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Review Article

How body burden from exposure to endocrine disruptors effects accelerated aging?

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ABSTRACT

This paper reviewed various studies on the effects of endocrine disruptors on human health, focusing on accelerated aging in the younger generation. In particular, we analyzed how the modern lifestyle and ignorance of endocrine disruptors in the younger generation are accelerating aging, and how the concentration of endocrine disruptor exposure in the human body affects the body's burden. Based on existing papers, we conducted a systematic review using Web of Science, Google Scholar, and Scopus to comprehensively investigate and summarize the definition of endocrine disruptors, their effects on hormones, and the physical burden of continuous exposure to endocrine disruptors. Research has shown that persistent exposure to endocrine disruptors disrupts homeostasis in the body and creates oxidative stress that can lead to aging and chronic inflammation. These characteristics were also found to be significant in the observation of telomere length, which is a measure of aging. Therefore, in order to prevent accelerated aging in the younger generation, we can suggest ways to minimize exposure to endocrine disruptors and slow down normal aging in the entire public health, including the 3040s, in the long term.

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INTRODUCTION

Environmental pollutants typically consist of dozens of environmental chemicals that are harmful to human health. Many of these substances can interact with genetic and epigenetic mechanisms to alter the normal course of development [1]. One particularly harmful environmental factor is endocrine disrupting chemicals (EDCs). EDCs are widespread in the environment we live in. When exposed to EDCs, organisms are highly sensitive to perturbations by substances with hormone-like activity, which negatively affects their development [2, 3]. EDCs have been shown to interfere with endocrine system function, either by suppressing hormone production or by altering the way hormones move through the body, affecting the functions they regulate. Modern humans are exposed to EDCs because most EDCs are persistent or widely used substances in our environment, including synthetic chemicals such as dioxin-like compounds, dioxins, phthalates, polychlorinated biphenyls, pharmaceuticals, pesticides, and heavy metals [2–5]. Endocrine-disrupting chemicals (EDCs) disrupt the synthesis, metabolism, or function of hormones, leading to disturbances in the usual regulatory processes of the body or reproductive functions [6]. In both animal and human studies, early childhood exposure to EDCs has been shown to impede normal development and lead to negative health outcomes such as lifelong tumor development [7, 8]. Some EDCs have also been shown to interfere with epigenome programming [9]. The main focus of this review is on aging caused by EDC exposure. Studies report that continued exposure to EDCs

