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Associations of serum persistent organic pollutant concentrations with incident diabetes in midlife women: the Study of Women's Health Across the Nation Multi-Pollutant Study

Amelia Grant-Alfieri[1], **William H. Herman**[2,3], **Deborah J. Watkins**[1], **Stuart Batterman**[1], **Carrie Karvonen-Gutierrez**[2], **Sung Kyun Park**[1,2]

[1]Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan, USA

[2]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan, USA

[3]Department of Internal Medicine, Division of Metabolism, Endocrinology, and Diabetes, University of Michigan Medical School, Ann Arbor, Michigan, USA

Abstract

Background: Organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), and polychlorinated biphenyls (PCBs) are persistent organic pollutants (POPs) that can negatively impact metabolic health through pathways including endocrine disruption. Few studies have evaluated diabetes risk associated with PBDEs. Little is known about the joint effect of exposure to POP mixtures on diabetes risk.

Objectives: We investigated the relationship between POPs, individually and as mixtures, and diabetes development over 18 years (1999–2016) in midlife women.

Correspondence: Sung Kyun Park, ScD, MPH, Departments of Epidemiology and Environmental Health Sciences, University of Michigan, School of Public Health, 1415 Washington Heights, Ann Arbor, MI 48109-2029, Fax: (734)936-2084, sungkyun@umich.edu.

Author Contributions

Amelia Grant-Alfieri was responsible for data cleaning and analysis, interpretation of results, and writing – original draft, revisions, and editing. William H. Herman and Deborah Watkins contributed to results interpretation and manuscript revisions. Stuart Batterman oversaw POPs method development and measurement analysis, laboratory administration, and contributed to results interpretation and manuscript revisions. Carrie Karvonen-Gutierrez contributed to funding acquisition, project administration, and manuscript revisions. Sung Kyun Park was responsible for funding acquisition, study design protocols, oversight of statistical analysis, interpretation of results, project administration, and writing.

Competing interests

The authors declare no competing interests.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Methods: We measured lipid-standardized serum concentrations of 34 PCBs, 19 OCPs, and 14 PBDEs in 1,040 midlife women aged 45–56 years from the Study of Women's Health Across the Nation. We tested the association between POPs measured in 1999/2000 and incident diabetes using Cox proportional hazards models. We evaluated diabetes risk associated with the overall POP mixture using Quantile-Based G-Computation (QBGC).

Results: For most mixture components, single pollutant and mixtures analyses indicated null associations with diabetes risk, however results were inconsistent. After adjustment, hazard ratios (HRs) of developing diabetes (95% CI) associated with upper exposure tertiles (T2/T3) compared with the first tertile (T1), were 1.7 (1.0, 2.8) at T2 and 1.5 (0.84, 2.7) at T3 for hexachlorobenzene and 1.9 (1.1, 3.3) at T2 and 1.6 (0.88, 2.9) at T3 for PCB 123. A doubling of PBDE 47 was associated with 1.11 (1.00, 1.24) times the risk of T2D. QBGC identified no association for the overall joint effect of the POP mixture on diabetes (HR=1.04 [0.53, 2.07]).

Conclusion: Exposure to a mixture of PCBs, OCPs, and PBDEs was not associated with incident diabetes in midlife U.S. women, although some individual POPs demonstrated significant yet inconsistent associations with diabetes. Non-linear and non-monotonic dose-response dynamics deserve further exploration. More research is needed on the diabetogenic effects of PBDEs.

