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The Effects of Environmental Contaminant Exposure on Reproductive Aging and the Menopause Transition

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Abstract

Purpose of Review—Menopause marks the end of a woman's reproductive lifetime. On average, natural menopause occurs at 51 years of age. However, some women report an earlier age of menopause than the national average. This can be problematic for women who delay starting a family. Moreover, early onset of menopause is associated with increased risk of cardiovascular disease, depression, osteoporosis, and premature death. This review investigates associations between exposure to endocrine-disrupting chemicals (EDCs) and earlier onset of menopause.

Recent Findings—Recent data suggest exposure to certain EDCs may accelerate reproductive aging and contribute to earlier onset of menopause.

Summary—Human and rodent-based studies identify positive associations between exposure to certain EDCs/environmental contaminants and reproductive aging, earlier onset of menopause, and occurrence of vasomotor symptoms. These findings increase our understanding of the detrimental effects of EDCs on female reproduction and will help development of strategies for the treatment/prevention of EDC-induced reproductive aging.

Keywords

Endocrine-disrupting chemicals; Menopause; Ovary

Introduction

The menopause transition is a natural, progressive decline in fertility and is marked by the depletion of ovarian follicles over a woman's reproductive lifetime [1]. The ovarian follicle is the functional unit of the ovary and is composed of an oocyte surrounded by theca and granulosa cells [2]. With each ovarian cycle, immature ovarian follicles (primordial follicles) will undergo maturation to antral then pre-ovulatory follicles to produce and release a fertilizable oocyte [2]. Additionally, the theca and granulosa cells work in a concerted manner to produce steroid hormones such as estrogen and progesterone that support reproductive health and pregnancy [2].

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At birth, the human ovary contains 1–2 million primordial follicles [1]. This population of primordial follicles is the ovarian reserve and represents the finite pool of follicles available to a woman in her lifetime [3]. This number drops to approximately 400,000 primordial follicles at menarche [1]. By the onset of menopause, the ovarian reserve declines to fewer than 1000 primordial follicles [1]. This progressive decline in the ovarian reserve over a woman's lifetime is due to follicles being recruited for ovulation (less than 1%) or being lost due to death via atresia (about 99%) [3].

In addition to a decline in the ovarian reserve, the menopause transition is associated with hormonal changes. In a normally cycling, premenopausal woman, ovarian hormone production is tightly regulated. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary act on the ovarian follicle to promote the production of ovarian estrogen and progesterone [2]. These hormones enter circulation and act on target tissues, including the anterior pituitary to negatively regulate the release of LH and FSH [2]. During the menopause transition, the decline in follicles results in a decline in the production of ovarian estrogens and progestogens [4]. Additionally, the production of ovarian peptide hormones inhibin B, a hormone that suppresses FSH production, and anti-Müllerian hormone (AMH), a hormone that regulates follicle maturation, is also reduced during menopause [5]. Together, these changes in ovarian hormones and subsequent loss of ovarian feedback on the anterior pituitary result in elevated LH and FSH levels [4].

Fluctuating hormone levels during the menopausal transition contribute to the onset of vasomotor symptoms, the most common of which are hot flashes [6, 7]. Hot flashes are transient sensations of heat spreading over the upper body and face, accompanied by flushing of the skin and perspiration [7]. Although the duration of hot flashes is relatively short (1–5 min), their occurrence can be disruptive to a woman's productivity and well-being [7]. Some women benefit from menopausal hormone therapy for the treatment of vasomotor symptoms [8].

Although the timing of the menopausal transition can vary by individual, the mean age at natural menopause is 51 years [9]. Recent evidence suggests that exposure to environmental endocrine-disrupting chemicals (EDC) is associated with early onset of menopause. This is problematic because it shortens a woman's reproductive lifespan and accelerates the onset of vasomotor symptoms associated with menopause. In addition, early menopause is associated with increased risk of cardiovascular disease, depression, osteoporosis, and early death [10–14]. EDCs are chemicals that can interfere with the body's ability to produce and respond to hormones. This review will address how select EDCs (per- and polyfluoroalkyl substances, cigarette smoke, polychlorinated biphenyls and dioxins, phthalates, bisphenols, and pesticides) affect reproductive aging and onset of menopause in human populations and also describe the potential mechanisms elucidated using rodent studies.

Per- and Polyfluoroalkyl Substances

Per- and polyfluoroalkyl substances (PFAS) are in consumer goods such as carpet, leather and apparel, textiles, paper and packaging, coatings, rubber, and plastics. People are exposed to PFAS through contaminated soil, drinking water, food packaging, and air contamination [15]. The National Health and Nutrition Examination Survey (NHANES) study conducted by the Centers for Disease Control and Prevention in the USA provides the most comprehensive description of serum PFAS in the adult population across the country from 1999 to the present. Of the twelve PFAS investigated in NHANES, perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexanesulfonate (PFHxS), and perfluorononanoic acid (PFNA) were detectable in a high percentage of the participants [16]. Because of phase-out programs such as the PFOA Stewardship Program, some PFAS are no longer manufactured in the USA; however, they are still present in the environment due to their persistence and they are produced internationally [17].

The majority of studies that have investigated the associations between PFAS exposure and menopause indicated a positive association between PFAS exposure and early menopause. The C8 Health Project (C8HP) analyzed the risk of menopause in a West Virginia population exposed to PFOA from the Du-Pont Washington Works Plant [18, 19]. PFOA levels in the population exceeded those in NHANES by 500%, whereas the PFOS levels did not differ markedly from those found in NHANES [16]. Odds of menopause for women with elevated PFOA levels were statistically significantly higher in the second through fifth quintiles relative to women in the first quintile in women of childbearing age as well as women of postmenopausal age (Table 1), without a linear dose relationship [18]. PFOA exposure was not associated with risk of menopause among the perimenopausal group. In both the perimenopausal and eldest women (Table 1), higher odds ratios for menopause in PFOS groups showed an increasing linear relationship. Analyses of estradiol levels revealed no statistically significant association with PFOA. In contrast, increasing PFOS sera levels were inversely associated with estradiol concentrations in the perimenopausal ($p < 0.0001$) and menopausal ($p = 0.007$) age groups [18].

A study reporting both PFAS levels and menopause status using data collected in 1999–2010 from the NHANES study consistently indicated that women with higher levels of PFAS had earlier menopause compared to women with lower PFAS levels [20]. Proportional hazard models, indicating hazard ratios (HRs) for the onset of natural menopause as a function of age and serum PFAS levels, showed higher HRs for all PFAS investigated, PFOA, PFOS, PFNA, and PFHxS. The association between PFOA, PFNA, and PFHxS and menopause was linear in nature (Table 1). Moreover, the study reported that the levels of all four PFAS increased with each additional year since natural menopause [20]. These increased levels may be a consequence of the cessation of lactation and menstruation, as both have recently been shown to be modes of PFAS excretion [21, 22].

The Study of Women's Health Across the Nation (SWAN) Multipollutant Study provides convincing data on the association between PFAS exposure and menopause [23]. Women completed interviews annually to record their final menstrual period (FMP), which is a more precise way to obtain time of menopause onset than a one-time cross-sectional interview [24]. PFOA and PFOS were associated with earlier age of FMP when statistical models were adjusted for race/ethnicity, study site, education, parity, body mass index (BMI) at baseline, physical activity, smoking status, and prior hormone use at baseline [23]. Elevated levels of both n-PFOS and the sum of branched isomers of PFOS (Sm-PFOS) were associated with earlier median time to natural menopause, with a linear dose relationship (Table 1). Elevated levels of PFOA, but not PFNA or PFHxS, were also associated with earlier menopause. However, when analyses were completed by racial group, White women with higher PFOA and PFNA levels had earlier natural menopause, whereas Black women and Asian women with higher PFOA and PFNA sera levels did not have early menopause. In contrast, a longitudinal analysis of age at menopause in women from Ohio that were exposed to high levels of PFOA did not show an association between PFOA and age of menopause for either retrospective or prospective analysis [25]. Collectively, these data suggest that PFAS exposure may be associated with earlier age at menopause, but further research is needed to strengthen this observation.

Polychlorinated Biphenyls and Dioxins

Polychlorinated biphenyls (PCBs) are synthetic, chlorinated, organic chemicals that were widely produced for hundreds of industrial and commercial applications including electrical and hydraulic equipment, thermal insulation materials, and plasticizers in paints and plastics as well as dyes and pigments [26]. As a result, many items in use and in landfills contain PCBs. In 1979, the production of PCBs was banned by the Environmental Production Agency (EPA) under the Toxic Substances Control Act because PCBs caused birth defects and cancer in laboratory animals and were suspected of causing cancer and adverse skin and liver effects in humans [27, 28].

Although current production of PCBs is prohibited, PCBs persist in the environment today because they are stable and do not readily breakdown in the environment. Some PCBs have half-lives of over 20 years [29], and are still found in soil and air, resulting in bioaccumulation in terrestrial and aquatic food chains [30•]. Foods such as fish, meat, and dairy are sources of human PCB exposure. In addition to dietary intake, PCB exposure can occur by inhalation, dermal contact, and ingestion of dust and soil [29].

