thyroid function was not impaired, this intervention suggests that behavioral interventions can reduce TCS and TCC exposure, especially through the use of replacement products and personalized questionnaires.

Two studies evaluated both phthalate and phenol exposures. In the Harley et al. (Harley et al., 2016) community-based intervention study, 100 Latina girls participated in a 3-day intervention to evaluate if using products without phenols or phthalates listed in their ingredients could reduce exposure (Harley et al., 2016). Participants were provided with “low-chemical” replacement PCPs and four cosmetic items. Participants completed three interviews and a computer-assisted and interviewer-administered questionnaire. Spot urine samples were collected pre- and post-intervention. Following the intervention there was a nonsignificant decrease in mono-ethyl phthalate (MEP; 27.4 % [95 % CI: –39.3 to –13.2]), MP (43.9 % [95 % CI: –61.3 to –18.8]), PP (45.4 % [95 % CI: –63.7, –17.9]), TCS (35.7 % [95 % CI: –53.3 to –11.6]); largest decrease among participants with alternative toothpaste use), and BP-3 (36.0 % [95 % CI: –51.0 to –16.4]); however, ethyl paraben and butyl paraben increased in some samples (Harley et al., 2016). This study highlights the importance of product labeling to identify clean replacements and the potential for participants to introduce additional exposures due to free products (that they otherwise would not have used).

The Kim et al. (Kim et al., 2021) intervention employed a randomized controlled trial that used a one-month, web-based behavioral intervention to reduce phthalates and phenols among 51 mothers (26 intervention; 25 control) and their children (Kim et al., 2021). The web-based behavioral intervention targeted exposures from diet, PCPs, and home sources using an educational video, a game to locate sources, educational resources, and a question/answer mode. Notably, educational interventions are often supported by observational studies that are non-specific to EDCs; Kim et al. (Kim et al., 2021) specifically referenced studies on behavioral control and planned behavior to support their use of an educational intervention (Ajzen et al., 1985; Ajzen and Madden, 1986). Kim et al. sent short messages/called participants for one month and encouraged participants to use the web-based program. The control group was mailed written educational materials. Both groups completed questionnaires and provided spot urine samples pre-, mid-, and post-intervention. At intervention completion, researchers observed a significant decrease in phthalates among the intervention group (mono [2-ethylhexyl] phthalate [MEHP], $p = 0.011$; mono [2-ethyl-5-oxohexyl] phthalate [MEOHP], $p = 0.036$) and phenols (BPA, $p = 0.039$; MP, $p = 0.013$; EP, $p = <0.001$; PP, $p = 0.044$); there was also a significant decrease in the urinary geometric mean values of all chemicals except EP after one month among the intervention group, (MEHP: 3.8 %; MEHOP: 16.3 %; BPA: 28.4 %; MP: 9.2 %; PP: 24.4. %) (Kim et al., 2021).

There was no significant change observed for TCS ($p = 0.494$) or MEHHP ($p = 0.051$) among the intervention group. There was an unexpected significant change in EP among the control group pre- and post-intervention ($p = 0.036$) (Kim et al., 2021). This study supports the use of web-based platforms/educational interventions to reduce exposure to phthalates and phenols.

Common limitations of these studies included small sample sizes, potential for within-person variability among spot urine samples, inadequate measurements of behavioral or lifestyle change, undetected exposures, and residual chemicals in replacement products (especially among those that were not pre-tested). Poor reproducibility was a major limitation of the Huang et al. (Huang et al., 2021) study and urinary concentrations did not reflect high intraclass correlation coefficients until they were adjusted for toxicokinetic parameters (unadjusted intraclass correlation coefficients: 0.125–0.295 vs. adjusted: 0.695–0.886) (Huang et al., 2021). Additionally, the study led by Ley et al. (Ley et al., 2017) was not blinded and participants may have used alternate products (though they attempted to use quartile groups for urinary TCS concentrations to control for this) (Ley et al., 2017). Overall, educating participants about EDCs (web-based programs, interviews, questionnaires, counselors, and meetings) and providing participants with alternative products were the most common behavioral strategies.

4.3. Residential interventions

We identified one residential intervention study that fit our inclusion criteria by Rutkowska et al. (Rutkowska et al., 2020) (Table 5) (Rutkowska et al., 2020). This community-based study aimed to understand if changes in the indoor home environment over a 6-month period could effectively reduce EDC exposure. The intervention included 26 volunteers (14 males; 12 females) from nine households located in Poland. A social media campaign was implemented to set-up meetings for participants over the 6-month intervention period to discuss ways to reduce EDC exposure—lifestyle changes were completely voluntary. Exposure to phthalates and phenols was evaluated using single mid-stream urine samples ($n = 22$; 60 mL) and dust samples ($n = 7$; from living room shelves and bedroom floors) collected pre- and post-intervention. At the end of the intervention, the concentrations of all selected EDCs were significantly lower in urine samples, except for DiBP (BPA: $p = 0.003$; BPS: $p = 0.004$; 4-nonylphenol [4-NP]: $p = <0.001$; DEHP: $p = <0.001$; DEP: $p = 0.012$) (Rutkowska et al., 2020). There was a significant decrease in dust concentrations for BPS ($p = 0.042$), 4-NP ($p = 0.017$), and DEHP ($p = 0.017$); correlations between EDC concentrations in household dust and urine were observed (Rutkowska et al., 2020). Although 60 mL of urine was collected, it appears that only one morning urine sample was analyzed pre- and post-intervention, suggesting within-person variation. Additionally, dust samples were only taken from two locations in the living space and the sample size was small. While there were some limitations, given the significant decreases in EDCs, residential interventions may be useful to reduce exposure.

4.4. Comparison of selected interventions and percent change

While every intervention employed different approaches and often measured different EDCs, we could compare interventions using percent (%) change to capture differences beyond

their p-values (significance). At least some phenols decreased in every behavioral and residential intervention. Conversely, two dietary interventions did not observe any changes (one did not observe changes in BPA, while the other did not observe any changes in phthalates). BPA concentrations increased after meals, especially when canned food was consumed, and decreased during the fasting intervention conducted by Christensen et al. (Christensen et al., 2012) (Christensen et al., 2012). Rudel et al. (Rudel et al., 2011) and Christensen et al. (Christensen et al., 2012) both observed ~ 66 % decrease in BPA concentrations, but no interventions successfully eliminated internal BPA concentrations. Notably, Christensen et al. only had five participants and Rudel only had 20 participants (Rudel et al., 2011; Christensen et al., 2012). Though not all interventions measured changes in EDC concentrations directly, 13 interventions reported decreased urinary concentrations of phenols and or phthalates post-interventions. The greatest change was reported by Huang et al. (Huang et al., 2021), who observed up to an 88.3 % decrease in parabens post-intervention (Huang et al., 2021). Given the small sample size in many studies and failure to pool urine samples, it is possible that observed reductions were due to within-person variability.

5. Discussion

5.1. Key elements for phthalate and phenol interventions

Among the 21 interventions reviewed, the most successful interventions at reducing EDC concentrations had the most comprehensive strategies (i.e., providing replacement products and/or diets and targeting multiple routes of exposure). Interventions that also incorporated personalized and interactive educational components were effective (e.g., counselors, interviews, and online games). While the importance and/or role of interventional adherence remains unclear, the interventions included reinforcements through self-incentives, meetings, support groups, direct texts/calls with the researchers, and encouragement typically observed a reduction in EDC concentrations (i.e., ten interventions used some of these techniques, six of which observed significant reductions in EDCs). Most interventions measured phenols, especially BPA or BPA-alternatives, while only eight of the 21 interventions measured phthalates. Six of the eight interventions that included phthalates observed a significant decrease in phthalate concentrations, illuminating a current gap in knowledge regarding phthalate-specific intervention strategies. Urine was commonly collected (n = 20), but venous blood (n = 1), colostrum (n = 1), dust (n = 2), and drinking water (n = 1) were also used to measure changes in EDCs. Only five studies pooled their urine samples in some way. Overall, the most effective techniques (greatest % change in EDC concentrations) included 1) providing participants with accessible and interactive educational materials (web-based platforms), 2) replacing products that were relevant to individual exposure patterns and or products that are known sources of exposure, and 3) encouraging participants to reduce their exposure using personalized support and feedback from the study team (Fig. 3).