Keywords

persistent organic pollutants; PCBs; pesticides; PBDEs; women; diabetes

1. Introduction

Type 2 Diabetes (T2D) is increasingly prevalent and a leading cause of morbidity and mortality. Diabetes was responsible for 6.7 million deaths worldwide in 2021 (International Diabetes Federation, 2021). Global diabetes prevalence is projected to rise 46% from 1 in 10 adults in 2021 to 1 in 8 adults in 2045, with growth most rapid in low- and middle-income countries (International Diabetes Federation, 2021; World Health Organization, 2022). T2D comprises over 95% of diabetes cases (World Health Organization, 2022). In the United States (U.S.), 1 in 10 adults have T2D, 1 in 3 have prediabetes, and 1 in 5 are undiagnosed (Centers for Disease Control and Prevention, 2023, 2022). People with T2D are at higher risk of stroke, cardiovascular disease, kidney failure, cancer, complications from SARS-CoV-2, and death (Centers for Disease Control and Prevention, 2021; Chatterjee et al., 2017; Vargas-Vázquez et al., 2021). T2D is characterized by insulin resistance, the inability of glucose to be used to produce energy and its subsequent accumulation in the blood. Risk of T2D increases with lack of exercise, obesity, and family history, yet genetics only explain 10% of cases (Billings and Florez, 2010). Increasingly, environmental chemical exposures are explored as risk factors for T2D.

Persistent organic pollutants (POPs) are a broad class of chemicals that include, among others, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and organochlorine pesticides (OCPs). PCBs have been used in dielectric and coolant fluids, paint, plastics, and pesticides. PCBs and OCPs were banned by many high-income countries, including the U.S., in the 1970s and 1980s due to health risks at high doses (Centers

for Disease Control and Prevention, n.d.). Additional countries have since banned OCPs (Sharma et al., 2019). PBDEs have been used as flame retardants, manufactured in several commercial mixtures including decaBDE in electronics, octaBDEs in plastics, and pentaBDEs in upholstery foam, three types prohibited in the U.S. by 2013 (Agency for Toxic Substances and Disease Registry, 2017). Although POPs are often considered historical contaminants, climate change may exacerbate exposure worldwide as more intense and frequent floods remobilize and redistribute POPs from industrial sites, river sediment, and landfills (Crawford et al., 2022; Erickson et al., 2019). Furthermore, research emerges on POP contamination of microplastics, which are ubiquitous in our environment and bodies (Joo et al., 2021).

POPs can persist in the human body and act as endocrine disruptors (Bonefeld-Jørgensen et al., 2014; Gore et al., 2015; Wahlang, 2018). The main exposure pathway is diet, primarily animal-based fatty foods (Agency for Toxic Substances and Disease Registry, 2000). Indoor air is another source of PCBs and PBDEs, which then accumulate in dust (Agency for Toxic Substances and Disease Registry, 2017; Kraft et al., 2021). High lipophilicity allows POPs to accumulate in adipose tissue, where they can induce adipocyte dysfunction regardless of obesity (Lee et al., 2018). Hormonal receptor-mediated mechanisms including low-grade inflammation in adipose tissue are linked to insulin resistance and T2D (Lee et al., 2014; Lind and Lind, 2018).

The relationship between diabetes and PCBs and OCPs is a popular topic of research, however, findings often differ by compound. In the case of PCBs, many prospective studies found PCBs to increase diabetes risk (Lee et al., 2011; Vasiliu et al., 2006; Wang et al., 2008; Wolf et al., 2019) while others found no link (Charles et al., 2022; Lee et al., 2010; Magliano et al., 2021; Rignell-Hydbom et al., 2007; Wu et al., 2013). Prospective studies of OCPs suggest compound-specific positive associations with diabetes risk (Charles et al., 2022; Lee et al., 2010; Rignell-Hydbom et al., 2007; Turyk et al., 2009; Wu et al., 2013) or no associations (Magliano et al., 2021; Wolf et al., 2019). One limitation to compare some prospective studies is the failure to standardize serum POP concentrations by serum lipids (Rignell-Hydbom et al., 2009; Turyk et al., 2009; Vasiliu et al., 2006; Wang et al., 2008).

Few studies have investigated the relationship between PBDEs and diabetes, and of those that do, most address gestational diabetes. Studies relevant to non-gestational diabetes are contradictory with inconsistent dose-response curves. The most robust prospective studies found no associations after serum lipid adjustment (Lee et al., 2010; Magliano et al., 2021). PBDE exposure calculated using dietary intake and food contamination data, rather than serum concentrations, had a positive, non-linear association with T2D risk (Ongono et al., 2019).