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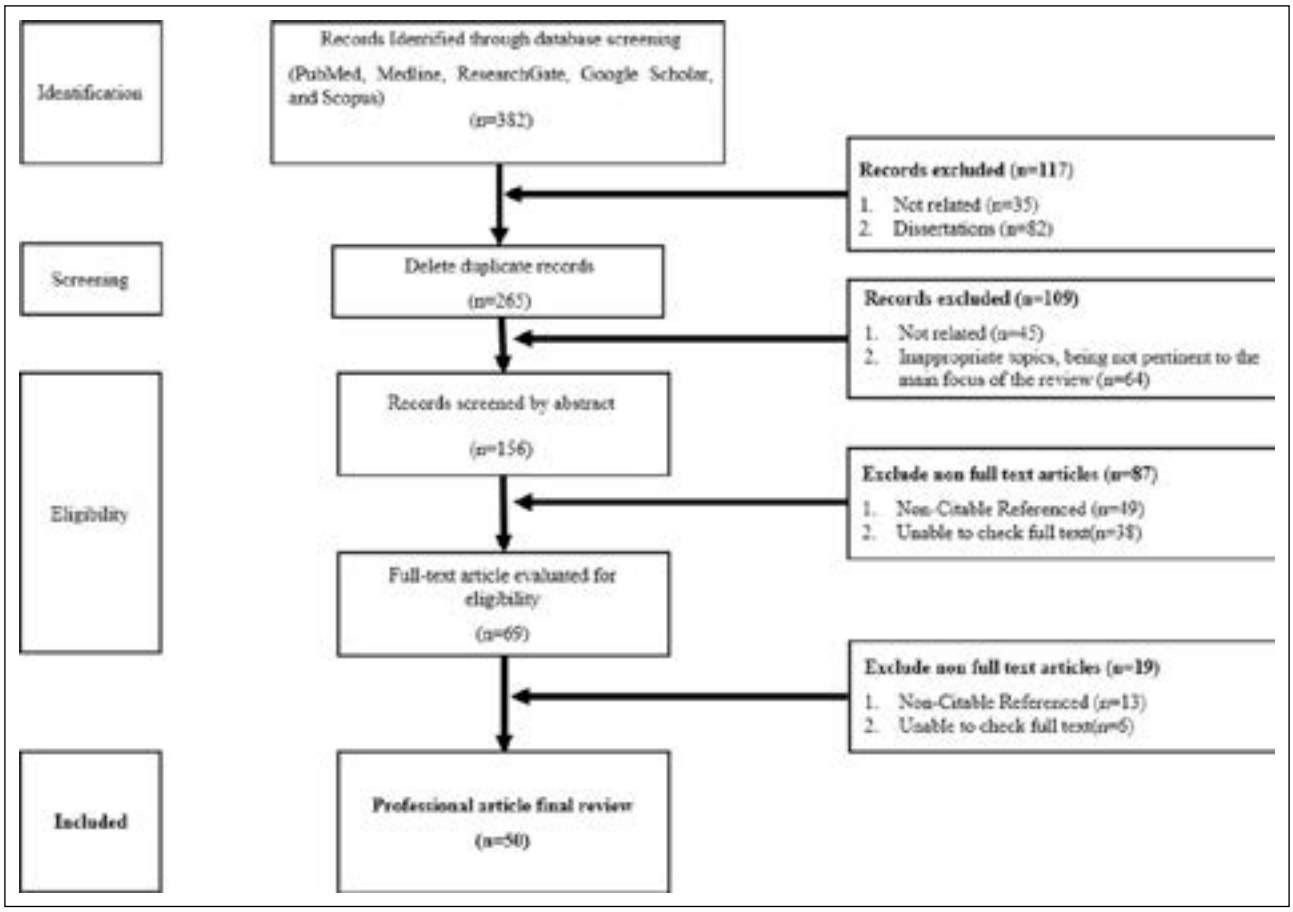

Figure 1. PRISMA flow chart for literature review search results.

may increase the risk of developing chronic diseases associated with aging, including obesity, cardiovascular disease, diabetes, and cancer, as well as several mental and behavioral disorders, such as schizophrenia and mood disorders [10]. Especially in recent years, the prevalence of chronic diseases such as hypertension, diabetes, and obesity has been increasing in the younger age group of 3040. This is associated with accelerated aging. In fact, in people who developed chronic inflammation and disease due to exposure to endocrine disruptors, mRNA levels of markers of aging (GLB1, p16, p21, p53) and inflammation (IL-6, TNF-α) were significantly higher, and telomere length was also shortened. From an epigenetic perspective, the key to the biological conditions that accelerate aging are lifestyle habits that create chronic inflammation and insulin resistance [11]. The purpose of this study is to review how continuous exposure to EDCs contributes to the total amount of EDCs in the body as a body burden. We provide a summary of recent research findings that indicate factors that may accelerate aging, especially in younger generations. We suggest lifestyle choices that may reduce the total amount of EDCs entering the body.

MATERIALS AND METHOD

Noting the increasing exposure to endocrine disruptors in modern society, this review aims to update the current state of research on endocrine disruptors, with a focus on whether they may play a role in accelerating ageing when absorbed by the body and added to the body's burden. Below we describe in detail our search strategy, article selection methods, and data synthesis procedures.

Search Strategy

For this review, we searched six databases in the natural sciences, biology, medicine, and health and wellbeing, following PRISMA flow guidelines: PubMed, Scopus, Medline, ResearchGate and Google Scholar using the keyword sets (a) 'endocrine disruptors' and 'endocrine system organs' (b) 'body burden' (c) 'accelerated ageing' and 'ageing agents' as search terms. Figure 1 is a flowchart showing the process of selecting studies for inclusion in this review.

Eligibility Criteria

Articles included in this review had to meet the eligibility criteria for this review, which included selecting studies related to the following: types of endocrine disruptors, characteristics of endocrine disruptors, endocrine disruptors and body burden, body burden and accelerated ageing, and ageing substances.

Screening and Data Extraction

The following articles were included in the corpus: (1) investigated the association between endocrine disruptors and body burden, (2) included increased body burden and

aging, (3) included post-absorptive properties of endocrine disruptors, (4) included the effects of endocrine disruptors on accelerated aging, (5) were peer-reviewed, and (6) were included in the corpus if they were journal articles or conference presentations.