5.2. Educational interventions

Out of the 21 primary interventions, 11 interventions had a large educational component that often included online or paper materials and or meetings and interviews with professionals

or research staff. (Barrett et al., 2015; Sathyanarayana et al., 2013; El Ouazzani et al., 2021; Park and Chung, 2021; Galloway et al., 2018; Kim et al., 2020; Kim et al., 2021; Ley et al., 2017; Hagobian et al., 2017; Harley et al., 2016; Hagobian et al., 2021) Among these 11 interventions, six observed a significant reduction in at least some EDCs. The interventions that observed significant decreases in EDCs commonly had weekly meetings, support groups, and or interviews to provide encouragement and feedback to participants in a personalized and accessible setting. The five that did not report a significant reduction had other issues with contamination of provided products or cultural barriers (Galloway et al., 2018; Barrett et al., 2015; Sathyanarayana et al., 2013; Kim et al., 2020; Harley et al., 2016). For example, Sathyanarayana et al. (Sathyanarayana et al., 2013) witnessed a significant increase in DEHP likely due to contamination of provided foods (Sathyanarayana et al., 2013). Additionally, these five interventions did not meet with participants at all or as frequent and tended to have a less comprehensive or personalized educational approach. Additionally, it is possible that the study by Harley et al. (Harley et al., 2016) did not account for cultural preferences or other barriers when reading product labels or purchasing alternatives (Harley et al., 2016). Given the variety of product use patterns and, therefore, risk of exposure among different racial/ethnic groups, designing personalized educational interventions that provide participants with frequent support and feedback is essential to reducing exposure during routine activities (Dodson et al., 2021). Researchers should account for community-relevant factors when designing and implementing clinical and community interventions (Munakampe et al., 2021).

Of the 11 interventions that included educational components, five interventions provided replacement products—three of which observed a significant decrease in EDCs (Ley et al., 2017; Hagobian et al., 2017; Huang et al., 2021). Out of the six behavioral interventions identified, one did not provide replacement products, but administered online resources to the intervention group and written informational packets to the control group instead. Still, this study observed significant reductions ($p < 0.05$) in urinary geometric mean values among the intervention group compared to the control group (MEHP: 3.8 %; MEOHP: 16.3 %; BPA: 28.4 %; MP: 9.2 %; PP: 24.4 %) (Kim et al., 2021). Four interventions solely relied on an educational approach to reduce EDC concentrations, two of which reported significant reductions; however, these two interventions also provided participants with frequent meetings and accessible (online) resources—further reinforcing the potential benefit of online educational materials (Park and Chung, 2021; Galloway et al., 2018) Kim et al. (Kim et al., 2021) only used a web-based intervention and observed a significant decrease in several phthalates and phenols (Kim et al., 2021). Kim et al. (Kim et al., 2021) also routinely encouraged participants to use their online, interactive web-based platform during the four-week intervention period. In sum, educational approaches should aim to be personalized, accessible, and integrated with support groups and frequent meetings throughout the intervention period to provide participants with the knowledge and motivation to reduce their exposure.

5.3. Replacement products

Seven dietary interventions supplied replacement diets/items to participants and five behavioral interventions provided alternative PCPs; many of these studies (six out of the

seven dietary and four out of the five behavioral interventions) saw a significant change in urinary concentrations of some phthalates and or phenols—alluding to the potential for dietary interventions to influence exposure to EDCs. Barrett et al. (Barrett et al., 2015) was the only dietary intervention that did not observe a significant change, possibly due to participant unwillingness to change their behavior (Barrett et al., 2015). Behavioral interventions often provide alternative PCPs and cosmetics based on ingredient lists; however, Harley et al. (Harley et al., 2016) discussed the potential for seemingly “clean” alternatives to still have residual EDCs that are not explicitly listed (from processing or the containers products are stored in)—which they claimed partially contributed to their nonsignificant results (Harley et al., 2016). Another example of contaminated alternatives includes the study by Sathyanarayana, et al. (Sathyanarayana et al., 2013) which reported a significant increase in DEHP ($p < 0.0001$) and BPA ($p < 0.05$) among intervention participants that were provided with “fresh” and organic foods (Sathyanarayana et al., 2013). Lax labeling regulations challenge the identification of phthalate and phenol free alternatives; however, investigators may consider pre-testing their products to ensure clean alternatives.

Dietary interventions focused on canned items or other known sources of EDCs (plastic packaging) and tended to provide “fresh” and organic foods that were not packaged in plastic or canned. Investigators often advised participants to avoid fast foods/delivery foods and provided plastic free to-go containers (e.g., stainless steel water bottles and BPA-free glass storage containers). Three dietary interventions designed their study exclusively around canned items, all of which witnessed a significant change in BPA levels (Szybiak et al., 2017; Carwile et al., 2011; Rudel et al., 2011). For example, in a randomized crossover trial, BPA was detected in 77 % of urine samples before eating canned soup and 100 % of samples after eating canned soup (Carwile et al., 2011). Additionally, BPA concentrations decreased with avoidance of canned food, whereas BPA concentrations increased among individuals consuming canned food. While other studies broadened their restrictions to plastic packaging and organic foods, these three studies demonstrate the power of targeting easily avoidable, specific sources. More so, organic foods are often more expensive than nonorganic items (i.e., lower socioeconomic groups might not be able to afford to adhere to a completely organic diet) and plastic packaging is difficult to avoid (i.e., some items, such as cheese or bread, might not be sold without plastic packaging). Similarly, several PCPs and cosmetic products are packaged in plastic bottles and containers that make it difficult to completely avoid phthalates and phenols, even if they are not listed as ingredients.

Accounting for sources that substantially contribute to internal concentrations, measuring alternatives that might contaminate products, and recognizing specific manufacturing uses for EDCs are important considerations when designing future interventions. For example, HMW phthalates are often used in the manufacturing of plastic food packaging, while LMW phthalates are commonly used in personal care products to maintain fragrance. Both behavioral interventions that studied LMW phthalates reported decreases in their chemical concentrations, although only one was significant. Additionally, three of the five dietary interventions that measured phthalates found significant changes in DEHP (HMW phthalate) and one intervention found a significant decrease in LMW phthalates, though this was attributed to behavioral change (i.e., handwashing). Future interventions should

explore strategies to reduce EDC exposure, especially among LMW phthalates, incorporate strategies that targeting specific sources of exposure, encourage behavioral change (i.e., handwashing), and pre-test alternatives items for contamination.

5.4. Personalized support and monitoring

In addition to providing accessible/personalized education and strategic replacement products, participants support and feedback throughout the intervention was effective. Kim et al. (Kim et al., 2021) contacted participants to remind them to access the online educational materials and observed a significant decrease in multiple phthalates and phenols in their exclusively web-based intervention (Kim et al., 2021). Additionally, Hagobian et al. (Hagobian et al., 2021) and Hagobian et al. (Hagobian et al., 2017) had participants meet with counselors who encouraged behavioral strategies, specifically self-monitoring and goal setting (Hagobian et al., 2017; Hagobian et al., 2021). At weekly face-to-face meetings with these counselors, participants were provided with feedback and positive reinforcement that may have contributed to the significant results found in both studies. Studies often used social media campaigns to organize meetings and form support groups, specifically in the residential study by Rutkowska et al. (Rutkowska et al., 2020) and dietary study by Park & Chung (Park and Chung, 2021)—both of which observed significant decreases in urinary EDC concentrations (Park and Chung, 2021; Rutkowska et al., 2020).