Some clinical studies have investigated the association between PCBs and reproductive aging. One study reported higher serum concentrations of dioxin-like PCBs (DL-PCBs) in women presenting with primary ovarian insufficiency (POI), a gynecologic disease that is characterized by early menopause before the age of 40, compared to women without POI [31]. A dose–response relationship was observed between the sum of DL-PCBs and the risk of POI (Table 2) [31]. In a cross-sectional survey using NHANES data (1999–2008), Grindler et al. found that women with elevated urine or serum levels of polychlorinated biphenyl congeners − 70, − 99, − 105, − 118, − 138, − 153, − 156, − 170, and − 183 had mean ages of menopause that were 1.9 to 3.8 years earlier than women with lower levels of these congeners [32]. Secondary analysis of the same PCBs examined in women 45–55 years of age indicated that women with high PCBs were between 1.28 and 6.59 times more likely to be menopausal, depending on the specific congener for each log increase in PCB level, indicating a dose–response relationship between higher PCB levels and earlier menopause [32]. In contrast, other studies have not found an association between PCB exposure and age at menopause (Table 2) [33–35]. However, the participants in these studies cover a much wider span of age than the 45–55 year age group used in Grindler et al. (Table 2).

Coplanar PCBs are classified as dioxin-like chemicals. Dioxins are a related group of synthetic, organic chemicals produced as unwanted products of manufacturing processes. Although the EPA regulates the production of dioxins, these chemicals persist in our environment. Like non-dioxin PCBs, the association between dioxins and early menopause is not entirely clear. A clinical study using data from the Seveso Women's Health Study (SWHS) examined the levels of 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) in relation to age at menopause in an Italian population exposed to TCDD in a chemical plant explosion in 1976. A tenfold increase in serum TCDD levels measured shortly after the chemical plant explosion was associated with a 6% statistically non-significant increase in the risk of early menopause [36]. In contrast, in the Grindler et al. study, 1,2,3,4,6,7,8-hepta-chlorodibenzofuran, the only dioxin analyzed to pass the level of detection, did not have an association with age at menopause [32].

Because menopause is associated with shifts in FSH and LH, investigators have examined the levels of these hormones in association with PCB and dioxin levels. Using NHANES data (1999–2002), Lambertino et al. found that in postmenopausal women, a doubling of mono-ortho PCB levels was inversely and statistically significantly associated with a decrease in LH levels, and a doubling of anti-estrogenic PCBs was associated with a decrease in LH levels [37]. Borderline statistically significant, inverse relationships were found between DL-PCBs and LH levels as well as estrogenic PCBs and LH levels [37]. FSH serum levels, however, were not associated with PCB levels [37]. Regarding dioxins, a doubling of dioxin-like toxic equivalents (combined effects of polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and PCBs) was associated with a decrease in LH levels of 11.9%, but no associations with FSH levels were found [37].

Based on the current studies, the relationship between PCB/dioxin exposure and early menopause is unclear. The conflicting observations made from these studies may be due to the varying age spans of participants included in each study. Further research is needed to better understand the effects of PCBs/dioxin on menopause.

Pesticides

Many pesticides that are used agriculturally and in the home are known EDCs [38, 39]. Humans are exposed to these chemicals through food, water, soil, and air, with the highest exposures among those working in agriculture [40]. The most well-studied pesticide is 2,2-bis(pchlorophenyl)-1,1,1-trichloroethane (DDT). In response to the Green Revolution of the 1960s and evidence of health risks associated with DDT, the US government banned the use of DDT in 1972. In the Fourth National Report on Human Exposure to Environmental Chemicals, the Centers for Disease Control and Prevention reported that of 1956 participants in NHANES (2003–2004), a small percentage had detectable serum *p,p*'-DDT, the major isomer of DDT [41]. However, the majority of the sample population had detectable levels of 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene (*p,p*'-DDE), a metabolite of *p,p*'-DDT.

Cooper et al. completed a study investigating the association of DDE with menopause in a cohort recruited for the Carolina Breast Cancer Study. After concluding similar findings for women with breast cancer (cases) and women without breast cancer (controls), data from all women were combined for analyses. Elevated DDE levels were statistically non-significantly associated with earlier menopause [34].

In another study, a number of organochlorine pesticides were assessed to determine associations with age at menopause in a Hispanic population. Women with elevated levels of *p,p*'-DDT were at risk of earlier menopause by an average of 5.7 years [42]. Women in the fifth quintile of *p,p*'-DDE also had earlier menopause than women in the first quintile, although with borderline statistical significance (Table 3). Women with elevated levels of β-hexachlorocyclohexane (β-HCH), had menopause an average of 3.4 years earlier than women with low levels of β-HCH [42]. Further, women with serum trans-nonachlor equal to or above 2.00 ppb had an earlier menopause by an average of 5.2 years compared to women with low levels of trans-nonachlor [42]. Women with elevated levels of dieldrin, hexachlorobenzene (HCB), or oxychlordane did not have differences in age of menopause compared to women in lower level reference groups (Table 3).

The use of a large number of pesticides was investigated in relation to age of menopause in over 50,000 farmers in the Agriculture Health Study (AHS). Either applicators or their spouses completed the Female and Family Health Questionnaire and self-reported age at last menstrual period as well as use (yes/no) of pesticides [43]. When considering all pesticides analyzed, women with pesticide use experienced menopause at a later age than those who had never used pesticides (Table 3). Women who used hormonally active pesticides had later menopause than those who had never used pesticides [43]. Additionally, users of atrazine had later menopause than never users [43]. Women that used carbaryl, carbon tetrachloride, *p,p*'-DDT, lindane, or mancozeb/maneb did not have a different age of menopause when compared to nonusers [43]. It is interesting that the AHS found an association between pesticide exposure and later age at menopause [43], whereas other studies found an association between pesticide exposure and earlier menopause [32, 42]. Differences in study outcome could be due to self-reported pesticide use in the AHS compared to blood measures of pesticides in other studies.

NHANES data (1999–2008) were analyzed for associations between pesticide exposure and age of menopause [32]. Women with elevated levels of mirex, β-HCH, and *p,p*'-DDE had earlier menopause than women with low levels of mirex, β-HCH, and *p,p*'-DDE (Table 3). Secondary analyses of women aged 45–55 years indicated that women with elevated levels of mirex were 3 times more likely to be menopausal compared to women with lower levels of mirex [32]. Elevated levels of β-HCH or *p,p*'-DDE did not increase the odds of altered age of menopause onset in the 45–55 age group. Further, HCB, heptachlor epoxide, dieldrin, and endrin exposure were not associated with age at menopause [32].

A case–control study in a Chinese female population found that women with elevated levels of *p,p*′-DDT had a 1.54 increased risk of POI compared to women with low levels of *p,p*′-DDT [31]. Elevated levels of heptachlor were associated with a 1.27 increase in risk of developing POI compared to women with low levels, with borderline statistical significance. Elevated sera *p,p*′-DDE, as well as elevated levels of β-HCH, γ-HCH, and HCB, did not increase the odds of POI compared to low levels of *p,p*′-DDE, β-HCH, γ-HCH, and HCB [31].

Overall, these studies show that select pesticides, such as β-HCH and *p,p*'-DDE, are associated with earlier onset menopause, while many others are not. This differential effect could be due to the differing chemical properties and mechanisms of action of each pesticide.

Phthalates

Phthalates are a class of chemicals used as plasticizers in products containing polyvinyl chloride plastics, such as food containers and medical tubing, and as excipients in personal care products [2]. Several studies suggest an association between phthalate exposure and reproductive aging. In an analysis of menopausal women from NHANES (1999–2008), women with the highest 10% of concentration of di (2-ethylhexyl)phthalate (DEHP) metabolites in their urine experienced earlier menopause by 3.17–3.8 years [32]. Similarly, two studies found associations between urinary monobutyl phthalate and monoisobutyl phthalate and POI (Table 4) [44, 45].

Additionally, phthalates are associated with changes in hormone levels consistent with the menopause transition. In postmenopausal women from NHANES (2013–2016), urinary metabolites of DEHP and its replacements 1,2-cyclohexane dicarboxylic acid di-isononyl ester (DINCH) and (2-ethylhexyl)terephthalate (DEHTP) were associated with decreased levels of steroid hormones (Table 4) [46].

Several studies have identified a positive association between phthalate exposure and symptoms of menopause. The Midlife Women's Health Study (MWHS) was a prospective longitudinal cohort study of pre- and perimenopausal women aged 45 to 54 that was conducted from 2006 to 2015 to assess risk factors for hot flashes during the menopause transition [47]. Phthalate metabolites were measured in urine samples from the first year of the study and have been associated with increased frequency of hot flashes, altered hormone levels, sleep disruptions, and 1-year BMI change (Table 4) [48•, 49–52]. Collectively, these epidemiology studies suggest a link between phthalate exposure, ovarian disruption, and menopause symptoms in midlife women.

Rodent studies, many focusing on DEHP exposure, provide additional evidence of phthalate-induced reproductive aging (Table 4). In adult mice orally exposed to DEHP for 10 days, estrous cyclicity and inhibin B levels were disrupted, and follicle numbers were decreased at 9 months post dosing [53]. In a follow-up study of DEHP and diisononyl phthalate (DiNP) with the same experimental design, cyclicity was disrupted at 12 and 15 months post dosing, with more time spent in estrus, a marker of reproductive aging [54]. Moreover, the numbers of primordial and primary follicles were decreased, suggesting accelerated folliculogenesis [54]. In addition, both DEHP and DiNP exposure at the lowest dose tested, 20 μg/kg/day, decreased fertility at 12 months. In mice prenatally exposed to moderate to high doses of mono(2-ethylhexyl)phthalate (MEHP), a primary metabolite of DEHP, exposure resulted in premature reproductive senescence including prolonged estrus and altered hormone levels [55]. In a study of late-life transgenerational effects of prenatal exposure to DEHP, mice in the F1, F2, and F3 generations had altered hormone levels and follicle numbers at 1 year of age [56]. Mice in the F1 generations had increased ovarian cysts, a marker of reproductive aging. Overall, these studies of late-life effects of phthalates on female mice suggest that phthalates may be accelerating reproductive aging. Additional evidence is provided by studies of the reproductive effects of phthalate exposure in younger adult rodents, which display similar disruptions including accelerated folliculogenesis, altered hormone levels, and disrupted cyclicity [57–59]. Further studies on additional phthalates in aging animals should be performed to assess whether the effects observed for DEHP are representative of all phthalates.