We excluded articles that (1) did not investigate the nature of endocrine disruptors, (2) did not investigate the association between endocrine disruptors and body burden, or (3) did not investigate the effects of endocrine disruptors on aging.

We considered a range of article types, including original articles, full-text articles, internet articles, summary reports, and series, and did not impose restrictions on publication date or language. Exclusion criteria included inaccessible full text, full text without raw data, inappropriate topics, and doctoral dissertations; these articles were retrieved through the ProQuest Dissertations and Theses Global Database.

Study Selection and Data Extraction

We used a literature review approach. A total of 382 references were selected from the major journal search sites PubMed, Google Scholar, ResearchGate, Medline, and Scopus using the PRISMA flowchart. This resulted in a total of 50 articles that were finally selected. The PRISMA flowchart is shown in Figure 1.

ENDOCRINE DISRUPTORS

The role of the endocrine system is to regulate metabolism through carbohydrates, proteins, and fats to ensure that the body always has the energy it needs. Hormones play an important role in keeping blood sugar levels steady. They also store extra fuel when it's available and mobilize it when needed. Therefore, hormonal changes are dangerous because they can lead to metabolic imbalances [12]. An endocrine disrupting chemical (EDC) is an exogenous substance or mixture of substances that has an adverse effect on an organism's endocrine system. Typically, they act on the receptor to mimic the natural hormone, perturbing the receptor to activate the receptor and cause a response (agonistic effect), or they bind to the receptor and prevent the activation of the natural hormone (antagonistic effect) [13]. Humans and even wildlife are exposed to EDCs that adversely affect biological systems. Many of these substances have been detected in various environmental matrices, including water, sediments, soil, and lipid tissues of animals [14].

Types of Endocrine Disruptors and Routes of Exposure

Endocrine-disrupting chemicals (EDCs) are external compounds that disrupt the equilibrium and control of the body's endocrine system or that of its progeny. These substances typically exhibit chemical durability, resist easy degradation, accumulate within organisms, and exert adverse effects on their descendants [15]. Some EDCs occur naturally - phytoestrogens are an example - but most EDCs are synthetic chemicals that have been released into the environment by anthropogenic human activities with little or no impact or concern for ecosystems and human health. Humans are constantly exposed to chemicals in pesticides, herbicides, industrial and household plastics, detergents and flame retardants, and ingredients in personal care products, both indoors and out. These substances can enter the human body through a variety of routes, including oral, inhalation, and dermal absorption [16].

It describes the origins and endocrine disrupting actions of some of the most common and well-known endocrine disruptors that we are exposed to.

Bisphenol A and phthalates are substances used in the manufacture of plastics. Bisphenol A (BPA) has cross-linking properties and is used to make polycarbonate plastics and epoxy resins, which are now widely used in everyday consumer products such as water bottles, water pipe linings, food and beverage can coatings, thermal paper, and dental sealants [12]. Phthalates and other components utilized in plastics have been identified within human tissues, with these substances being emitted from plastic items [17, 18]. Phthalates serve as primary plasticizers employed to enhance flexibility, clarity, resilience, and lifespan. They find extensive application in the production of consumer goods, encompassing polyvinyl chloride (PVC), a multitude of adhesives, paints, packaging materials, children's toys, electronics, flooring, medical devices, personal care items, air fresheners, food packaging, pharmaceuticals, and textiles. In 2004, the OECD listed phthalates as a mass-produced chemical as a top endocrine disruptor [19, 20].

Polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls, which are currently detectable in human tissue, are the main ingredients in flame retardants [21]. Serum PBDE levels showed a significant positive correlation with certain thyroid hormones and antibodies, including free triiodothyronine (fT3), total triiodothyronine (tT3), total thyroxine (tT4), and thyroid peroxidase antibodies (TPO-Ab), which provides new evidence for the thyroid disruptive and hepatotoxic effects of PBDEs [22].

4-Nonylphenol is a commonly employed surfactant in both industrial manufacturing and everyday household items, such as detergents and plastics. Additionally, it has been documented to impact female fertility by either mimicking or inhibiting the activity of the estrogen receptor (ER) [23].