Given the conflicting literature and the reality of simultaneous and correlated exposures, it is critical to evaluate the overall effect of mixtures of PCBs, OCPs, and PBDEs. To our knowledge, only two studies, both cross-sectional, have employed mixtures methods (Reina-Pérez et al., 2023; Tan et al., 2022). PCB and OCP mixtures in adipose tissue were linked to higher prevalence of metabolic syndrome (Reina-Pérez et al., 2023). Serum mixtures of PCBs were associated with increased prevalence of diabetes (Tan et al., 2022).

Women may be at greater risk of diabetes due to POPs exposure (Vasiliu et al., 2006; Wang et al., 2008). Midlife and older women may be at a particularly increased risk of disrupted glucose homeostasis associated with chronic exposure to POPs, independent of body mass index (BMI), due to compounded effects of multi-decade POPs exposure and possible interactions of POPs with aging-related physiological processes (Suarez-Lopez et al., 2015). The Study of Women's Health Across the Nation (SWAN) is one of the most carefully phenotyped population samples with respect to the menopausal transition and numerous heath markers. This study investigated whether serum concentrations of PCBs, PBDEs, and OCPs, individually and as mixtures, were associated with incident diabetes among U.S. midlife women in SWAN.

2. Methods

2.1. Study Population

The SWAN Multi-Pollutant Study (MPS) is part of the larger, ongoing SWAN, which has been detailed previously (Sowers et al., 2000). SWAN is a multi-site, multi-ethnic cohort study launched in 1996 to follow 3,302 premenopausal women between age 42 and 52 through the menopausal transition. Across 15 follow-up visits from 1996/97 to 2015/16, SWAN collected data on metabolic and reproductive biomarkers and health outcomes, in addition to socio-demographic, lifestyle, and other risk factors. SWAN retained approximately 75% of living participants over the study period (Wang et al., 2020). The institutional review board at each site approved the study protocol and all participants provided written, signed informed consent at each study visit.

The MPS characterizes environmental exposures in a subset of SWAN. The design of SWAN MPS is illustrated in Supplemental Figure A.1. Environmental exposure data were collected from biobanked specimens at the MPS baseline visit (1999/2000). The MPS was designed to evaluate environmental chemicals in serum and urine, one class at a time and as mixtures; therefore, participants who had sufficient volumes of both serum and urine were eligible. After further excluding participants with insufficient serum or urine samples, the final MPS totaled 1,400 women from Boston, MA, Los Angeles, CA, Oakland, CA, Pittsburgh, PA, and southeast Michigan, which limited the sample to white, Black, Japanese, and Chinese women.

2.2. POPs Measurements

Serum concentrations of PBDEs, PCBs, and OCPs were measured using blood samples collected from the 1,400 women in the SWAN MPS at baseline (1999/2000). We analyzed serum samples for 34 PCB congeners, 14 PBDEs, and 19 OCPs including dichlorodiphenyltrichloroethane (DDT) metabolites p,p'-DDT, p,p'-DDE, and p,p'-DDD, chlordanes, and hexachlorobenzene (HCB) among others (see Supplemental Table A.1 for the complete list). Laboratory procedures, including quality assurance (QA), have been detailed previously (Grant-Alfieri et al., 2024). A number of samples were flagged by two QA checks. Background levels in some samples and/or blanks exceeded method detection limits (MDLs), especially lower molecular weight PCBs which are widespread in many older buildings. Additionally, some samples showed low response of the internal standards,

a companion measurement and QA check, which is compensated by boosting the results. Because these issues likely increase reported concentrations, these samples were excluded from further consideration. Concentrations below the MDL were replaced with MDL/√2.

Lipid-standardized POP concentrations are preferable to wet weight concentrations because POPs are lipophilic, circulate bound to lipids, and distribute in the body according to a tissue's lipid content (Heindel et al., 2017; Yu et al., 2011). Standardizing serum POP concentrations by serum lipids has been the most common method employed in studies of serum POPs because it eliminates the influence of recent fat intake on serum lipids and enables the comparison of exposure across individuals (O'Brien et al., 2016). Total cholesterol and triglycerides were measured by enzymatic methods (Hitachi 747–200 analyzer Boehringer Mannheim Diagnostics, Indianapolis IN). The total lipid concentration was imputed using linear regression to address missing observations of total cholesterol and triglycerides. O'Brien and colleagues (2016) recommended traditional standardization in addition to model adjustment for serum lipids when serum POPs are the exposure of interest (O'Brien et al., 2016).

$$S = C/OTL \times 102.6$$

$$OTL = (2.27 * TC) + TG + 62.3$$

where S is lipid-standardized serum POP concentration (ng/g lipid); C is wet weight serum POP concentration (ng/g); OTL is observed total lipid concentration (mg/dl) (Centers for Disease Control and Prevention, n.d.); TC is total cholesterol concentration (mg/dl); and TG is triglycerides concentration(mg/dl).