Collectively, these studies indicate positive associations between phthalate exposure, reproductive aging, and menopause. Moreover, there is strong evidence to support that phthalate exposure can exacerbate vasomotor symptoms associated with menopause and reduce a woman's quality of life.

Bisphenol A

Bisphenol A (BPA) is a plasticizing chemical used in food packaging, thermal receipt papers, and dental cements [60]. It is well-established that BPA is an endocrine-disrupting chemical that can have devastating effects on female fertility [61]. Despite this, relatively little is known about potential associations between BPA and occurrence of early-onset menopause. Cao et al. reported elevated levels of BPA measured in the follicular fluid of women diagnosed with diminished ovarian reserve (DOR) compared to women without DOR (Table 5) [62]. In the DOR patients, BPA concentration was negatively correlated with follicular fluid levels of estradiol and AMH [62]. Souter et al., using data from the Environment and Reproductive Health Study, reported no association between urinary BPA levels and incidence of premature ovarian insufficiency or changes in FSH levels, but did observe a negative association between BPA and antral follicle counts in women undergoing infertility treatments, suggesting BPA may contribute to accelerated follicle loss (Table 5) [63]. In rodents, adult exposure to BPA altered estrous cyclicity, increasing the time spent in diestrus [62]. Additionally, BPA decreased serum estradiol and AMH levels, consistent with the hormone profiles of women with DOR expressing detectable levels of BPA in follicular fluid (Table 5) [62]. Although the association between BPA and early menopause is unclear, BPA exposure has been shown to promote oxidative stress and inflammation, both of which are hallmarks of reproductive aging [64]. More work is needed to identify a clearer link between BPA, as well as BPA-replacement chemicals such as BPS and BPF, and menopause and underlying mechanisms of action.

Cigarette Smoke

In the USA, 12% of adult women and 8% of adolescent girls identify as smokers [65]. Smoking is immensely detrimental to one's health and can contribute to a number of diseases, including cancer, chronic obstructive pulmonary disease, and heart disease [66]. Cigarette smoke represents a complex mixture of chemicals. When burned, cigarettes release smoke that contains approximately 7000 chemical compounds, including aldehydes, aromatic amines, aromatic hydrocarbons, phenols, and heavy metals [67–69]. While not every chemical component in cigarette smoke is an endocrine disruptor, cigarette smoke as a whole can have profound effects on endocrine function. Cigarette smoke can have deleterious effects on fertility by interfering with ovarian follicular development, maintenance of pregnancy, and assisted reproductive technology outcomes [70]. Furthermore, it is well-documented that cigarette consumption is linked to early-onset menopause in various populations of women worldwide (Table 6) [71–78]. Other studies report evidence of diminished ovarian reserve, a contributing factor to onset of menopause, in women who smoke (Table 6) [79, 80]. Being a current smoker can increase the risk of early menopause by as much as 43–50% [81–83]. Epidemiological studies report that menopausal symptoms occurred approximately 1–2 years earlier in current smokers compared to non-smokers [71, 73, 78, 81]. The association between smoking and menopause may differ by race, as Fleming et al. using data collected through NHANES (1988–1994), reported that smokers of color had greater odds for earlier age of menopause (12 times increased in Black participants and 6 times increased in Hispanic participants, compared to race matched non-smokers) compared to White participants (2 times increased compared to race matched non-smokers) (Table 6) [73].

Cessation of smoking 10 + years prior to menopause can decrease the risk and occurrence of early-onset menopause [71, 72, 76, 83]. A 2011 follow-up to the 1989 Nurses' Health Study II reported that the risk of early menopause is similar in women who quit smoking by the age of 25 and whose cigarette consumption was less than 1 pack per day to women who never smoked (Table 6) [83]. These observations are encouraging for younger smokers and serve as further motivation to quit smoking to preserve reproductive health.

It is less clear whether passive smoking or exposure to second-hand smoke can accelerate the onset of menopause. Some studies report no association between passive smoke exposure among non-smokers and earlier onset of menopause compared to unexposed non-smokers [71, 72, 77]. Other studies report second-hand smoke can decrease the mean age of menopause onset by approximately 1 year in non-smokers [78, 84].

In addition to direct effects on the smoker, evidence suggests that smoking during pregnancy may affect age of menopause in female offspring. Analysis conducted using maternal data collected from the New England Collaborative Perinatal Project and the California Child Health and Developmental Study birth cohorts and offspring data from the follow-up Early Determinants of Mammographic Density Study showed that daughters exposed in utero to cigarette smoke reached menopause earlier than those without exposure [77]. Moreover, odds of early menopause were further increased in women who were current smokers and exposed in utero compared to unexposed non-smokers (Table 6) [77]. In contrast, Honorato et al., in an 18-year follow-up to the Avon Longitudinal Study of Parents and Children cohort, found no association between in utero smoke exposure and earlier age at onset of menopause [85•]. However, when stratified by smoking status, current smokers who were exposed in utero showed a greater hazard ratio relative to unexposed non-smokers [85•]. It is important to note that in both studies, maternal smoking during pregnancy was self-reported. It is possible that these studies may be subject to social desirability bias, with smoking during pregnancy being under-reported due to societal taboos. In light of this, in utero cigarette smoke exposure may have a more profound effect on menopause than these studies indicate.

Changes in both pituitary and ovarian hormones are part of the etiology of menopause. Current smoking is associated with elevated levels of FSH (up to 23% greater than non-smokers) (Table 6) [86, 87]. However, increased FSH levels were not detected in former smokers compared to non-smokers [86]. This observation is consistent with studies documenting decreased risk of early menopause in former smokers versus current smokers [71, 72, 76, 83]. Another study reported lower levels of serum estradiol in current smokers compared to non-smokers [87]. Additionally, others have reported decreased serum concentrations of AMH and inhibin B, indicative of ovarian aging, in smokers compared to non-smokers (Table 6) [80, 88]. These smoking-induced changes in hormone levels are consistent with studies documenting early-onset menopause in current smokers [71, 72, 74–78].

Cigarette smoking is linked to vasomotor symptoms of menopause. Several epidemiological studies have shown positive associations between past and current smoking and the incidence and duration of hot flashes (Table 6) [47, 89–91]. Moreover, smoking is positively correlated with the severity of hot flashes, with increasing severity reported with increasing cigarette consumption per day [89]. Additionally, passive smokers report greater incidence and severity of hot flashes compared to unexposed non-smokers [89]. Interestingly, while hormone levels of current smokers differ from non-smokers, including increased androstendione and a decreased ratio of total androgens/total estrogens, this change in hormone profile does not appear to mediate the associations between smoking and the occurrence of hot flashes [90]. Smith et al. found that women who quit smoking more than 5 years prior to menopause had lower odds, severity, and frequency of hot flashes than current smokers, suggesting that quitting smoking may ease the menopausal transition [92].

The mechanisms by which cigarette smoking is associated with early onset of menopause and exacerbate vasomotor symptoms are unclear. Using data and biological samples collected from participants in the Penn Ovarian Aging study, Butts et al. found that individuals expressing a single-nucleotide polymorphism (SNP) for cytochrome P450 (CYP) enzymes *CYP3A4*1B* or *CYP1B1*3* had a greater risk of early menopause compared to individuals carrying wild-type alleles, and this risk was greatly increased in smokers carrying these SNPs compared to non-smoking carriers (Table 6) [93]. Interestingly, these CYP enzymes are involved in estrogen metabolism, and these SNPs/variants possess greater enzymatic activity than wild-type variants [93]. It is possible that excessive activation of these enzymes could further reduce already declining estrogen levels, contributing to the imbalance of pituitary and ovarian hormones and the vasomotor symptoms characteristic of menopause. In addition, rodent studies have provided valuable insight into how cigarette smoke can affect the ovarian reserve. Multiple studies have demonstrated that cigarette smoke or its constituent benzo[a]pyrene (BaP) induces oxidative stress and lipid peroxidation, reduces ovarian expression of antioxidant enzymes, and leads to DNA damage and follicle loss [94–97]. Cigarette smoke also induces autophagy in the granulosa cells of exposed ovaries, leading to destruction of the follicle [94, 98]. Further research is critical to fully understand the role and mechanisms of cigarette smoking in early-onset menopause.

Together, these studies show strong links between cigarette smoking and earlier age of menopause and severity of vasomotor symptoms. Additionally, both second-hand and in utero smoke exposure can hasten the onset of menopause. Because cigarette smoke is a complex mixture, it is unclear what constituent chemical(s) are contributing to this effect. Further research is needed to identify these chemicals and explore their mechanisms of action.

Conclusion

It is well-established that environmental contaminants, including PFAS, cigarette smoke, PCBs, phthalates, bisphenols, and pesticides, can have endocrine-disrupting actions, making them a concern for public health [99, 100]. Exposure to these chemicals can be particularly problematic for women because many of the chemicals have been shown to be reproductive toxicants. The studies reviewed here suggest that these chemicals also can accelerate reproductive aging and lead to an earlier age at onset of menopause. Earlier onset of menopause shortens a woman's reproductive lifespan, limiting her ability to have children, and hastens the onset of intrusive menopause symptoms, such as hot flashes [101]. Furthermore, early menopause is associated with increased risk of cardiovascular disease, depression, osteoporosis, and early death [10–14]. In light of this, it is important to understand how these chemicals can affect reproductive health. By increasing our understanding of how EDCs impact menopause, we may be able to better develop strategies to prevent or treat EDC-induced early menopause.