Park & Chung (Park and Chung, 2021) also studied adherence using a dietary modification score and reported that there was significant decrease in urinary BPA concentrations irrespective of adherence level (Park and Chung, 2021). Additionally, the “BPA risk score” measured by Galloway et al., (Galloway et al., 2018) to evaluate adherence was not related to urinary BPA concentrations (Galloway et al., 2018). Together, these studies support that significant reductions in EDCs may be independent of high interventional adherence; however, one dietary intervention that failed to observe changes in urinary levels indicated that individual willingness and compliance with dietary interventions is an important aspect of an intervention. It is possible that EDCs have an impact on behavior that may influence compliance. For example, participants in the dietary intervention by Ouazzani et al. (2022) had a significant increase in their risk perception score (control: +15.73, intervention: +21.03) and psychosocial score (control: +12.39, intervention: +16.20), but there was no significant difference in canned food consumption or phenols (except BuP) (El Ouazzani et al., 2021). Future interventions should clarify the role of adherence and motivation, though it is assumed that participants that have adequate resources and are willing to follow the intervention would have greater success than participants who did not change their lifestyle to reduce their exposure.

5.5. General strategies for future interventions

Notably, only six of 21 interventions pooled their samples. A major limitation of the primary interventions includes within-person variability due to spot urine sample collection. Peng et al. (Peng et al., 2019) highlights the importance of consistently gathering urine and being weary of when participants ate. They found that urinary BPA levels peaked four hours after eating (compared to two and six hours) (Peng et al., 2019). Additionally, the intervention led by Christensen et al. (Christensen et al., 2012) observed BPA concentrations

to decrease after two days of fasting (Christensen et al., 2012). Both of these studies highlight the rapid metabolism of EDCs and the importance of using consistent spot urine samples for pooling methods in future interventions. Regardless, the 21 primary interventions support intervention strategies that target specific, known sources of exposure, educate participants with interactive and personalized techniques, and reinforce or encourage behavior through individual meetings and support groups. Since phthalates and phenols are nearly inescapable, it is essential that interventions acknowledge all possible and practical routes of exposure relevant to the study population and attempt to reduce exposure from all sources. Additional intervention strategies are briefly outlined in Fig. 4.

5.6. Supplementary interventions and epidemiological studies

To further refine these strategies and supplement the limited number of intervention studies involving individuals during their reproductive years, additional studies that did not meet our inclusion criteria but identified important predictors of EDC exposure were reviewed (Table 1S and Table 2S). Findings from these studies may inform future interventions involving reproductive age men and women. The supplementary interventions continue to support the successful use of digital or online tools. For example, in a randomized controlled trial involving preconception women, use of an online (conversational and computerized) nurse that informed intervention participants about preconception risks increased awareness of reproductive health risks (Christensen et al., 2012). While the computerized nurse (Gabby system) was useful for educating participants about preconception health risks, other online resources and apps are available specifically for phthalate and phenol intervention studies. Web-based approaches may be especially valuable when designing interventions for rural communities or during pandemic-periods, such as the current COVID-19 pandemic. Notably, that not all communities have equal access to electronics or the internet, and such factors should be reviewed prior to designing an intervention that relies exclusively on web-based approaches. Educational interventions that are not online and are community-based have still been shown to increase EDC awareness. For example, in the supplementary intervention by Priya et al. (2016), a community-based educational program among 300 students found a significant increase ($p < 0.001$) in knowledge about plastics (Jack et al., 2020).

Observational studies also validated the targeting of known sources of exposure, among other intervention strategies. Makris et al. (Makris et al., 2013) focused solely on BPA concentrations from polycarbonate (PC) packaged water (Makris et al., 2013). A significant interaction was observed between gender and PC water consumption ($p < 0.05$) and a significant positive association was found between PC packaged water and urinary BPA levels ($p = 0.017$) in females. A recent residential study involving pregnant women and children found lower concentrations of certain phthalate metabolites (12–17 % lower) among children who lived in cleaner (less dusty) homes compared to children living in dustier homes. These findings suggest that dust may be an important exposure target for residential interventions (Sears et al., 2020). The second supplementary residential intervention by Butterfield et al. (Butterfield et al., 2011) focused on the effectiveness of interventions led by rural public health nurses to educate parents about household environmental health risks, including EDCs (Butterfield et al., 2011). Individuals that

adopted advice from nurses significantly benefited from the intervention. Consistent with other interventions in this review, this study demonstrated the importance of effective educational materials and motivating participant adherence to the intervention protocol or recommendations using a personalized approach.

Not surprisingly, in a crowdsourced biomonitoring study led by Dodson et al. (Dodson et al., 2020), participants who scrutinized their product ingredients to avoid certain EDCs, like parabens, had lower concentrations of these toxicants compared to participants who did not (Dodson et al., 2020). Accordingly, the proposed strategies partially depend on the willingness and motivation of participants to remove or avoid EDCs. Educating participants and encouraging them to seek alternatives to crucial for future interventions. Additionally, the epidemiological study by (Zota et al., 2016) supported that future interventions should target fast food, in addition to canned foods, as a potential source of exposure to DEHP and DiNP (Zota et al., 2016). Philippat et al. (2016) further explored specific EDC sources and found that PCPs are an important source of exposure to parabens and DEP in adults (Philippat et al., 2015). Additionally, this study reported that the total number of PCPs was positively associated with urinary concentrations of parabens and DEP. Therefore, targeting a specific source and reducing overall exposure may be promising.

Additionally, of the phthalate and phenol interventions identified during our literature search, eight dietary interventions and one residential intervention included men. No behavioral interventions or other non-dietary lifestyle interventions required or included paternal or male participation, even though men commonly use hygiene products that contain phthalates and phenols. Future interventions need to address this gap by including both sexes and should recognize the immense influence that paternal health has on birth outcomes and fetal and infant health. Though it is not essential that both men and women are included in the same intervention study, encouraging male participation and inclusion in clinical and community interventions will.

further our understanding about how to minimize phthalate and phenol exposures for both sexes.

and reduce adverse couple-based pregnancy outcomes.

5.7. Evaluating the role of policy

Although interventions can be useful when targeting individual-level EDC exposure, as seen in our earlier discussions, policy-level interventions may be more efficient at preventing or influencing long-term, population-wide exposure through the removal of certain chemicals. Increasing the efficacy of ingredient testing and requiring companies to list all potential ingredients would improve both individual-level and population-level interventions. Current EDC policies involve the most well-studied phthalates and phenols with consistent adverse health effects such as BPA, TCS, and DEHP. More specifically, during the first decade of the 21st century the FDA was urged to ban BPA products after a wide breadth of research warned about the harmful health outcomes associated with this chemical. This movement resulted in the production of BPA-free alternatives that were manufactured using BPF, BPS, and BPB, structural analogs of BPA that have similar potencies (Paciência et al., 2019).

In 2010, TCS was removed from plastic packaging that came into contact with food or other dietary items in European Union (EU) countries; however, it took until 2016 for the United States Food and Drug Administration (FDA) to ban TCS from household products (Dann and Hontela, 2011). A year later, in 2017, the Consumer Product Safety Commission prohibited the use of eight *ortho*-phthalates in children's products (CPSC prohibits certain phthalates in children's toys and Child Care Products, n.d.).