Parabens (alkyl esters of p-hydroxybenzoic acid) are used as antimicrobial agents for the preservation of personal care products, food, pharmaceuticals, and paper products. Parabens are widely present in human tissues, including breast tissue, and have estrogenic properties [24].

HOW ENDOCRINE DISRUPTORS AFFECT AGING?

Endocrine Disruptors and Chronic Inflammation

Plasticizers, synthetic compounds, are extensively utilized in various items such as children's toys, food packaging, construction materials, medical equipment, cosmetics, and inks. They have been associated with detrimental impacts

on human thyroid function and the development of allergic diseases. As the prevalence of plasticizer utilization rises, these substances are increasingly detected in the environment, within animals and humans, concurrently with a surge in the presence of plasticizer derivatives, a subgroup of endocrine-disrupting chemicals (EDCs) [25]. Previous studies have shown that the prevalence of allergic diseases has increased rapidly and dramatically in Westernized countries in recent decades and that persistent exposure to EDCs is associated with the development of allergic diseases. Various EDCs are considered to be key factors in the development of chronic inflammatory and allergic diseases across the lifespan, from prenatal to old age. What we've learned from test tube and animal studies is that most EDCs not only cause but also enhance allergic inflammation [26]. The dramatic increase in chronic inflammatory diseases, particularly asthma and allergies, is thought to be linked to the increased consumption of phthalates, which are used in PVC materials and many consumer products. For example, PVC flooring in the home has been implicated as a factor in increasing the risk of asthma and allergic rhinitis [27].

Endocrine-disrupting chemicals (EDCs) have the capacity to disrupt the production of cytokines, immunoglobulins, and inflammatory signaling molecules, thereby modifying the responses of T helper (Th) cells. For instance, the administration of nonylphenol (NP) and 4-octylphenol (OP) inhibits key Th1-associated chemokine IFN-ɣ-inducible protein-10 (IP-10) and Th2-associated chemokine macrophage-derived chemokine (MDC) induced by lipopolysaccharide, implying that EDCs might suppress Th1 responses against intracellular pathogens and Th2 responses to bacterial and parasitic infections. EDCs exert their influence on allergic diseases and inflammation by reshaping Th cell responses, potentially by inducing Th2 polarization through the modulation of antigen-presenting cells (APCs). This hypothesis gains support from observations involving benzophenone, p-octylphenol, and tributyltin chloride, which reduce IL-12 production by splenic APCs, elevate IL-10 levels, and skew the immune response towards the Th2 end of the spectrum. Furthermore, it has been demonstrated that EDC treatment leads to a significant reduction in glutathione levels within APCs, exacerbating airway inflammation [28]. Inflammation is a necessary process for normal tissue self-regulation and reproduction (e.g., implantation and parturition) and can be viewed as a host defense against pathogenic invasion. However, uncontrolled inflammation poses a serious health risk, because unresolved inflammation leads to impaired tissue function and the risk that the affected target tissue will develop cancer in the future. This misregulation of inflammation leads to accelerated aging, chronic disease, and dysfunction of all physiological systems and associated comorbidities [29].

Endocrine Disruptors and Hormones

Chemicals are an inevitable part of everyday life. However some chemicals classified as endocrine disruptors have adverse effects on the body's endocrine system, especially the hormonal system. Hormones, in trace amounts and at precise moments, regulate physical development and growth, reproduction and metabolism, and immunity. Endocrine disruptors in particular disrupt natural hormone systems, so exposure to EDCs can not only have lifelong effects on you, but can also affect the next generation [30].

To summarize the main mechanisms of action by which EDCs cause adverse health effects, they are as follows. (1) binding to hormone receptors to activate signaling pathways, (2) binding to hormone receptors to inhibit signaling pathways, (3) interaction with components of hormone signaling pathways downstream of the receptor, (4) stimulation or (5) inhibition of endogenous hormone biosynthesis, (6) binding to circulating hormone-binding proteins, (7) stimulation or inhibition of hormone-binding protein synthesis or degradation, (8) stimulate or (9) inhibition of hormone receptor expression [31].

EDCs also affect endogenous free active hormone concentrations. This may be associated with aging. EDCs are generally hydrophobic and compete for hormones and transport proteins from hydrophobic hormones (steroids and thyroid hormones) that contribute to aging. In summary, EDCs directly interfere with hormone-binding transport proteins in the body. Many EDCs compete for blood levels of endogenous hormones, and it has been shown that many EDCs interact with steroid hormone-binding protein (SHBG) or α-fetoprotein (AFP), which can interfere with the transport and blood levels of steroid hormones.