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Table 1

Associations between per- and polyfluoroalkyl substances and menopause*

Author	Study design	Selected findings				
Human						
Knox et al., 2011 [18]	Cross sectional analyses of the C8HP in West Virginia; cohort consists of 25,957 women over the age of 18 years; serum levels of PFAS and estradiol were analyzed	**Age**	**Exposure**	**OR for menopause**	**CI**	**χ^2 overall**
		18 ≤ 42 years	PFOA quintile 1	1	Ref	
			PFOA quintile 2	0.9	0.5–1.6	
			PFOA quintile 3	0.9	0.5–1.5	
			PFOA quintile 4	0.9	0.5–1.7	
			PFOA quintile 5	1.2	0.7–2.1	0.009
			PFOS quintile 1	1	Ref	
			PFOS quintile 2	1.1	0.7–1.9	
			PFOS quintile 3	0.8	0.4–1.4	
			PFOS quintile 4	1.0	0.6–1.8	
			PFOS quintile 5	1.1	0.6–2.1	0.804
		> 42 ≤ 51 years	PFOA quintile 1	1	Ref	
			PFOA quintile 2	1.4	1.1–1.8	
			PFOA quintile 3	1.2	0.9–1.6	
			PFOA quintile 4	1.4	1.1–1.9	
			PFOA quintile 5	1.4	1.1–1.8	0.839
			PFOS quintile 1	1	Ref	
			PFOS quintile 2	1.2	0.9–1.5	
			PFOS quintile 3	1.4	1.1–1.8	
			PFOS quintile 4	1.4	1.1–1.8	
			PFOS quintile 5	1.4	1.1–1.8	0.028
		> 51 ≤ 65 years	PFOA quintile 1	1	Ref	
			PFOA quintile 2	1.5	1.1–2.1	
			PFOA quintile 3	1.6	1.2–2.2	
			PFOA quintile 4	1.4	1.1–1.9	

Author	Study design	Selected findings				
Human						
			PFOA quintile 5	1.7	1.3–2.3	0.041
			PFOS quintile 1	1	Ref	
			PFOS quintile 2	1.5	1.1–2.1	
			PFOS quintile 3	1.8	1.3–2.5	
			PFOS quintile 4	2.0	1.5–2.6	
			PFOS quintile 5	2.1	1.6–2.8	<0.0001
Taylor et al., 2014 [20]	Cross-sectional analysis of NHANES; data from 2732 women aged 20–65 years; serum PFAS levels were analyzed	**Exposure ng/mL**	**HR for menopause**		**95% CI**	
		PFOS				
		0.14 to 9	1		Ref	
		> 9 to 18.4	1.23		1.04–1.44	
		> 18.4	1.16		0.91–1.48	
		PFOA				
		0.07 to 2.5	1		Ref	
		> 2.5 to 4.4	1.22		0.92–1.62	
		> 4.4	1.36		1.05–1.75	
		PFNA				
		0.07 to 0.80	1		Ref	
		> 0.80 to 1.5	1.43		1.07–1.91	
		> 1.5	1.47		1.14–1.90	
		PFHxS				
		0.07 to 0.90	1		Ref	
		> 0.90 to 1.8	1.42		1.08–1.87	
		> 1.8	1.70		1.36–2.12	
Dhingra et al., 2016 [25]	Analysis of C8HP data from Ohio; cohort consists of 8759 women ≥ 40 years of age; serum levels of PFAS and estradiol were analyzed	**Exposure: retrospective cohort**	**HR for natural menopause (CI)**		***p*-value**	
		PFOA quintile 1 (0–0.11 mg/L)	1		Ref	
		PFOA quintile 2 (0.11–0.19 mg/L)	1.06 (0.93–1.21)		0.37	
		PFOA quintile 3 (0.19–0.40 mg/L)	1.13 (0.99–1.29)		0.07	

Author	Study design	Selected findings		
Human				
		PFOA quintile 4 (0.40–2.13 mg/L)	1.09 (0.96–1.25)	0.18
		PFOA quintile 5 (> 2.13 mg/L)	1.11 (0.97–1.26)	0.14
Ding et al., 2020 [23]	Prospective study of the SWAN cohort; data from 1120 premenopausal women aged 42–52 years; serum PFAS levels were quantified	**Exposure**		
		n-PFOS	**HR for incidence of natural menopause (95% CI)**	***p*-value for trend**
		Tertile 1	1 (Ref.)	
		Tertile 2	1.06 (0.86–1.31)	
		Tertile 3	1.26 (1.02–1.57)	0.03
		Sm-PFOS		
		Tertile 1	1 (Ref.)	
		Tertile 2	1.11 (0.90–1.37)	
		Tertile 3	1.27 (1.01–1.59)	0.03
		n-PFOA		
		Tertile 1	1 (Ref.)	
		Tertile 2	1.12 (0.90–1.40)	
		Tertile 3	1.31 (1.04–1.65)	0.01
		PFNA		
		Tertile 1	1 (Ref.)	
		Tertile 2	1.18 (0.95–1.47)	
		Tertile 3	1.20 (0.97–1.49)	0.10
		PFHxS		
		Tertile 1	1 (Ref.)	
		Tertile 2	1.05 (0.84–1.30)	
		Tertile 3	1.11 (0.90–1.37)	0.33
		Exposure	**Racial group**	**HR for incidence of natural menopause (95% CI)**
		n-PFOA	White	1.23 (1.06–1.44)
		n-PFOA	Black	1.04 (0.84–1.29)
		n-PFOA	Asian	0.94 (0.77–1.14)

Author	Study design	Selected findings		
Human				
		PFNA	White	1.33 (1.13–1.56)
		PFNA	Black	1.01 (0.80–1.27)
		PFNA	Asian	0.95 (0.80–1.13)

*CI, confidence interval; *C8HP*, C8 Health Project; *HR*, hazard ratio; *NHANES*, National Health and Nutrition Examination Survey; *OR*, odds ratio; *PFAS*, per- and polyfluoroalkyl substances; *PFHxS*, perfluorohexanesulfonate; *PFNA*, perfluorononanoic acid; *PFOA*, perfluorooctanoic acid; *PFOS*, perfluorooctane sulfonate; *Ref.*, reference; *Sm-PFOS*, sum of branched isomers of PFOS; *SWAN*; Study of Women's Health Across the Nation; χ^2, chi-squared

Table 2

Associations between polychlorinated biphenyls/dioxins and menopause*

Author	Study design	Selected findings		
Human				
Yu et al., 2000 [33]	Cross-sectional analysis of Yucheng cohort; 356 Taiwanese women poisoned with PCBs and 312 unexposed women; serum PCB levels were quantified	**Subjects**	**Mean age at menopause**	
		All Yucheng women	47.3 ± 0.76	
		Control women	46.7 ± 0.94	
		Yucheng women serum PCB ≤ 46 mg/g	46.7 ± 1.10	
		Yucheng women serum PCB > 46 mg/g	47.9 ± 1.10	
Cooper et al., 2002 [34]	Cross-sectional analysis of the Carolina Breast Cancer Study; 861 cases and 790 controls aged 21 to 74 years; data were combined from cases and controls for analyses; plasma levels of PCBs were quantified	**Exposure**	**HR for organochlorine levels and natural menopause**	**95% CI**
		PCB all women		
		≥ equal to 90% percentile	0.9	0.6–1.3
		continuous measures	1.0	0.8–1.3
		PCB African-Americans		
		≥ equal to 90% percentile	0.7	0.4–1.4
		continuous measures	0.8	0.5–1.2
		PCB Non-African-Americans		
		≥ equal to 90% percentile	1.0	0.6–1.6
		continuous measures	1.1	0.8–1.6
Blanck et al., 2004 [35]	Cross-sectional analysis of the Michigan Female Health Study composed of 791 women, equal to or above 24 years of age and less than 80 years of age; serum PCB levels were quantified	**Exposure**	**Menopause ratio (time to menopause)**	**95% CI**
		PCB low (≤ 5 ppb)	1.00	Ref

Author	Study design	Selected findings		
Human				
		PCB moderate (> 5–11 ppb)	1.28	0.88–1.87
		PCB high (≥ 11 ppb)	1.08	0.68–1.71
Eskenazi et al., 2005 [36]	Cross-sectional analysis of SWHS; cohort consists of 981 women ≥ 35 years of age; serum TCDD levels were quantified	**Exposure**	**HR for onset of menopause**	**95% CI**
		Continuous log10 TCDD	1.02	0.8–1.3
		<20.4 ppt TCDD	1.0	Ref
		20.4–34.2 ppt TCDD	1.1	0.7–1.8
		34.3–54.1 ppt TCDD	1.4	0.9–2.3
		54.2–118 ppt TCDD	1.6	1.0–2.7
		> 118 TCDD	1.0	0.6–1.8
Grindler et al., 2015 [32]	Cross-sectional study from NHANES; data from 31,575 menopausal women > 30 years of age; secondary analyses with women 45–55 years of age; serum levels of pesticides were quantified	Primary analyses, all women		
		Exposure	**Average change in age of menopause β (SE) in years**	***p*-value**
		PCB-74	−0.28 (0.214)	0.201
		PCB-99	−0.37 (0.180)	0.051
		PCB-105	−0.36 (0.126)	0.008
		PCB-118	−0.37 (0.189)	0.062
		PCB-138	−0.71 (0.186)	<0.001
		PCB-153	−0.61 (0.200)	0.005
		PCB-156	−0.52 (0.169)	0.004
		PCB-170	−0.26 (0.231)	0.272
		PCB-183	−0.31 (0.145)	0.040
		Secondary analyses, women 44–45 years		
		Exposure	**OR of being menopausal**	**95% CI**