Extending this ban to reduce the use of phthalates in food processing and packaging may more effectively lower population level exposure. While there are no apparent studies evaluating the specific impact of these regulations, various states within the US have proactively worked to phased out BPA (with BPA alternatives), leading to a decrease in BPA exposure among the US population but a potential increase in exposure to BPA alternatives that remain understudied. The European Food Safety Authority (EFSA) has studied BPS and authorized its use in food packaging; however, they recommend additional studies to clarify potential adverse health effects (Lin et al., 2020). Given that the EU has enacted stricter bans, according to EFSA, Americans are exposed to dangerously high concentrations of BPA compared to individuals living in the EU (Bisphenol, 2022). Although TCS was banned by the FDA, it still remains in a variety of PCPs such as toothpaste, mouthwash, and hand sanitizers; therefore, it is unclear how much population exposure has changed after the ban (Weatherly and Gosse, 2017). Additionally, DEHP is thought to have decreased, however, like BPA, exposure to its alternatives has likely increased (Di(2-ethylhexyl)phthalate (DEHP), 2017). Numerous studies using urine samples have demonstrated that populations around the world are exposed to a variety of well-studied and understudied EDCs—indicating the potential opportunity that policy-level interventions will have compared to individual-level interventions (Silva et al., 2019; Silva et al., 2017).

5.8. Review limitations

This review article has several limitations since some routes of exposure to phthalates and phenols have not been fully characterized and gaps remain in our understanding of the consequences following environmental exposure to phthalates and phenols. Thoroughly understanding phthalate and phenol exposure is essential when designing effective clinical or community interventions, but there is a relative lack of intervention studies to reduce exposure to EDCs. Notably, this limited our analyses to 21 interventions. In comparison to other intervention categories, it is apparent that residential interventions are lacking and should be increased to evaluate potential residential intervention strategies to reduce household EDC exposure. Additionally, it is possible that our research criteria failed to capture every intervention. While we mentioned the limitations of the selected interventions, we believe this review provides a valuable framework for future phthalate, phenol, and other EDC interventions and hope that the limitations of this review stress the tremendous need for additional interventions.

6. Concluding remarks

Phthalates and phenols have grown unavoidable in personal care products, foods and drinks, and indoor environments. Though the interventions presented in this review provide tools and approaches to address phthalate and phenol exposures, resources and literature remain insufficient and lacking. Increasing the breadth of knowledge concerning EDC exposure sources and their harmful effects on reproductive health will allow for the development of efficacious and targeted intervention strategies in the future. Novel approaches, such as web-based or digital health intervention and educational tools, targeted replacement products, and personalized interactions are useful strategies for future interventions. Environmental exposure to EDCs is a constant threat to reproductive and population health and should motivate further implementation and refinement of intervention strategies to address environmental phthalate and phenol exposures.

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Data availability

No data was used for the research described in the article.

List of abbreviations

7.

EDCs	Endocrine-disrupting chemicals
PC	packaged Polycarbonate
BPA	Bisphenol A
BPB	Bisphenol B
BPF	Bisphenol F
BPS	Bisphenol S
TCS	Triclosan
TCC	Triclocarban
BP-3	Benzophenone-3
4-NP	4-Nonylphenol
MCBPA	Bisphenol A mono-chlorinated
DCBPA	Bisphenol A di-chlorinated
TCBPA	Bisphenol A tri-chlorinated

TTBPA	Bisphenol A tetra-chlorinated
DMP	Dimethyl phthalate
MMP	Monomethyl phthalate
DEP	Diethyl phthalate
MEP	Mono-ethyl phthalate
DiBP	Diisobutyl phthalate
MiBP	Monoisobutyl phthalate
DnBP	Di-n-butyl phthalate
MnBP	Mono-n-butyl phthalate
MBP	Mono-butyl phthalate
DBP	Dibutyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DEHTP	Di(2-ethylhexyl) terephthalate
DiNP	Di-isononyl phthalate
DPHP	Di-isopropyl heptyl phthalate
DINCH	Di(isononyl)cyclohexane-1,2,-dicarboxylate
MEHP	Mono(2-ethylhexyl) phthalate
MEHHP	Mono(2-ethyl-5-hydroxylhexyl) phthalate
MEOHP	Mono(2-ethyl-5-oxohexyl) phthalate
MECPP	Mono(3-carboxypropyl) phthalate
MbzP	Monobenzyl phthalate
MnHP	Mono-n-hexyl phthalate
MnBP	Mono-n-butyl phthalate
MP	Methylparaben
EP	Ethylparaben
PP	Propyl paraben
BuP	Butylparaben
LMW	Low-molecular weight
HMW	High-molecular weight

PCPs	Personal care products
PPARs	Peroxisome proliferator activated receptors
PVC	Polyvinyl chloride

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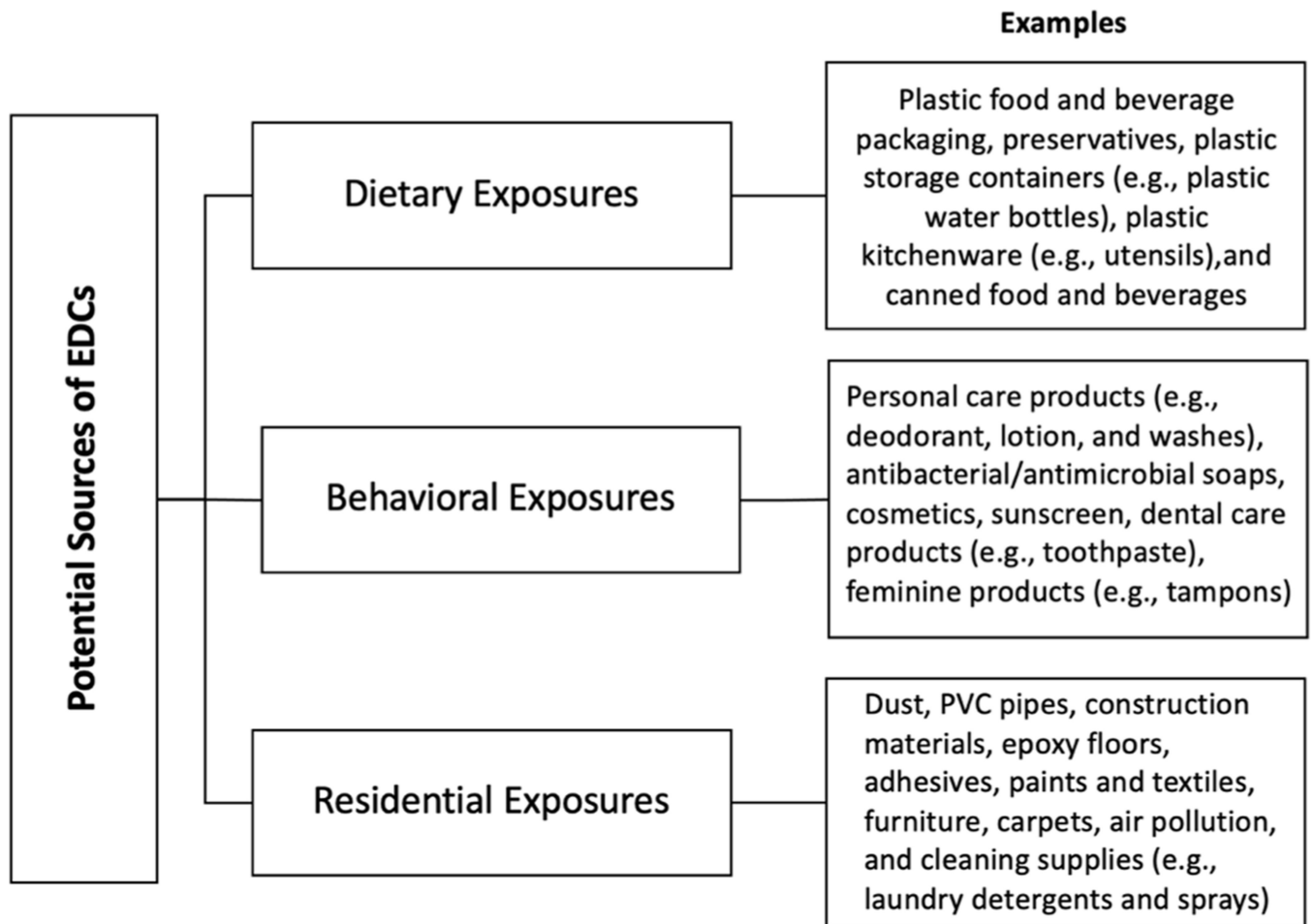


Fig. 1.
Common routes of exposure to non-persistent EDCs (targeted by interventions).