EDCs that exert their effects through this mechanism can compete for binding to hormone-binding transport proteins because they are structurally similar to the hormones [32, 33].

Accelerated Aging

Continued exposure to endocrine disruptors also accelerates the aging process. Inflammation and stress are important features of aging. They also cause telomeres to shorten faster. Inflammation and oxidative stress not only affect aging itself, but also contribute to the development of several diseases such as atherosclerosis, hypertension, or diabetes. In general, oxidative stress is caused by the overproduction of reactive oxygen species (ROS). ROS can damage a variety of tissues. The main source of ROS is the mitochondria, and the situation is exacerbated when mutant mitochondria inhibit mitophagy. In this case, pro-inflammatory changes are rapidly magnified [34].

There is ample research showing that endocrine disruptors cause inflammation in our bodies, and it is this inflammation that induces aging between our immune and central nervous systems [35]. This body burden of endocrine disruptors leads to overproduction of reactive oxygen species (ROS). ROS damage cells and create negative changes in macromolecular metabolism. A typical example is the development of aging phenotypes [36]. ROS-induced oxidative stress is also associated with telomere length [37]. Various factors, encompassing genetic, psychosocial, environmental, and behavioral elements, such as DNA damage, psychological stress, dietary habits and obesity, as well as

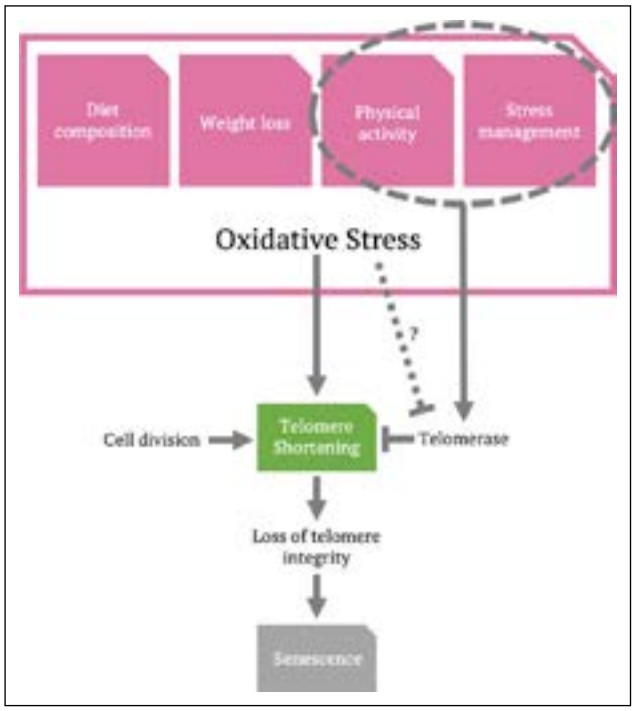

Figure 2. *Accelerated telomere shortening and aging due to endocrine disruptor accumulation. Excessive telomere shortening disrupts the integrity of telomeres, leading to cellular senescence, one of the hallmarks of organismal aging. The accumulation of senescent cells contributes to the loss of tissue homeostasis and the development of age-related pathologies* (Jorge D. Erusalimsky, Oxidative stress, telomeres and cellular senescence: What non-drug interventions might break, 2020).

tobacco smoking, have the potential to expedite the attrition of telomeres, ultimately culminating in premature cell aging and mortality [38] (Fig. 2).

Several cytokine-related effects are observed with aging. Characteristically, levels of anti-inflammatory cytokines decrease and pro-inflammatory cytokines (interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α)) increase. The combination of these changes and alterations in the innate immune response is called "inflammation." Subclinical inflammation is characterized by altered immune responses resulting from inflammatory diseases. Serum tests of aging subjects show only a slight increase in pro-inflammatory cytokine levels [39]. Inflammation is linked to the consequences of immune aging, implying an inadequate response of adaptive immunity to pathogen exposure and other types of chronic stress in aging subjects [40]. The onset and progression of reproductive aging are predominantly influenced by a combination of genetic and environmental factors. While most research has historically emphasized genetic predisposition, it is increasingly recognized that environmental hormones, particularly endocrine-disrupting chemicals (EDCs), may have a significant impact and potentially accelerate the process of reproductive aging, resulting in a shorter reproductive lifespan. Emerging studies suggest that exposure to EDCs during critical developmental phases, notably during prenatal and early childhood stages, can induce molecular and cellular alterations that ultimately affect the function of affected tissues in later life. This concept is referred to as the fetal/developmental basis of adult disease. Animal research has demonstrated that EDCs such as MXC, BPA, and dioxins can expedite the aging of the reproductive system. Recent epidemiological findings also indicate that exposure to environmental hormones during childhood, including diethylstilbestrol and perfluorocarbons, is associated with an accelerated onset of menopause. Additionally, BPA has been shown to promote oxidative stress and inflammation, potentially increasing the susceptibility of postmenopausal women to age-related health issues [41].