2.3. Diabetes Incidence

From 1999/2000 (baseline) through 2015/16, participants were defined as having incident diabetes if they met one or more of the following criteria: (1) use of an anti-diabetic medication at any visit; (2) fasting glucose ≥7 mmol/l at two consecutive visits while not taking corticosteroids including glucocorticoids; and (3) any two visits with self-reported diabetes and at least one visit with fasting glucose ≥7 mmol/l. Most if not all of the diabetes cases in this population of midlife women are likely T2D. See Supplemental Methods Section 1 for additional information on incident diabetes ascertainment.

2.4. Covariates

Potential confounders of the relationship between serum POP concentrations and diabetes incidence were selected a priori. Age can influence exposure especially for historical contaminants such as PCBs, OCPs, and PBDEs. In addition, T2D risk increases with age, notably after 45 years of age (Centers for Disease Control and Prevention, n.d.). Study sites included Los Angeles, CA, Oakland, CA, Pittsburgh, PA, Boston, MA, and Southeast MI. Self-reported race/ethnicity, financial hardship, and education were assessed by a self-administered questionnaire in 1996/97. Black and white women were recruited from Boston, Southeast MI, and Pittsburgh; Chinese and white women from Oakland; Japanese

and white women from Los Angeles. Race was not a proxy for biological or genetic differences yet was included because it is implicit in systems, policies, and institutions that shape individuals' environments and experiences (The Aspen Institute, 2017). Differences in lifestyle, resources, and historical contamination may result from structural racism, "a system in which public policies, institutional practices, cultural representations, and other norms work in various, often reinforcing ways to perpetuate racial group inequity" (The Aspen Institute, 2017). Weekly dietary intake frequency of meat, high fat dairy, fish and shellfish were collected in 1996/97 using a semiquantitative adaptation of the Block Food Frequency Questionnaire.

At baseline (1999/2000), age, smoking status, alcohol consumption, and menopausal status were self-reported. Smoking status was defined as never, current, or past. Alcohol consumption was categorized as 0, <1, 1–7, or >7 drinks per week. Menopausal status was categorized as i) pre-menopause or early peri-menopause, ii) late peri-menopause or post-menopause due to surgical or natural processes, or iii) unknown due to hormone therapy. Waist circumference (WC) was measured to the nearest 0.1 cm at baseline. WC was the most appropriate proxy for visceral fat mass, considering the invasiveness of collecting adipose tissue and the high degree of missingness for body composition scan data, (Dirinck et al., 2015) and may better predict diabetes incidence (Fan et al., 2020). Physical activity during the prior 12 months was scored from 3 to 15 with 15 indicating the most activity, as previously detailed (Wang et al., 2020). If women were missing physical activity observations from baseline (1999/2000), we used observations from 1997/99. Parity was defined as parous or nulliparous based on live and stillbirths. Uniform protocols were used to collect covariate data across study sites.

2.5. Statistical Analysis

Women with POPs data meeting surrogate recovery and other QA criteria were considered for further analysis. Of the 1,400 participants, this excluded 166 women with OCP data, 405 with PCB data, and 281 with PBDE data, in turn creating three subsamples by POP type. We excluded women for insufficient serum lipids (cholesterol) information: two from the PCB subsample, two from the PBDE subsample, and one from the OCP subsample. We retained POP compounds detected in at least 70% of samples. We did not apply the 70% detection frequency (DF) cutoff to p,p'-DDT, p,p'-DDE, and p,p'-DDD. Notwithstanding the low detection frequencies of DDT metabolites, approximately 40%, their high lipophilicity and persistence, endocrine disruption and carcinogenicity, and continued use worldwide warranted special consideration (U.S. Environmental Protection Agency, 2023). After these exclusions, 14 PCBs, 7 OCPs, and 1 PBDE remained.