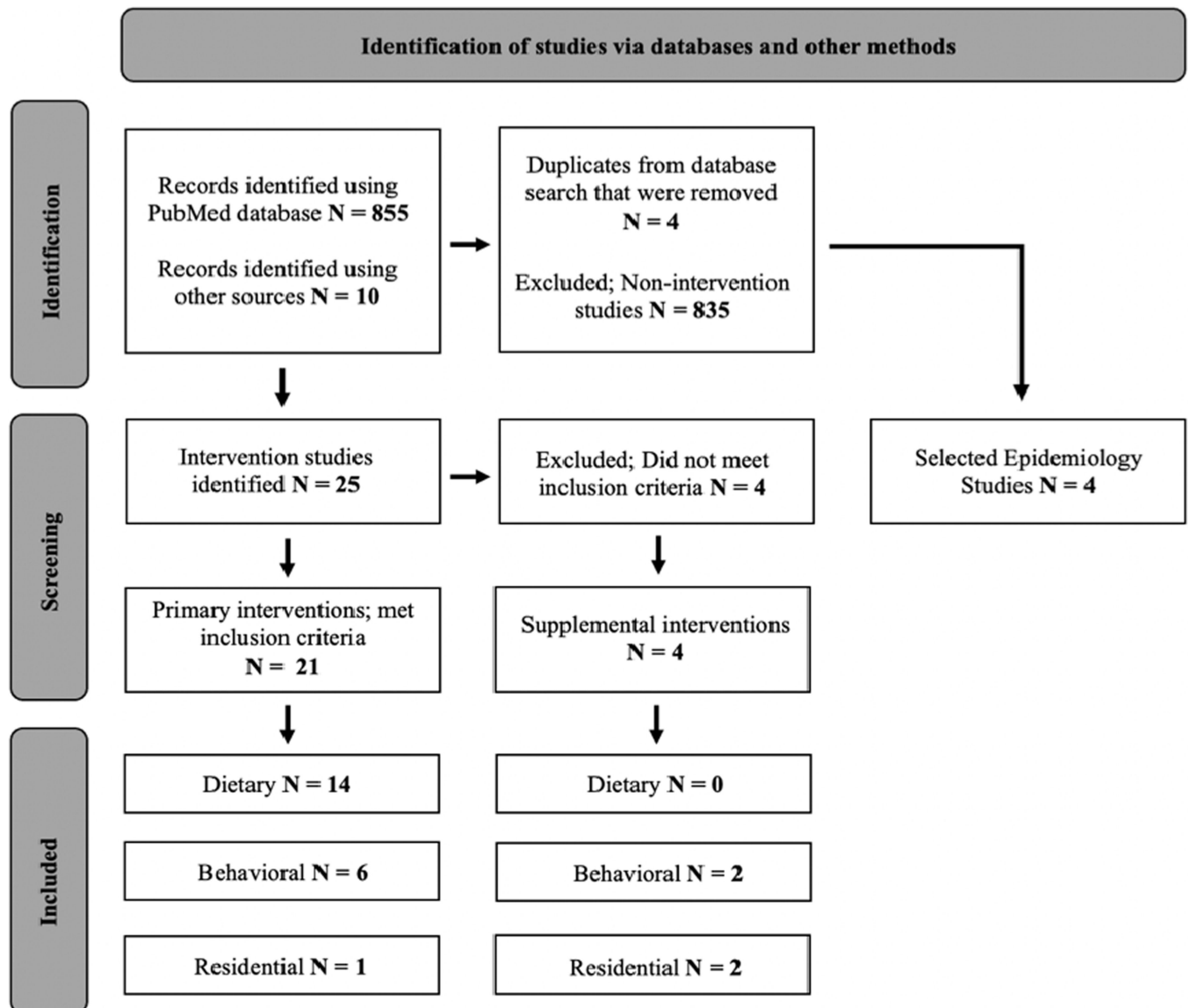


Fig. 2.
Visual display of studies identified during the database search.

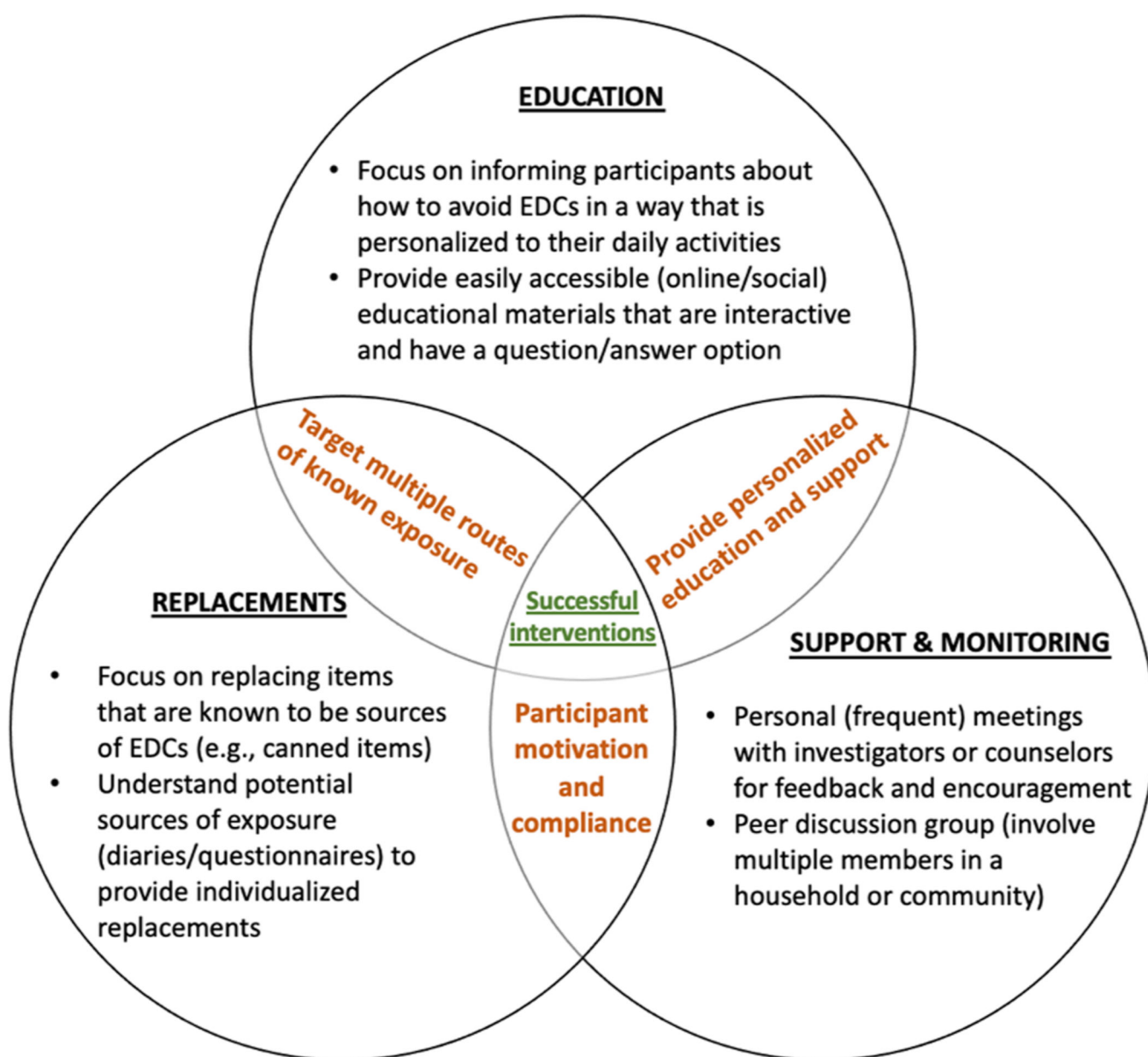


Fig. 3.
Key elements for phthalate and phenol interventions.