One of the biggest causes of accelerated aging is hidden in everyday life. From an epigenetic perspective, the key to the biological conditions that accelerate aging is a lifestyle that creates chronic inflammation and insulin resistance - a "hedonistic" environment that allows us to take it easy. Examples include a diet of ultra-processed foods, alcohol and tobacco use, lack of exercise, binge-watching TV shows, falling asleep late, and accumulating stress from worrying about an uncertain future. All of these causes of accelerated aging are prevalent in the 3040s and in society today.

Reduced Body Burden from Endocrine Disruptors

The danger of endocrine disrupting chemicals (EDCs), or environmental hormones, is that even at very low concentrations, they disrupt normal hormone action and cause adverse health effects [42]. Due to the pervasive presence of endocrine-disrupting chemicals (EDCs) in various consumer goods such as electronics, construction materials, cosmetics, medical equipment, and food packaging, individuals can encounter inadvertent exposures when these substances are released into the environment [43, 44]. However, public awareness and knowledge of endocrine disruptors is reported to be low. While a variety of studies exist on the risks of EDCs to human health, a qualitative study on the topic found that the majority of participants were unaware of endocrine disruptors. Even those who were aware of some specific endocrine disruptors, such as pesticides and BPA, were found to have poor awareness of the chemicals [45]. Suggestions for developing and implementing effective strategies to prevent exposure to EDCs are needed to prevent the acceleration of age-related health problems that are becoming increasingly prevalent in younger generations [42].

The best way to reduce chemical burden is to reduce EDC concentrations in the body, and the most effective strategy is to use alternative products and foods. Information transfer through counseling, interviews, and interactive education about endocrine disruptors, such as online games, is also needed. Interventions that include self-incentivization, phone calls, or encouragement have generally been shown to reduce EDC concentrations [46]. Dietary interventions to reduce canned foods and other plastic packaging known to contain environmental hormones focus on

using "fresh" organic foods without chemical packaging. We also avoid fast food and delivery as much as possible. When they do need to use containers, they are encouraged to use takeout containers such as stainless steel or glass rather than plastic. The dietary intervention studies that observed these changes all showed significant changes in BPA levels, even though they were designed to target only canned foods [47–49].

Aging has the property of compounding. Once it starts, the problems of aging pile up and get faster and faster. Eat fresh foods to avoid chronic inflammation and stay away from artificial, ultra-processed foods. You should also make it a habit to use natural cosmetics instead of artificial chemicals, and glass and stainless steel instead of plastic to reduce the total amount of endocrine disruptors that enter the body. Lastly, to slow down the rate of aging, we should do at least three sessions a week of moderate to vigorous cardio, strength training, and stretching [50].

CONCLUSION

Environmental exposure to endocrine disruptors is an ongoing threat to reproductive and population health, and should motivate further implementation and refinement of intervention strategies to address persistent exposure to these substances. Accelerated aging is occurring in younger populations, especially due to modernized lifestyles, with the current 3040 generation being the first generation to age faster than their parents. Endocrine disruptors have become unavoidable in personal care products, food and beverages, and indoor environments. The interventions presented in this review offer products and approaches to reduce exposure and body burden, along with awareness of endocrine disruptors, but there is still a dearth of data. Increasing the body of knowledge on the harmful effects of exposure to endocrine disruptors as a contributor to accelerated aging will enable the development of effective and targeted intervention strategies in the future. Novel approaches such as web-based or digital health interventions and educational tools, targeted alternative products, and personalized interactions are useful strategies for future interventions.

DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICS

There are no ethical issues with the publication of this manuscript.

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