The distributions of POPs were characterized using the median and various quantiles. We reported the 33^{rd} and 66^{th} percentiles because they defined tertiles (T1, T2, T3). We reported concentrations using traditional lipid-standardization to facilitate comparison with previous studies. We visualized Spearman correlations between serum POP concentrations using a heatmap.

Compiling data on T2D diabetes and covariates, we applied additional inclusion and exclusion criteria. We excluded women who had diabetes at or before 1999/2000: 67 from

the OCP subsample, 52 from the PCB subsample, and 60 from the PBDE subsample. Additionally, we omitted participants lacking key covariate information, leaving 1,071 women in the OCP subsample, 866 in the PCB subsample, and 972 in the PBDE subsample. To compute inverse probability weights (IPW) to account for potential selection bias, we omitted participants missing IPW predictors. Details about IPW are described in the Supplemental Methods Section 2. After restricting to observations with IPW, the final OCP subsample was reduced to 1,040 (102 cases), the PCB subsample to 838 (85 cases), and the PBDE subsample to 943 (92 cases). Supplemental Figure A.1 illustrates this process. Mixtures analyses were conducted in a slightly reduced population of 809 women who had complete observations for PCBs, OCPs, *and* PBDEs.

Cox proportional hazard models were constructed to evaluate the association between serum POP concentrations and diabetes incidence over an 18-year follow-up period. Serum POP concentrations, standardized using traditional lipid-standardization, were the independent variables (O'Brien et al., 2016). We treated serum POP concentrations as continuous, log2-transforming them and interpreting hazard ratios (HRs) and 95% confidence intervals (CIs) per doubling of concentration. To explore non-linearity and non-monotonicity, we assessed POP tertiles. We assessed DDT metabolites using a binary exposure variable (detect vs. non-detect) as well as a three-level exposure variable treating non-detection as the reference group and dividing detectable concentrations at the median to create moderate and high exposure groups.

In single pollutant and mixture analyses, final models were adjusted for age, study site, race/ethnicity, education, financial strain, alcohol, smoking, parity, physical activity, high fat dairy intake, meat intake, fish/shellfish intake, and serum lipids (Model 3). We first investigated crude models (Model 0) followed by models adjusted for demographic and socioeconomic covariates (Model 1). Model 2 further adjusted for serum lipids as recommended when exposures are serum concentrations of lipid-soluble chemicals (O'Brien et al., 2016). All models were adjusted for joint stabilized IPWs. IPW lessens the impact of selection bias on risk estimates that may arise from selective participation into SWAN MPS (see Supplemental Methods).

Model 0	=	Unadjusted
Model 1	=	Joint stabilized inverse probability weights + demographic and socioeconomic variables: age, race/ethnicity, study site, education, and financial strain
Model 2	=	Model 1 + serum lipids
Model 3 (final)	=	Model 2 + behavioral and reproductive variables: alcohol consumption, smoking status, parity, physical activity, high fat dairy intake, meat intake, and fish/shellfish intake

As a sensitivity analysis, we additionally adjusted for baseline WC, however, this may be an over-adjustment, therefore Model 3 was selected a priori as our main model. Menopausal status in 1999/2000 and change in WC between 1997/99 and 1999/2000 were explored as potential confounders and ultimately not included (data not shown).

We quantified the overall effect of the POP mixture using Quantile-Based G-Computation (QBGC). The strong positive correlations between POP concentrations informed our

decision to use a mixtures approach (Figure A.2). QBGC combines the strengths of the Weighted Quantile Sums regression (WQS) and the causal effect estimation method, G-Computation (Keil et al., 2020). Compared to WQS, QBGC does not assume directional homogeneity, linearity, or additivity of mixture components. Thus, using QBGC, we computed a weighted index of POPs based on tertiles of exposure. The scaling allowed for comparability across POP mixture components. We then built Cox proportional hazards models using a single weighted index exposure term. The overall mixture effect was computed as the sum of estimated regression coefficients of all POP variables and can be interpreted as the HR of incident diabetes associated with a one-tertile increase in the serum concentrations of all POPs after controlling for covariates. The R package 'qgcomp' was used in this analysis (Keil, 2022).