Author	Study design	Selected findings						
Human								
		PCB-74	2.56			1.54–4.26		
		PCB-99	2.01			1.26–3.22		
		PCB-105	6.31			2.68–14.8		
		PCB-118	2.00			1.30–3.10		
		PCB-138	2.07			1.24–3.46		
		PCB-153	2.73			1.60–4.66		
		PCB-156	1.28			1.14–1.43		
		PCB-170	4.29			2.22–8.31		
		PCB-183	6.59			2.31–18.9		
Pan et al., 2019 [31]	Case–control study with 157 POI cases and 217 healthy controls in a Chinese population; serum levels of pesticides were quantified	**Exposure**	**OR for POI (CI)**			***p*-value**		
		Dioxin-like PCBs						
		PCB-77	1.84 (1.39–2.43)			<0.001		
		PCB-81	1.53 (1.18–1.99)			0.001		
		PCB-105	1.88 (1.44–2.45)			<0.001		
		PCB-118	1.88 (1.43–2.47)			<0.001		
		PCB-123	1.68 (1.29–2.19)			<0.001		
		PCB-126	2.03 (1.54–2.67)			<0.001		
		Non-dioxin-like PCBs						
		PCB-8	0.94 (0.72–1.22)			0.628		
		PCB-18	1.25 (0.97–1.61)			0.085		
		PCB-28	1.08 (0.83–1.41)			0.544		
		PCB-52	0.95 (0.74–1.23)			0.720		
		PCB-138	1.61 (1.23–2.10)			0.001		
		PCB-153	1.54 (1.17–2.03)			0.002		
		PCB-187	1.03 (0.79–1.34)			0.813		
		PCB-195	0.82 (0.63–1.08)			0.158		
Lambertino et al., 2021 [37]	Cross-sectional study from NHANES data of 89 postmenopausal women ≥ 40 years of age; serum levels of LH, FSH, and PCBs were quantified		**LnFSH**			**LnLH**		
		Exposure	**Effect estimate**	**95% CI**	***P***	**Effect estimate**	**95% CI**	***P***
		All PCBs	−2.5	−9.5, 5.1	0.51	−6.5	−14.0, 1.6	0.11

Author	Study design	Selected findings						
Human								
		Non-dioxin-like PCBs	−2.5	−9.5, 5.1	0.51	−5.5	−12.9, 2.5	0.17
		Mono-ortho PCBs	−6.1	−13.1, 1.5	0.11	−8.6	−16.1,−0.4	0.04
		Dioxin-like PCBs	−4.2	−11.5, 3.6	0.27	−7.7	−15.5,0.8	0.07
		Cooke anti-estrogenic PCBs	−4.5	−12.9, 4.8	0.32	−10.7	−19.4,−1.1	0.03
		Wolff anti-estrogenic PCBs	−3.5	−11.0, 4.5	0.37	−8.2	−16.0, 0.3	0.06
		Cooke estrogenic PCBs	−2.8	−8.9, 3.7	0.39	−5.5	−12.0, 1.5	0.12
		Wolff estrogenic PCBs	−4.1	−11.4, 3.7	0.29	−5.8	−13.6, 2.7	0.17

* *CI*, confidence interval; *FSH*, follicle-stimulating hormone; *HR*, hazard ratio; *LH*, luteinizing hormone; *LnFSH*, natural logarithm of FSH serum concentration; L*nLH*, natural logarithm of LH serum concentration; *NHANES*, National Health and Nutrition Examination Survey; *OR*, odds ratio; *PCBs*, polychlorinated biphenyls; *POI*, primary ovarian insufficiency; *ppb*, parts per billion; *ppt*, parts per trillion; *SE*, standard error; *SWHS*, Seveso Women's Health Study; *TCDD*, 2,3,7,8-tetrachloro-dibenzo-p-dioxin; *β*, beta coefficient represents the change in mean age of menopause attributed to a one-decile increase in PCB

Table 3

Associations between pesticides and menopause*

Author	Study design	Selected findings		
Human				
Cooper et al., 2002 [34]	Cross-sectional analysis of the Carolina Breast Cancer Study; 861 cases and 790 controls, aged 21 to 74 years; data were combined from cases and controls for analyses; plasma levels of *p,p'*-DDE were quantified	**Exposure**	**HR for organochlorine levels and natural menopause**	**95% CI**
		DDE all women		
		≥ equal to 90% percentile	1.4	0.9–2.1
		continuous measures	1.1	1.0–1.3
		DDE African-Americans		
		≥ equal to 90% percentile	1.3	0.7–2.6
		continuous measures	1.1	0.8–1.4
		DDE Non-African-Americans		
		≥ equal to 90% percentile	1.7	0.9–3.0
		continuous measures	1.2	1.0–1.4
Akkina et al., 2004 [42]	Cross-sectional study of Hispanic Health and Nutrition Examination Survey; data from 219 menopausal women; serum levels of pesticides were quantified	**Exposure**	**Mean age at menopause + SE**	***p*-value**
		β-HCH		
		Below detection limit < 1.00 ppb	48.45 ± 0.43	
		Above median > 2.09 ppb	46.83 ± 0.74	0.07
		p,p′-DDT		
		Below detection limit < 2.00 ppb	48.80 ± 0.40	
		Above median > 3.43 ppb	46.04 ± 0.79	<.01
		Dieldrin		
		Below detection limit < 1.00 ppb	48.24 ± 0.34	

Author	Study design	Selected findings		
Human				
		Above median > 1.30 ppb	48.61 ± 1.52	0.30
		HCB		
		Below detection limit < 1.00 ppb	48.24 ± 0.33	
		Above median > 1.33 ppb	47.71 ± 1.66	0.75
		Oxychlordane		
		Below detection limit < 1.00 ppb	48.28 ± 0.33	
		Above median > 1.13 ppb	47.08 ± 1.57	0.45
		trans-Nonachlor		
		Below detection limit < 1.00 ppb	48.34 ± 0.35	
		Above median > 1.50 ppb	46.42 ± 1.15	0.11
		p,p′-DDE		
		Lowest quintile < 5.46 ppb	48.19 ± 0.77	
		Highest quintile > 23.60	46.51 ± 0.73	0.13
Farr et al., 2006 [43]	Cross-sectional study from Agricultural Health Study derived data of 8,038 women aged 35–55 years living and working on farms in Iowa and North Carolina; exposures to pesticides were estimated by interview	**Exposure**	**HR for pesticide exposure and timing of menopause**	**95% CI**
		Any pesticide	0.87	0.78–0.97
		Hormonally active or ovotoxic pesticides	0.86	0.77–0.97
		Hormonally active pesticides	0.77	0.65–0.92
		Atrazine	0.79	0.63–0.99
		Carbaryl	0.89	0.79–1.00
		Carbon tetrachloride	0.63	0.31–1.27
		DDT	0.82	0.62–1.09

Author	Study design	Selected findings		
Human				
		Lindane	0.74	0.51–1.08
		Mancozeb/maneb	0.78	0.53–1.16
Grindler et al., 2015 [32]	Cross-sectional study from NHANES data of 31,575 menopausal women > 30 years of age; secondary analyses with women 45–55 years of age; serum levels of pesticides were quantified	Primary analyses, all women		
		Exposure	**Average change in age of menopause ß (SE) in years**	***p* value**
		p,p′-DDE	−0.34 (0.162)	0.043
		β-HCH	−0.32 (0.078)	0.004
		Mirex	−0.12 (0.049)	0.021
		Secondary analyses, women 44–55 years		
		Exposure	**OR of being menopausal**	**95% CI**
		p,p′-DDE	1.44	0.98–2.13
		β-HCH	1.43	0.86–2.38
		Mirex	3.00	1.57–5.73
Pan et al., 2019 [31]	Case–control study with 157 POI cases and 217 healthy controls in a Chinese population; serum levels of pesticides were quantified	**Exposure**	**OR for POI (95% CI)**	**p-value**
		p,p′-DDT	1.54 (1.18–2.01)	0.001
		p,p′-DDE	0.99 (0.77–1.28)	0.938
		β-HCH	1.12 (0.86–1.45)	0.413
		γ-HCH	1.24 (0.95–1.62)	0.118
		HCB	0.81 (0.61–1.07	0.132
		Heptachlor	1.27 (0.99–1.62)	0.057

* *CI*, confidence interval; *DDE*, 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene; *DDT*, 2,2-bis(pchlorophenyl)-1,1,1-trichloroethane; *HCB*, hexachlorobenzene; *HCH*, hexachlorocyclohexane; *HR*, hazard ratio; *OR*, odds ratio; *SE*, standard error; *β*, beta coefficient represents the change in mean age of menopause attributed to a one-decile increase in PCB