Strategies	
Dietary	<ul style="list-style-type: none">• Choose fresh or frozen foods instead of canned, processed, or packaged foods. Avoid drinking beverages from cans or plastic bottles.• Cook more meals at home, instead of eating fast food or takeout.• Buy organic produce, meat, and dairy products, when possible.• Avoid microwaving food and beverages in plastic containers.• Store food and beverages in glass, stainless steel, or ceramic containers, instead of plastic.
Behavioral	<ul style="list-style-type: none">• Check the labels of personal care and beauty products. Choose products that do not contain phthalates, parabens, or fragrances.• Minimize use of personal care products and cosmetics.• Use mineral-based sunscreens, containing zinc oxide or titanium dioxide, instead of chemical sunscreens.• Avoid perfume, cologne, scented body sprays, and other products with fragrance.• Limit use of nail polish and nail polish remover.
Residential	<ul style="list-style-type: none">• Reduce household dust using a wet mop or cloth, or HEPA filter vacuum.• Wash your hands regularly, avoid using antibacterial or scented hand soaps.• Choose safer cleaning products. Avoid products that contain scents or fragrances, harsh chemicals, or antibacterial/antimicrobial chemicals.• Avoid scented products including air fresheners, candles, detergents, and soaps.

Fig. 4.
Dietary, behavioral, and residential tips to reduce exposure to EDCs.

Table 1

Common sources of phenol metabolites and related health outcomes.

<i>Possible EDCs of Interest (Phenols)</i>	Potential Sources	Associated Health Outcomes	Reference (s)
Bisphenol A (BPA) Bisphenol A mono-chlorinated (MCBPA) Bisphenol A di-chlorinated (DCBPA) Bisphenol A tri-chlorinated (TCBPA) Bisphenol A tetra-chlorinated (TTBPA)	Polycarbonate plastic products (toys, electronics, waterbottles), thermal papers (receipts), dental sealants, epoxy resin-based lining of containers (canned food), polyvinyl chloride (medical devices), food packaging	Type II diabetes, cardiovascular disease, obesity, asthma, autoimmunity, poor oocyte-quality and maturation, decreased sperm production and quality, ovary function, spontaneous abortion, and other adverse birth effects	23–26, 72, 83, 85, 89–94
Bisphenol B (BPB)	BPA alternative; epoxy resins, powdered milk, beverages, indoor dust, canned food	Estrogenic and anti-androgenic activity, oxidative stress, decreased sperm count, compromised sperm morphology, and reduced sperm quality	56, 58, 152, 153
Bisphenol F (BPF)	BPA alternative; manufactured polycarbonates, epoxy resins, food packaging, beverages (including water supply pipes), meat products, vegetables	Induces oxidative stress, toxic effects on testes and spermatogenesis, reduced testosterone	58
Bisphenol S (BPS)	BPA alternative; epoxy resins, thermal papers, infant feeding bottles	Adverse birth defects, disrupted hormone levels (plasma estradiol (E2))	85, 110, 58
Benzophenone-3 (BP-3)	Sunscreen agent, cosmetics, fragrances, water additive	Birthweight, decreased in length of gestation (spontaneous abortion), semen motility and male fertility, and other birth adverse reproductive outcomes	111, 112
Triclosan (TCS) Triclocarban (TCC)	Antimicrobial soaps (triclosan: liquid soap, triclocarban: bar soap), hand sanitizers, toothpaste, mouthwash, indirect food and water additive	Disrupts immune and mitochondrial function, calcium signaling, thyroid function, cardiovascular function, fecundity, birthweight, promotes cancer development, spontaneous abortions	21, 73, 74, 92, 93
4-Nonylphenol (4-NP)	Pharmaceutical drugs, fungicides, insecticides, dyes, dark leather	(Limited) estrogenic and anti-androgenic activity	113

Table 2

Typical sources of phthalate metabolites and associated health outcomes.

Possible EDCs of Interest (<i>Phthalates</i>)	Potential Sources	Associated Health Outcomes	Reference (s)
*Low-molecular weight (LMW) Dimethyl phthalate (DMP) Monomethyl phthalate (MMP) Diethyl phthalate (DEP) Monoethyl phthalate (MEP) Diisobutyl phthalate (DiBP) Monoisobutyl phthalate (MiBP) Di-n-butyl phthalate (DnBP) Mono-n-butyl phthalate (MnBP) Dibutyl phthalate (DBP) Monobutyl phthalate (MBP)	<i>(General products: LMW phthalates)</i> Pharmaceuticals, plastics (children's toys, adhesives, flooring, coatings) food (dairy products), paints and textiles, cosmetics, fragrances, and other personal hygiene products	<i>(Generalized endocrine effects)</i> Disrupts prenatal and postnatal development, LH/testosterone ratio, and androgen activity; reduces genital size, sperm motility, fecundity, spontaneous abortion	30, 32, 114, 115
High-molecular weight (HMW) Di(2-ethylhexyl) phthalate (DEHP) Di-isononyl phthalate (DiNP) Di-isopropyl heptyl phthalate (DPHP) Mono(2-ethylhexyl) phthalate (MEHP) Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) Mono(3-carboxypropyl) phthalate (MECPP) Monobenzyl phthalate (MbZP) Di-isononyl phthalate (DiNP) Di-isopropyl heptyl phthalate (DPHP)	<i>(General products: HMW phthalates)</i> Vinyl flooring, PVC pipes, plastic tubing, construction materials, carpets, furniture, food packaging and containers, medical devices, car accessories, clothing, paints, cleaning products, personal care products	<i>(Generalized endocrine effects)</i> Disrupts sperm motility and quality, oocyte growth and maturation, and Leydig cell function; lowers androgen activity, spontaneous abortion	30, 32, 116, 117
Di(isononyl)cyclohexane-1,2,-dicarboxylate (DINCH)	DEHP, DPHP, and DiNP alternative; cosmetics, plastic products (e.g., PVC materials)	Decreased estradiol and retrieved oocyte counts, impair Leydig function, may cause premature aging	96, 97
Di-2-ethylhexyl terephthalate (DEHTP)	DEHP alternative; substituted in a variety of plastic products (e.g., medical devices, food packaging, adhesives and sealants)	*No human toxicology studies; minor effect on liver weight in animal studies	98–100

Table 3

Dietary interventions.