3. Results

3.1. Participant Characteristics

The characteristics of women at SWAN MPS baseline (or first available timepoint, in the case of sociodemographic characteristics) are presented in Table 1. The median age at baseline was 49 years (IQR: 47–51). Approximately one quarter of women were from Los Angeles, a quarter from Oakland, and those remaining were relatively evenly distributed among Pittsburgh, Boston, and southeast MI. In terms of race/ethnicity, approximately half were white. Half of the participants attained a college education at minimum. Most women reported little to no alcohol use and no smoking history. Approximately 30% of women experienced moderate or high financial strain. The median WC at baseline was 81 cm (IQR: 73–93). Approximately 80% of women were parous. Between 1999 and 2016, 10% of women developed diabetes with 85 cases in the PCB subsample, 92 in the PBDE subsample, and 102 in the OCP subsample.

3.2. Exposure to POPs

Serum POP concentrations at baseline (1999/2000) are displayed in Table 2. PCBs were detected at the highest frequencies. 14 PCBs, PBDE 47, HCB, cis-chlordane, trans-chlordane, and trans-nonachlor met DF criteria (Table A.1). PCB 118, 138, 153, and 180 had the highest median (IQR) concentrations of 263.4 ng/g lipid (138.4, 402.8), 366.0 (176.0, 643.4), and 215.6 (120.8, 353.4), respectively. PCB 105, PCB 180, and PBDE 47 also had relatively elevated concentrations of 73.8 (38.3, 122.4), 39.1 (24.6, 60.1), and 38.5 (22.8, 80.7), respectively.

3.3. POPs and Diabetes Incidence

Single pollutant models identified few statistically significant results and suggested both positive and negative associations (Table 3). After adjustment (Model 3), HCB and PCB 123 were associated with increased diabetes risk with HRs (95% CI) of 1.67 (1.00, 2.79) and 1.87 (1.06, 3.29), respectively, when comparing T2 to T1. No significant effects were observed when comparing T3 versus T1, although the HRs remained above 1.0, suggesting a positive, non-linear relationship. Neither HCB nor PCB 123 had a significant trend across tertiles, which is consistent with a failure to reach statistical significance when analyzed continuously. In contrast, a doubling of PBDE 47 was associated with increased diabetes

risk with an HR (95% CI) of 1.11 (1.00, 1.24), yet HRs from tertile analysis did not reach levels of statistical significance. Findings for PCBs, besides PCB 123, suggest a protective relationship although none were statistically significant. All single pollutant results from Models 0, 1, and 2 are presented in Tables A.2–A.4. Moderate and high exposures to p,p'-DDE, p,p'-DDT, and p,p'-DDD were not significantly associated with diabetes risk, relative to non-detection (Table 4). Detection of DDT metabolites was also not associated with diabetes risk, relative to non-detection (Table A.5).

QBGC survival analysis suggested a null overall joint effect of the POP mixture. After adjustment, a one-tertile increase in the serum concentrations of all POPs was not associated with diabetes risk (HR = 1.04 [95% CI: 0.53, 2.07]). Further adjustment for baseline WC did not significantly impact the estimate (HR = 1.15 [95% CI: 0.57, 2.29]). Examining the contributions (weights) of individual compounds on the overall joint effect of the POP mixture, it appeared that the direction of effect was compound dependent (Figure A.3).

4. Discussion

4.1. POPs and Diabetes Development

This study attempted to elucidate the complex dynamics between POPs and diabetes by investigating the effects of individual pollutants and the overall mixture. Multiple comparisons in single pollutant analyses may explain why positive associations were suggested for PCB 123, PBDE 47, and HCB while the majority were null. Although many of our findings suggest non-linearity, the failure to reach significance at one or both tertiles impaired our ability to draw conclusions about dose-response shape. There is precedence for dose-response curves that plateau or resemble an inverted U, yet these studies do not explain our specific findings for PBDE 47, HCB, and PCB 123 (Lee et al., 2011, 2010; Tan et al., 2022). The mechanism underlying a non-linear association is unclear, although endocrine disruption is one proposed explanation. At low doses, endocrine disruptors may exert effects not seen at higher doses (Lee et al., 2014). There is moderate to strong evidence that EDCs including POPs have diabetogenic effects, which manifest in a non-monotonic manner (Gore et al., 2015).