Table 4

Associations between phthalates and menopause*

Author	Study design	Selected findings			
Human					
Grindler et al., 2015 [32]	Cross-sectional study from NHANES; data of 31,575 menopausal women; serum levels of phthalates were quantified	**Threshold analysis**			
		EDC > 90th percentile Phthalate		**Average change in age of menopause β *1 (SE) in years**	***p*-value**
		Mono-(2-ethyl-5-hydroxyhexyl)phthalate		−3.80 (0)	<0.001
		Mono-(2-ethyl-5-oxohexyl)phthalate		−3.17 (0)	<0.001
Ziv-Gal et al., 2016 [50]	Study from the MWHS; data from 195 pre- and perimenopausal women (ages 45–54); incidence and severity of hot flashes were assessed; urine levels of phthalate metabolites were quantified and analyzed as sum of phthalates metabolites present in personal care products (PCP), sum of DEHP metabolites (DEHP), and sum of phthalate metabolites with known androgenic activity (AA)	**Sum phthalate measures**	**Ever had hot flashes OR (95% CI)**	**Hot flashes in last 30 days OR (95% CI)**	**Daily hot flashes OR (95% CI)**
		Sum PCP	1.45 (1.07–1.96)	1.43 (1.04–1.96)	1.47 (1.06–2.05)
		Sum DEHP	1.36 (0.99–1.88)	1.27 (0.90–1.75)	1.35 (0.93–1.98)
		Sum AA	1.41 (0.98–2.03)	1.33 (0.90–1.96)	1.37 (0.89–2.10)
Özel et al., 2019 [44]	Cross-sectional case control study of 30 women with primary ovarian insufficiency (POI) and 30 healthy fertile controls; serum phthalate diesters measured	**Phthalate diesters**	**POI group**	**Control group**	***p*-value**
		Mono-ethyl phthalate	6.85 ± 2.46	5.83 ± 3.04	0.161
		Mono-(2ethylhexyl) phthalate	13.26 ± 3.9	11.4 ± 7.8	0.262
		Mono-benzyl phthalate	4.97 ± 2.05	4.0 ± 2.4	0.108
		Mono-butyl phthalate	8.45 ± 4.2 7.9	5.0 ± 3.47	0.001
Hatcher et al., 2020 [51]	Study from the MWHS; data from 762 pre- and perimenopausal women (ages 45–54); surveyed about sleep behaviors; urinary phthalate metabolites measured and analyzed as sum of phthalates metabolites present in personal care products (PCP), sum of DEHP metabolites (DEHP), sum of phthalate metabolites with known androgenic activity (AA), sum of phthalates found in plastics (PLASTIC), and sum of all phthalate measured (ALL)	**Sum phthalate measures**	**Sleep disturbances β *2 (95% CI)**	**Insomnia β *2 (95% CI)**	**Restless Sleep β *2 (95% CI)**
		sumPCP	−0.058 (−0.15, 0.036)	−0.040 (−0.14, 0.055)	−0.051 (−0.15, 0.047)
		sumDEHP	0.13 (−0.35, 0.60)	0.027 (−0.45, 0.50)	0.11 (−0.38, 0.59)
		sumAA	0.068 (−0.32, 0.45)	−0.097 (−0.49, 0.29)	0.18 (−0.22, 0.58)
		sumPLASTIC	0.14 (−0.31, 0.59)	0.014–0.44, 0.46)	0.14 (−0.33, 0.60)
		sumALL	−0.050 (−0.15, 0.046)	−0.027 (−0.12, 0.069)	−0.025 (−0.13, 0.074)

Author	Study design	Selected findings				
Human						
Cao et al., 2020 [45]	Case–control study of 173 women with premature ovarian failure (POF) and 246 control women in China; urinary phthalate metabolites measured	**OR (95% CI) for POF**				
		Phthalate	MiBP		MMP	MEP
		1st quartile	Ref		Ref	Ref
		2nd quartile	0.45 (0.23–0.89)		0.60 (0.31–1.15)	0.53 (0.27–1.03)
		3rd quartile	1.04 (0.54–2.00)		0.89 (0.46–1.73)	0.68 (0.35–1.32)
		4th quartile	1.38 (0.73–2.61)		1.05 (0.55–2.02)	1.02 (0.53–1.95)
		***p* for trend**	0.01		0.10	0.17
Chiang et al., 2021 [49]	Cross-sectional study from the MWHS; data from 718 pre- and perimenopausal women (ages 45–54); serum hormone levels measured; urinary phthalates measured and analyzed as sum of phthalate metabolites present in personal care products (PCP), sum of DEHP metabolites (DEHP), sum of phthalate metabolites with known androgenic activity (AA), sum of phthalates found in plastics (Plastics), and sum of all phthalate measured (Phthalates)	**% Change (95% CI) in Hormones**				
			Estradiol	**Testosterone**	**Progesterone**	**AMH**
		sumDEHP	4.9 (0.5, 9.6)	1.4 (−3.1, 6.1)	8.3 (1.5, 15.6)	4.4 (−2.1, 10.7)
		sumPlastics	5.1 (0.3, 10.0)	1.6 (−3.2, 6.6)	9.8 (2.4, 17.7)	5.4 (−1.3, 12.5)
		sumPCP	0.2 (−3.5, 4.1)	0.8 (−3.1, 4.9)	6.0 (0.2, 12.2)	−0.1 (−5.3, 5.4)
		sumAA	7.8 (2.3, 13.6)	3.5 (−2.0, 9.3)	12.9 (4.4, 22.1)	9.0 (1.3, 17.4)
		sumPhthalates	2.3 (−2.1, 6.9)	1.1 (−3.4, 5.9)	9.0 (2.1, 16.5)	2.0 (−4.2, 8.5)
Warner et al., 2021 [48•]	Cross-sectional study from the MWHS; data from 728 pre- and perimenopausal women (ages 45–54); surveyed on hot flashes; urinary phthalate metabolites measured and analyzed as sum of phthalates metabolites present in personal care products (PCP), sum of DEHP metabolites (DEHP), sum of phthalate metabolites with known androgenic activity (AA), sum of phthalates found in plastics (plastics), and sum of all phthalate measured (phthalates)	**Phthalate measure**		**OR (95% CI) for experiencing daily/weekly hot flashes (Ref. = never experiencing hot flashes)**		
		sumDEHP		**1.32 (1.08, 1.61)**		
		sumPlastics		**1.38 (1.11, 1.71)**		
		sumAA		**1.36 (1.074, 1.73)**		
		sumPhthalates		**1.26 (1.03, 1.54)**		
Long et al., 2020 [46]	Cross-sectional study from NHANES; data from 557 postmenopausal women; urinary phthalate metabolites and serum hormone levels measured	**% Change in hormone concentration in response to doubling of urinary phthalate concentration**				
		Phthalate	**Total testosterone % (95% CI)**			**Estradiol % (95% CI)**
		DEHP	−5.00 (−10.67, 1.02)			−9.09 (−16.27,−1.30)
		DINCH	4.75 (−0.22, 9.97)			5.46 (−6.31, 18.70)
		DEHTP	4.25 (−1.42, 10.25)			0.03 (−6.82, 7.40)
Rodent						
Moyer and Hixon, 2012 [55]	Pregnant C57/B16 mice were administered MEHP (100–1000 mg/kg/day) orally from GD17-GD19; reproductive assessments performed in resulting offspring	Premature reproductive senescence, prolonged estrus, altered hormone levels, and mammary hyperplasia in exposed animals				

Author	Study design	Selected findings
Human		
Hannon et al., 2016 [53]	Female CD-1 mice (10 weeks old) were mated and administered DEHP (20 μg/kg/day–500 mg/kg/day, in corn oil) orally from GD0-PND21; reproductive assessment performed at 6 and 9 months post dosing	Increased percentage of days spend in estrus, increased inhibit B levels at 9 months, decreased number of primordial follicles and total follicles at 9 months
Pocar et al., 2017 [57]	Pregnant CD-1 mice (F0; 7 weeks old) were administered DEHP (0.05–5 mg/kg/day) in their diet from GD0.5 through lactation; reproductive assessment performed in F1, F2, and F3 female offspring	Accelerated follicle recruitment, reduced oocyte quality, and disrupted gene expression in F1 adults; same altered reproductive morphological phenotype and gene expression profile in F2 and F3 adults
Rattan et al., 2018 [59]	Pregnant CD-1 mice (F0; 8 weeks old) were administered DEHP (20 μg/kg/day–750 mg/kg/day, in corn oil) orally from GD 10.5 to birth; reproductive assessment performed in F1, F2, and F3 female offspring	Precocious puberty and disrupted estrus cyclicity in F1, F2, and F3; disrupted fertility in F1 and F2; decreased female pup anogenital distance in F3
Brehm et al., 2018 [56]	Pregnant CD-I mice (F0; 8 weeks old) were administered DEHP (20 μg/kg/day-750 mg/kg/day, in corn oil) orally from GDI 1 to birth; reproductive assessment performed in F1, F2, and F3 female offspring at one year of age	Altered hormones and follicle numbers in all generations; altered cyclicity in F1 and F3; increased ovarian cysts in F1; decreased anogenital distance in F2
Chiang et al., 2019 [54]	Female CD-1 mice (5 weeks old) were administered DEHP or DiNP (20 μg/kg/day–200 mg/kg/day in corn oil) orally for 10 days; reproductive assessment performed at 12, 15, and 18 months post dosing	DEHP and DiNP disrupted estrous cyclicity, increased pregnancy loss, decreased fertility, altered the sex ratio of pups, altered ovarian follicle populations, and disrupted hormone levels

** AMH*, anti-Müllerian hormone; *CI*, confidence interval; *DEHP*, Di (2-ethylhexyl)phthalate; *DEHTP*, (2-ethylhexyl)terephthalate; *DINCH*, 1,2-cyclohexane dicarboxylic acid di-isononyl ester; *DINP*, Diisononyl phthalate; *EDC*, endocrine-disrupting chemicals; *F*, filial; *GD*, gestational day; *MEHP*, mono(2-ethylhexyl)phthalate; *MEP*, monoethyl phthalate; *MiBP*, monoisobutyl phthalate; *MMP*, monomethyl phthalate; *MWHS*, Midlife Women's Health Study; *NHANES*, National Health and Nutrition Examination Survey; *OR*, odds ratio; *PND*, postnatal day; *Ref.*, reference; *SE*, standard error; β^{*1}, beta coefficient represents the average change in age (in years) of menopause for each chemical between menopausal women with EDC level ≥ 90th percentile and those with EDC levels < 90th percentile; β^{*2}, represent the predicted likelihood of a change of the outcome (i.e., frequency of sleep disruptions) when the predictor variable (summary phthalates) changes by 1 unit