Author (Year)	Intervention Design	Study Population	Intervention Characteristics	Intervention Period	Exposure(s) of Interest	Biospecimen & Collection	Primary Outcome(s)	Percent (%) Change
Quazzani, et al. (2022)	Dietary , randomized controlled trial	n = 268 pregnant women (intervention); 230 pregnant women (randomized controlled trial, 78 control and 152 intervention); average age: 33 years	- Three workshops using RE-AIM method (reach, adoption, implementation) during second and third trimesters with a focus on indoor air quality, nutrition (canned food), and personal care products.	14 months	Phenols (BPA, MCBPA, DCBPA, TCBPA, TTBP, MePB, EtPB, PrPB, BuPB)	Urine collected pre-intervention, 2 months, childbirth, and 14 months; colostrum collected at childbirth	No significant difference in canned food consumption; * significant increase in risk perception score (+15.73 control, +21.03 intervention, p = 0.02); *significant difference in BuPB from colostrum (p = 0.03).	Difference in presence of BuPB in colostrum (13 % control, 3 % intervention); Greater number of women with decrease in MePB (19 % control, 32 % intervention).
Park & Chung (Park and Chung, 2021)	Dietary , community-based	n = 30 female college students; average age: 22.1 years	- Small group instruction, follow-up monitoring, and peer support via social network communication that targeted fast/processed food consumption.	4 weeks; 3-month study period	Phenols (BPA)	Urine collected pre-intervention and for three menstrual cycles following the intervention.	*significant decrease in urinary BPA concentrations until the 2nd menstrual cycle (p = 0.000), not dependent on adherence level (43.3 % highly adherent); * significant decrease in menstrual pain (p = 0.000)	The decrease in median BPA concentration creatinine-adjusted from entry (TO) to T3 was 27.2 % (p < 0.001)
van der Meer et al. (2021)	Dietary , randomized controlled trial	n = 218 individuals (male and female); age: 52 years old	- Dietary questionnaire (based on age, BMI, bodyweight, and exercise) - Four different energy- restricted weight reduction intervention diets	3 months	Phthalates (MMP, MEP, Mi BP, MnBP, MnHP, MEHHP, MEOHP, MECPP, MBzP, MiNP, MHNP, MiDP) Phenols (BPA, BPF, BPS, MeP, EtP, PrP, n-BuP, BzP)	Urine collected pre- and post-intervention	*Significant decrease in all HMW phthalates post-i nerve nti on (FDR < 0.0001), except MnHP; *Significant associations between MnBP (p = 0.031), MBzP (p = 0.005), and waist circumference (potential obesogenic properties)	The percent decreases ranged from 25 % to 35 % for the median HMW phthalates, while urinary paraben and bisphenol concentrations remained similar comparing follow-up to the baseline.
Kim, et al. (Kim et al., 2020)	Dietary , community-based	n = 37 families (93 subjects, mother- children pairs); age range 30–50 years old	- Participants were provided with educational materials - Asked to avoid canned or plastic-packaged food, fast food, and delivery foods. - Food and behavior diary -Communication via	3 days	Phenols (BPA, BPS)	Urine collected pre-, mid-, and postintervention; 2 samples per time point	Nonsignificant reduction in urinary BPA (p = 0.8669) and BPS (p = 0.0866) concentrations in mothers; *significant correlation between canned and fast food items, and BPA/BPS	(Average decrease in urinary concentrations among mothers) BPS: -63.9 %, (95 % CI: 37.1–79.3) BPA: -53.1 %, (95 % CI: 30.0–68.6)

Author (Year)	Intervention Design	Study Population	Intervention Characteristics	Intervention Period	Exposure(s) of Interest	Biospecimen & Collection	Primary Outcome(s)	Percent (%) Change
Jo, et al. (2019)	Dietary , community-based	n = 25 individuals (16 male, 9 female); age range: 13–64 years	social network service for questions - Strict buddist vegetarian diet without fast foods (no meat, eggs, dairy, or fish)	5 days	Phenols (MeP, EtP, PrP, BuP, BPs)	Urine collection pre- and post-intervention	concentrations (p < 0.05) *Significant decrease in BuP concentrations among males (p < 0.05); nonsignificant decrease in MeP, PrP, and BPs. EtP concentrations increased post-intervention among males (p < 0.05).	(Change in detection frequency pre- vs. post-intervention) MeP: -4 %, EtP: -4 %, PrP -8 %, BuP: -4 %, BP-1: 0 %, BP-3: 0 %.
Peng, et al. (Peng et al., 2019)	Dietary , randomized crossover	n = 20 college students (10 female, 10 male); age range: 21–32 years	- Subjects were given either canned food or fresh food (no beverages in cans or plastic containers were allowed).	2 days (2 days on, 1 day washout)	Phenols (BPA)	Urine collection pre-intervention and 2 h, 4 h, 6 h after meals on intervention assignment days	*Significant difference in urinary BPA concentrations between canned food and fresh foods at 2 h (p = 0.001), 4 h (p < 0.001), and 6 h (p < 0.001); BPA peaked 4 h post-meal.	Mean BPA concentrations at 2 h (152 %), 4 h (206 %), and 6 h (79 %) higher after consuming canned food
Galloway, et al. (Galloway, T. S., Baglin, N., Lee, B. P., Kocur, A. L., Shepherd, M. H., Steele, A. M., BPA Schools Study Consortium, & Harries, L. W, 2018)	Dietary , community-based	n = 94 teenagers; age range: 17–19 years	- Literature-informed guidelines that encouraged reducing processed or packaged foods (known BPA) - BPA risk score based on self-reported food diary	7 days	Phenols (BPA)	Urine collection pre- and post-intervention	No significant change in BPA levels post-intervention (p = 0.25); *significant positive association between participants who did experience a reduction (p = 0.003).	No change observed (<5 %)
Szybiak, et al. (Szybiak et al., 2017)	Dietary , randomized controlled trial	n = 20 women (10 control, 10 intervention) age range: 22–25 years	- Meal plan with or without canned products (estimated intake of BPA: 1.28 ug/kg of bw/d)	7 days	Phenols (BPA)	Venous blood samples pre-intervention, immediately post-intervention, and 7-days post-intervention	*Significant increase in BPA concentrations among participants who ate canned foods (p = 0.0008) and remained unchanged in control	Post-intervention BPA was found in 90 % of samples at baseline; post-intervention there was a ~ 105.8 % increase among the intervention group that consumed canned items
Chen, et al. (Chen et al., 2015)	Dietary , community-based	n = 30 girls; age range: 4–13 years	- Seven intervention strategies: handwashing, avoiding plastic containers, not eating plastic covered foods, not taking supplements, not microwaving foods, reducing personal care products, avoiding cosmetics (recorded frequency of use)	7 days	Phthalates (ZDEHP, MMP, MEHP, MBP, MBzP, MEHP, MEOPP, MECHPP)	Urine collection pre- and post-intervention	*Significant decrease in MBP (p = 0.009) and MMP (p = 0.07) in high-frequency handwashing group; *significant decrease in MEHHP (p = 0.038) and MECPP (p = 0.012) in group that used fewer plastic cups	Creatinine-adjusted percent decreases in medians post-intervention compared to pre-intervention: MEP: 72 %; MECPP: 57 %, MMP: 56 %, MEHP: 52 %, MEOPP: 51 %, MBzP: 47 %, MBP:

Author (Year)	Intervention Design	Study Population	Intervention Characteristics	Intervention Period	Exposure(s) of Interest	Biospecimen & Collection	Primary Outcome(s)	Percent (%) Change
Barrett, et al. (Barrett et al., 2015)	Dietary , community-based	n = 10 pregnant women; average age: 26 years	- Mostly fresh, organic, and low-phthalate catered diet - Semi-structured interviews to evaluate feasibility - Food diaries	3 days	Phthalates (ΣDEHP, MEHHP, MEOHP, MEHP, MECCP, MCOP, MCNP, MBP, MEP, MiBP, MBzP)	Urine collected pre-, mid-, and post-intervention	No significant changes in urinary phthalate concentrations across all three time points (p = 0.65); no reduction during the intervention compared to baseline (p = 0.51) interviews showed unwillingness to alter lifestyle.	45 %, ΣDEHP: 42 %, MBP: 31 % No change observed
Sathyanarayana, et al. (Sathyanarayana et al., 2013)	Dietary , two-arm randomized study	n = 10 families (21 intervention individuals; 19 control individuals) (adult ages not provided)	- Fresh and organic foods, without plastics (intervention) vs. educational handouts with recommendations (control). - Provided calendar, checklist, dietary questionnaire, and food storage containers	5 days	Phthalates (DEHP) Phenols (BPA)	Urine collection pre-, mid-, post-intervention	*Significant increase in urinary DEHP concentrations in intervention group (p < 0.0001), no change in control group; significant increase in urinary BPA concentrations (p < 0.05) in intervention group	(% change from baseline to intervention in geometric means) DEHP increased (MEHP: 1670 %, MEHHP: 2524 %, MEOHP: 2297 %, MCEPP: 2470 %) and BPA increased 100 % among the intervention group (Arm 1)
Christensen, et al. (Christensen et al., 2012)	Dietary , community-based	n = 5 individuals (2 males, 3 females); age range: 27–47 years	— 48hr fasting period (bottled water only) - Food and behavior diaries	2 days	Phenols (BPA)	All urine collected during 48hr intervention, and urine samples from pre- and post-intervention	No significant changes; day 1 consistent BPA concentrations, but day 2 BPA concentrations declined	BPA concentrations decreased ~ 66 % on average over the intervention period
Carwile, et al. (2012)	Dietary , randomized crossover trial	n = 75 individuals (51 female, 24 male) median age: 27 years	- First 5-days one group consumed fresh soup and the other group consumed canned soup, after 2-day washout, treatments were reversed	5 days (5 days on, 2 days off)	Phenols (BPA)	Urine collection on day 4 and day 5 (pooled for comparison)	*significant increase in urinary BPA concentrations following canned soup consumption (p < 0.001)	BPA detected in 77 % of samples after fresh soup, but 100 % of samples after canned soup
Rudel, et al. (Rudel et al., 2011)	Dietary , community-based	n = 20 individuals (5 families) average adult age: 40.5 years	- Regular diet followed by a catered “fresh foods” dietary intervention where foods were not canned or in plastic - Provided stainless steel water bottles and containers - Daily meetings with field director	3 days	Phthalates (ΣDEHP, MEHHP, MEOHP, MEHP, MBP, MBzP, MMEP) Phenols (BPA)	Urine collection pre-, mid-, and post-intervention (two samples per collection period)	*Significant decrease in BPA (p < 0.005) and DEHP (p < 0.05) during the dietary intervention period	(Decrease in geometric means postintervention) BPA: 66 % and DEHP metabolites 53–56 %.

Table 4

Behavioral interventions.

A intervention in the intervention group compared author (Year)	Intervention Design	Study Population	Intervention Characteristics	Intervention Period	Exposure(s) of Interest	Biospecimen & Collection	Primary Outcome(s)	Percent (%) Change
Kim, et al. (Kim et al., 2021)	Behavioral , randomized controlled trial	n = 51 mothers with young children (25 control and 26 intervention); average age: 35.1–35.8 years	- Web-based intervention with videos, interactive games, general info, and question/answer mode -Reinforcement and encouragement through texts/calls	4 weeks	Phthalates (MEHP, MEOHP, MEHHP), Phenols (BPA, TCS, MP, EP, PP)	Urine collected pre-, mid-, and post-intervention one month among the intervention group, except for EP	*Significant decrease (p < 0.05) in the urinary geometric mean values after intervention in the intervention group compared to the control) MEHP: 3.8 %, MEOHP: 16.3 %, BPA: 28.4 %, MP: 9.2 %, and PP: 24.4 %	(Significant decrease in urinary geometric means at post-intervention compared to during intervention in the intervention group compared to the control) MEHP: 3.8 %, MEOHP: 16.3 %, BPA: 28.4 %, MP: 9.2 %, and PP: 24.4 %
Huang, et al. (Huang et al., 2021)	Behavioral , community-based	n = 10 women; age range: 22–26 years old	- Participants used personal care products with the least amount of parabens - External exposure data was collected (diet, drinking water, and dust)	18 days (6 days control, 6 days intervention, 6 days control)	Phenols (MeP, EtP, PrP, BuP, BzP)	Urine collected pre-, mid-, and post-intervention; three additional urine samples taken daily	Parabens were found to account for > 99 % of total exposure; *significant (p < 0.05) decrease in urinary paraben concentrations during the intervention	Urinary levels of parabens decreased an average of ~ 68.6–88.3 % compared to control period post-intervention
Hagobian, et al. (Hagobian et al., 2021)	Behavioral , randomized controlled trial	n = 30 women (15 control and 15 intervention); average age: 21.1 years	- Exposure questionnaires - Weekly meetings and encouragement from counselor - Replacement products	3 weeks	Phenols (BPA, BPS, BPF)	Urine collected pre- and post-intervention	*Significant treatment × time effect on BPS (–1.42 ug/g creatinine intervention; –0.09 ug/g creatinine control)	(change in geometric means post-intervention) No changes in BPA and BPF concentrations; a 55 % decrease in BPS.
Ley, et al. (Ley et al., 2017)	Behavioral , randomized controlled trial	n = 154 women (76 control and 78 intervention); gestational age: 23 weeks	- Replacement products (products containing TCS/TCC or products without TCS/TCC) - Household visits and questionnaires used to gather demographics	20 weeks' gestation to 36' weeks (or post-delivery or post-enrollment)	Phenols (TCS, TCC)	Urine collected every visit (enrollment, home visit, second homevisit/ delivery)		

Blood sample collected at enrollment, second household visit, and 36 week visit or delivery

*Significant difference in exposed group; seven-fold higher urinary TCS/TCC concentration (median: 19.0 pg/μl in exposed vs. 2.7 pg/μl in TC arm.

179 % increase in the TC arm while there was ~ 70 % decrease in the non-TC arm.

Intervention in the intervention group compared author (Year)	Intervention Design	Study Population	Intervention Characteristics	Intervention Period	Exposure(s) of Interest	Biospecimen & Collection	Primary Outcome(s)	Percent (%) Change
	unexposed; p = 0.002).							
Hagobian, et al. (Hagobian et al., 2017)	Behavioral , randomized controlled trial (pilot study)	n = 24 women (11 control and 13 intervention); average age: 20.9 years	- Exposure questionnaires - Weekly meetings and encouragement from counselor - Replacement products	3 weeks	Phenols (BPA)	Urine collected pre- and post-intervention	*Significant decreased geometric mean urinary BPA of -0.71 ng/m in intervention group; *significant increased geometric mean urinary BPA of + 31 ng/m in control group.	(Change in geometric mean of BPA from entry to end of interventino period) control group: increased by 29 %, intervention group: decreased by 45 %
Harley, et al. (Harley et al., 2016)	Behavioral, community-based	n = 100 adolescent girls; age range: 14–18 years	- Coupons and replacement products without EDCs listed on the ingredients - Household visits, interviews, and questionnaires	3 days	Phthalates (MEP, MnBP, MiBP), Phenols (TCS, BP-3, MP, EP, BP, PP)	Urine collected pre- and post-intervention	Nonsignificant decrease in MEP, MP, PP, TCS, and BP-3; no significant change in MiBP or MnBP; EP and BP unexpectedly increased.	(post-intervention percent changes (95 % CI) in urinary concentrations) MEP: -27.4 (-39.3, -13.2), MnBP: -11.3 (-22.2, 1.1), MiBP: -0.5 (-12.6, 13.3), TCS: -35.7 (-53.3, -11.6), BP-3: -36.0 (-51.0, -16.4), MP: -43.9 (-61.3, -18.8) EP: +47.3 (-0.7, 118.4) BP: +101.7 (35.5, 203.2), PP: -45.4 (-63.7, -17.9)

Table 5

Residential intervention.

Biospecimen & Collection	Primary Outcome(s)	Percent (%) Change
Urine (n = 22) and dust (n = 7) collected pre- and post-intervention	*Significant decrease in urinary BPA (p = 0.003), BPS (p = 0.004), 4-NP (p=<0.001), DEHP (p=<0.001), and DEP (p = 0.012); *significant decrease in dust BPS (p = 0.042), 4-NP (p = 0.017), and DEHP (p = 0.017).	Pre-intervention: 100 % of samples contained BPA; decrease in detection rates in urine samples post-intervention BPA: 0 %, BPS: -32 %, 4-NP: -5 %, DEP: -9 %, DiBP: -41 %, DEHP: -45 %