Table 5

Associations between BPA and menopause*

Author	Study design	Selected findings				
Human						
Yang et al., 2009 [64]	Study of participants in the Biomarker Monitoring for Environmental Health program; data from 226 women pre- and postmenopausal); urine collected and assayed for BPA, creatinine, and cotinine; urine used to measure oxidative stress biomarkers (MDA, 8-OHdG) and inflammatory biomarkers (WBC, CRP)	**Biomarker**	**Pre-menopause β**	***p*-value**	**Postmenopause β**	***p*-value**
		MDA (log_{10})	−0.027	0.530	0.066	0.007
		8-OHdG (log_{10})	−0.022	0.713	0.103	0.008
		WBC (log_{10})	0.028	0.308	0.014	0.234
		CRP (log_{10})	0.094	0.268	0.113	0.029
Souter et al., 2013 [63]	Study of participants in the Environmental Exposures and Reproductive Health Study; data from 430 women undergoing infertility treatment; urinary BPA and antral follicle counts (AFC) measured	**Quartile (Q)**		**Adjusted mean % change in AFC (95% CI** (%))		***p*-value**
		Q1 (< 0.4–0.9 μg/mL)		1 (Ref.)		Ref
		Q2 (0.9–1.6 μg/mL)		−6.0 (−18, 8.2)		0.39
		Q3 (1.6–2.3 μg/mL)		−16 (−27,−3.5)		0.014
		Q4 (2.4–20.5 μg/mL)		−17 (−28,−4.7)		0.0089
Cao et al., 2018 [62]	Study of patients undergoing in vitro fertilization at the Zhongnan Hospital of Wuhan University; data from 54 women diagnosed with diminished ovarian reserve (DOR) and 67 women without DOR; follicular fluid levels of hormones and BPA measured		**Non-DOR**		**DOR**	***p*-value**
		BPA (ng/L) ± SD	193.3 ± 67.225		234.05 ± 81.736	<0.01
		Estradiol (pg/mL) ± SD	221.85 ± 32.632		209.72 ± 31.556	<0.05
		AMH (pg/mL) ± SD	587.18 ± 77.731		555.69 ± 74.224	<0.05
Rodent Cao et al., 2018 [62]	Female C57BL/6 mice (5 weeks old) were administered BPA (5, 50, and 500 μg/kg/day, in corn oil) orally for 28 days; serum collected for hormone analysis		**Estradiol (pmol/L) ± SD**	***p*-value**	**AMH (ng/mL) ± SD**	***p*-value**
		Control (corn oil)	38.02 ± 2.84	Ref	17.72 ± 2.53	Ref
		5 μg/kg/day BPA	33.47 ± 3.96	<0.05	15.29 ± 2.04	<0.05
		50 μg/kg/day BPA	37.50 ± 6.07	>0.05	16.30 ± 2.28	>0.05
		500 μg/kg/day BPA	34.42 ± 3.75	<0.05	16.09 ± 1.92	<0.05

* *AMH*, anti-Müllerian hormone; *B*, beta coefficient; *BPA*, bisphenol A; *CI*, confidence interval; *CRP*, C-reactive protein; *MDA*, malondialdehyde; *SD*, standard deviation; *WBC*, white blood cells 8-OHdG, 8-Oxo-2'-deoxyguanosine

Table 6

Associations between cigarette smoking and menopause *

Author	Study design	Selected findings				
Human						
Cooper et al., 1999 [71]	Menstruation and Reproductive History Study 51-year follow-up; data from 543 postmenopausal women; surveyed on smoking status and age at menopause	**Smoking status at menopause**		**Mean age at menopause + SE**		**95% CI**
		Never		50.7 ± 0.18		Ref
		Current		49.9 ± 0.32		−1.5–0
				Risk ratio of menopause		**95% CI**
		Never		1.0		Ref
		Current		1.3		1.0–1.7
Gallicchio et al., 2006 [89]	Case–control study of hot flashes among midlife women in the Baltimore metropolitan region; data from women 45–54 years of age (cases *n* = 353 women reporting experiencing hot flashes; controls n = 258 women reporting never experiencing hot flashes); surveyed for history of hot flashes and smoking status	**Smoking status**		**OR for hot flashes**		**95% CI**
		Never		1.00		Ref
		Former smoker		1.21		(1.01–1.44)
		Current Smoker		2.94		(1.53–5.56)
		Passive smoke exposure		**OR for hot flashes**		**95% CI**
		No		1.00		Ref
		Yes		3.05		(1.37–6.79)
Chang et al., 2007 [79]	Study of participants in the Korean Multicenter Cancer cohort; data from 2,668 women 30–69 years of age; surveyed for smoking status and factors associated with premature ovarian failure (POF) and early menopause (EM)	**Cigarette smoking**	**POF OR (95% CI)**	**Sig**	**EM OR (95% CI)**	**Sig**
		Never	1.0 (Ref.)	Ref	1.0 (Ref.)	Ref
		Ever	1.92 (1.16–3.19)	p<0.01	1.25 (0.85–1.84)	NS
Mikkelsen et al., 2007 [72]	Cross-sectional analysis of the Oslo Health Study; data from 2123 postmenopausal women; surveyed on smoking status, passive smoke exposure, and age at last menses	**Smoking status**		**OR for early menopause**		**95% CI**
		Never		Ref		Ref
		Former		1.18		0.82–1.71
		Current		1.71		1.21–2.42
		Cessation of smoking prior to menopause		**OR for early menopause**		**95% CI**
		Smoking at time of menopause		Ref		Ref

Author	Study design	Selected findings			
Human					
		1–10 years prior		0.74	0.39–1.42
		> 10 years prior		0.14	0.06–0.34
Cochran et al., 2008 [90]	Case–control study of hot flashes among midlife women in the Baltimore metropolitan region; data from women 45–54 years of age (cases $n = 362$ women reporting experiencing hot flashes; controls $n = 266$ women reporting never experiencing hot flashes); surveyed for history of hot flashes and smoking status; serum hormone levels measured		**Never smoker**	**Former smoker**	**Current smoker**
		Hormone	**Geo. mean (95%CI)**	**Geo. mean (95%CI)**	**Geo. mean (95%CI)**
		Testosterone (ng/mL)	0.47 (0.44–0.50)	0.47 (0.44–0.51)	0.47 (0.40–0.55)
		Androstendione (ng/mL)	1.93 (1.83–2.03)	2.11 (1.98–2.25)	2.20 (1.94–2.51)
		DHEA-S (ng/mL)	372.04 (349.67–396.23)	385.29 (358.17–414.47)	366.13 (315.13–425.39)
		Progesterone (pg/mL)	0.87 (0.74–1.01)	0.79 (0.66–0.95)	0.55 (0.38–0.79)
		Estradiol (pg/mL)	96.26 (88.24–104.90)	101.09 (91.38–111.83)	94.26 (76.63–116.05)
		Estrone (pg/mL)	134.56 (124.84–145.04)	132.16 (103.65–144.32)	124.09 (103.65–148.71)
		Androgens/ estrogens	9.88 (9.19–10.61)	10.76 (9.89–11.72)	11.68 (9.82–13.90)
Fleming et al., 2008 [73]	Cross-sectional study of participants in NHANES; data from 5,029 women 25–50 years of age; surveyed on smoking status, menstrual status, and race/ ethnicity	**Smoking status**		**Mean age of last period ± SE**	**95% CI**
		Non-smoker		48.55 ± 0.46	47.62–49.48
		Smoker		47.17 ± 0.48	46.22–48.13
		Race/ethnicity		**OR for early menopause (smoker vs. nonsmoker)**	**95% CI**
		White		2.34	0.70–7.82
		Black		12.34	3.03–50.21
		Hispanic		6.80	1.92–24.11
Freour et al., 2008 [80]	Retrospective analysis of 111 women undergoing IVF; surveyed on smoking status and IVF outcomes; serum hormone levels measured	**Smoking status**		**Basal serum AMH (μg/L) ± SD**	**AMH/mature oocytes retrieved**
		Non-smoker		3.86 ± 1.92	0.64

Author	Study design	Selected findings				
Human						
		Smoker		3.06 ± 1.68		0.14
Waylen et al., 2010 [88]	Retrospective analysis of an existing database data on age, smoking status and serum concentrations of hormones; data from 335 women 24–48 years of age	**Smoking status**	**Mean inhibin B (pg/mL)**	**Mean FSH (IU/L)**		**Mean AMH (ng/mL)**
		Non-smoker	79.8 (72.8–87.3)	5.1 (4.8–5.5)		1.074 (0.925–1.245)
		Ex-smoker	67.0 (58.2–76.9)	5.3 (4.8–5.8)		0.955 (0.760–1.199)
		Current smoker	64.4 (53.5–77.8)	5.3 (4.7–6.0)		0.869 (0.638–1.183)
Pokoradi et al., 2011 [75]	Prospective cohort study of the Royal College of General Practitioners' Oral Contraception Study; data from 5113 postmenopausal women; surveyed for timing of final menstrual period and smoking status	**Pack-years smoked**		**OR for early natural menopause (99% CI)**		***p*-value**
		0 years		1.00		Ref
		< 15 years		1.09 (0.85–1.41)		0.366
		15–30 years		1.84 (1.43–2.37)		<0.001
		> 30 years		1.82 (1.39–2.38)		<0.001
Yasui et al., 2012 [74]	Cross-sectional analysis of the Japan Nurses' Health Study; data from 24,152 pre- and postmenopausal women; surveyed on age of last period and smoking status	**Ever smoke before menopause**		**Median age of last period (95% CI)**		**HR for menopause (95% CI)**
		No		52.2 (52.1–52.3)		1.0 (Ref.)
		Yes		51.7 (51.5–51.9)		1.20 (1.12–1.29)
Hayatbakhsh et al., 2012 [76]	21-year follow-up of the Mater-University of Queensland Study of Pregnancy; data from 3545 women; surveyed for smoking status and age at menopause	**Smoking status at 21-year follow-up**		**Median age at menopause**		**HR for Menopause (95%) CI**
		Never smoked		49		1.00 (Ref.)
		Ex-smoker		48		0.93 (0.75–1.16)
		Current smoker		47		1.58 (1.27–1.98)
Butts et al., 2014 [93]	Longitudinal population-based study of participants in the Penn Ovarian Aging study; data from 410 women 35–47 years of age; surveyed for smoking status and menstrual status; buccal swabs used for genotyping	**Single-nucleotide polymorphism**	**HR for menopause (95% CI) in current vs. never smokers**	***p*-value**	**HR for menopause (95% CI) in former vs. never smokers**	***p*-value**

Author	Study design	Selected findings				
Human						
		CYP1B1*3$^{-/-}$	1.65 (0.62–4.4)	0.32	3.2 (1.27–8.06)	0.01
		CYP1B1*3$^{\pm}$ and CYP1B1*3$^{+/+}$	2.3 (1.32–4.0)	0.003	0.96 (0.5–1.86)	0.9
		CYP3A4*1B$^{-/-}$	2.12 (1.26–3.56)	0.005	1.78 (1.04–3.06)	0.04
		CYP3A4*1B$^{\pm}$ and CYP3A4*1B$^{+/+}$	18.3 (2.75–122.01)	0.003	1.2 (0.2–7.31)	0.85
Smith et al., 2015 [92]	Cohort study of hot flashes among midlife women in the Baltimore metropolitan region; data from 761 women 45–54 years of age; surveyed for history of hot flashes and smoking status	**Years since quitting smoking (current smoker as ref.)**		**Probability of hot flashes OR (95% CI)**	**Severity of hot flashes OR (95% CI)**	**Frequency of hot flashes OR (95% CI)**
		≤ 5 years		0.39 (0.11–1.38)	0.72 (0.41–1.27)	0.83 (0.46–1.49)
		> 5 years		0.44 (0.18–1.02)	0.62 (0.42–0.92)	0.67 (0.44–1.03)
Tawfik et al., 2015 [77]	Prospective study of participants in the Early Determinants of Mammographic Density Study; data from 1001 women 39–49 years of age whose mothers participated in the New England Collaborative Perinatal Project and the California Child Health and Development Study; surveyed for menopause status and cigarette smoke exposure	**Smoke exposure**		**OR for menopausal transition (95% CI)**		**OR for natural menopausal (95% CI)**
		Non-smoker, no prenatal exposure		Ref		Ref
		Non-smoker, prenatal exposure		1.1 (0.6–1.8)		2.7 (0.8–9.4)
		Current smoker, no prenatal exposure		1.4 (0.9–2.2)		2.8 (0.9–9.0)
		Current smoker, prenatal exposure		1.1 (0.7–1.7)		3.4 (1.1–10.3)
Ertunc et al., 2015 [84]	Study of attendants of Mersin University School of Medicine menopause clinic; data from 788 postmenopausal women; surveyed for age at menopause and cigarette smoke exposure	**Second-hand smoke exposure**		**Age at menopause ± SD**		***p*-value**
		Non-exposed women		48.1 ± 5.2		Ref
		Exposed women		47.0 ± 4.7		0.002
Smith et al., 2016 [91]	Cohort study of hot flashes among midlife women in the Baltimore metropolitan region; data from 647 women 45–54 years of age; surveyed for history of hot flashes and smoking status	**Smoking status**	**Mean duration of hot flashes in years**	**Range in years**		***p*-value**
		Never	2.31	1–25		Ref

Author	Study design	Selected findings			
Human					
		Former smoker	2.52	1–26	NS
		Current smoker	3.89	1–29	0.002
Hyland et al., 2016 [78]	Prospective study of participants in the Women's Health Initiative Observational Study; data from 93,676 women 50–79 years of age; surveyed for menopause status/age at menopause and cigarette smoke exposure	**Cigarette smoke exposure**		**OR for earlier age at menopause**	**95% CI**
		Never-smoker, second-hand smoke exposure none		1.0	Ref
		Never-smoker, second-hand smoke exposure		1.07	(0.99–1.15)
		Active ever-smoker		1.27	(1.18–1.37)
Whitcomb et al., 2018 [83]	Prospective study of participants in the Nurses' Health Study II; data from 106,256 women 25–42 years of age upon enrollment in 1989; surveyed for menstrual status and smoking status	**Smoking status**		**HR for risk of early natural menopause**	**95% CI**
		Never smoker		1.00	Ref
		Past smoker		1.09	1.00–1.21
		Current smoker		1.98	1.71–2.11
Honorato et al., 2018 [85•]	Cohort study within the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort; data from 2,852 daughters of parents who participated in ALSPAC; surveyed parent for smoking status and offspring for smoking status and menstrual status	**Smoke exposure**		**HR for earlier menopause (95% CI)**	***p*-value**
		Not exposed and non-smoker		Ref	Ref
		Not exposed and ever smoker		1.23 (1.01–1.50)	0.04
		In utero exposed and non-smoker		0.91 (0.72–1.14)	0.40
		In utero exposed and ever smoker		1.50 (1.09–2.06)	0.01
Szkup et al., 2018 [87]	Study of women in the general population of the West Pomerania Province in Poland; data from 345 women 35–53 years of age; surveyed for smoking status and serum hormone levels measured	**Smoking status**	**Estradiol (pg/mL) median (IQR)**	**Min–Max**	***p*-value**
		Non-smoking	85.9 (99.5)	4.3–841	Ref
		Smoking	64.4 (46.3)	4.9–279.3	0.020
		Smoking status	**FSH (mlU/mL) median (IQR)**	**Min–Max**	***p*-value**
		Non-smoking	6.2 (3.4)	2.3–497.5	Ref

Author	Study design	Selected findings			
Human					
		Smoking	7.4 (4.8)	3.8–115.0	0.034
		Smoking status	**AMH (ng/mL) median (IQR)**	**Min–Max**	***p*-value**
		Non-smoking	1.33 (2.37)	0.15–11.59	Ref
		Smoking	1.35 (2.14)	0.15–8.17	0.778
Rodent					
Gannon et al., 2012 [94]	Female C57BL/6 mice (8 weeks old) exposed to cigarette smoke twice daily, 5 days/week for 8 weeks using a whole-body smoke exposure system; ovaries collected upon termination	Exposure to cigarette smoke induced oxidative stress, decreased expression of superoxide dismutase 2, and induced autophagy in ovarian tissue			
Sobinoff et al., 2012 [95]	Female Swiss neonatal mice (PND 4) were administered 0, 1.5, or 3 mg/kg/day of BaP in sesame oil for 7 consecutive days; Animals were superovulated at 6 weeks of age and oocytes were isolated 12 h later	BaP exposure at both doses increased generation of reactive oxygen species and increased lipid peroxidation in isolated oocytes, compared to control-treated isolated oocytes			
Sobinoff et al., 2013 [97]	Female C57BL/6 mice (5 weeks old) were exposed via the nose-only to cigarette smoke (twelve 3R4F reference cigarettes) for 60 min twice/day, five times per week, for 12–18 weeks; control animals received room air; animals terminated at 8 weeks and ovarian tissue collected	Cigarette smoke exposure induced oxidative stress, lipid peroxidation, and DNA damage in ovaries and oocytes of exposed mice, compared to room air exposed control mice			
Gannon et al., 2013 [98]	Female C57BL/6 mice (8 weeks old) were exposed to cigarette smoke (twelve 3R4F reference cigarettes) 50 min twice daily, 5 days a week, for 8 weeks using a whole-body smoke exposure system; animals terminated at the end of exposure period and ovarian tissue collected	Cigarette exposure increased mitochondrial damage and induced autophagy in ovaries of exposed mice, compared to ovaries of room air exposed control mice			
Siddique et al., 2014 [96]	Preantral follicles from ovaries of F1 hybrid mice exposed in vitro to cigarette smoke condensate (30–130 µg/mL) or BaP (1.5–45 ng/mL) for 8 days	Both cigarette smoke condensate and BaP exposure increased the concentrations of oxidative stress biomarkers 8-isoprostane and 8-hydroxy-2-deoxy guanosine in spent media of the follicles, compared to spent media from control treated follicles			

* *AMH*, anti-Müllerian hormone; *BaP*, benzo[a]pyrene; *CI*, confidence interval; *CYP*, cytochrome P450; *DHEA-S*, dehydroepiandrosterone sulfate; *DNA*, deoxyribonucleic acid; *F*, filial; *FSH*, follicle-stimulating hormone; *Geo. mean*, geometric mean; *HR*, hazard ratio; *IQR*, interquartile range; *IVF*, in vitro fertilization; *Max*, maximum; *Min*, minimum; *NHANES*, National Health and Nutrition Examination Survey; *OR*, odds ratio; *PND*, postnatal day; *Ref.*, reference; *SD*, standard deviation; *SE*, standard error; *Sig.*, significance