Mechanisms linking POPs, insulin resistance, and T2D are complex in part because they involve adipose tissue, a major storage site for POPs. People with similar adiposity can vary widely in insulin resistance and T2D risk (Gregg et al., 2007; McLaughlin, 2007; Sims, 2001). The dysfunction of visceral adipose tissue may better predict metabolic health than adipose tissue mass itself (Barrett, 2013; Blüher, 2010; Dirtu et al., 2013; La Merrill et al., 2013; Lamat et al., 2022). Therefore, it is critical to look beyond adipose tissue mass to consider POPs accumulated inside the tissue, where they may exert inflammatory and/or endocrine disrupting effects (Barrett, 2013; La Merrill et al., 2013; Lee et al., 2014). Low-dose POPs exposure has been shown have to pro-inflammatory effects in adipose tissue (Lee et al., 2018). Endocrine mechanisms linking POPs and T2D include the disruption of estrogen, androgen, thyroid hormone, and glucocorticoid homeostasis (Charles et al., 2022; Lind and Lind, 2018). Additional mechanisms may include oxidative stress and mitochondrial dysfunction (Lee et al., 2014; Lind and Lind, 2018). In mitochondrial

dysfunction, diacylglycerol and fatty acid metabolites accumulate and suppress insulin signaling, leading to insulin resistance (Charles et al., 2022).

Existing literature demonstrates strong evidence for a relationship between T2D and low-dose exposure to OCPs and PCBs (Lee et al., 2018), moderate evidence for p,p′-DDE, (Lind and Lind, 2018), and strong evidence for chlordanes (Mendes et al., 2021). The link between POPs and insulin resistance is supported by *in vivo* studies (Enan et al., 1992; Gray et al., 2013; Ruzzin et al., 2010; Yau and Mennear, 1977). Most cross-sectional studies suggest positive relationships with some evidence of compound-specific non-linearity. One notable cross-sectional study assessed serum PCBs and OCPs at multiple timepoints and found increased risk of T2D up to 7 years before diagnosis with effect strength increasing as the time between serum collection and diagnosis decreased (Charles et al., 2022). Compared to cross-sectional studies, findings from prospective studies were less consistent in the shape and strength of dose-response relationships.

Results from prospective studies of PCBs are somewhat inconsistent, many finding that PCBs increase T2D risk (Lee et al., 2011; Vasiliu et al., 2006; Wang et al., 2008) and others finding no relationship (Charles et al., 2022; Lee et al., 2010; Magliano et al., 2021; Rignell-Hydbom et al., 2009; Wu et al., 2013). Two such PCB studies found significant positive relationships only in women (Vasiliu et al., 2006; Wang et al., 2008). Another study found that among people who never developed T2D, lipid-adjusted ∑PCBs were associated with reduced insulin sensitivity, most prominently in the 48–55 age group; no effect was observed among participants who developed T2D (Suarez-Lopez et al., 2015). Existing evidence does not explain why we observed a positive association for PCB 123 but not for other PCBs.

Prospective studies of OCPs suggest positive associations with compound-specific inconsistencies (Charles et al., 2022; Lee et al., 2010; Rignell-Hydbom et al., 2009; Turyk et al., 2009; Wu et al., 2013). One study found no association (Magliano et al., 2021). HCB and p,p’-DDE were associated with diabetes risk, however, the direction of effect and shape of dose-response curves were inconsistent (Rignell-Hydbom et al., 2009; Turyk et al., 2009; Wu et al., 2013). Findings from a 16-year study of T2D risk and adipose concentrations of PCBs and OCPs suggest a positive association although estimates did not reach levels of statistical significance. (Barrios-Rodríguez et al., 2021). The positive association we observed for HCB is supported by the literature.

Our finding of a marginal positive association for PBDE 47 is an important contribution given the dearth of epidemiological literature on T2D and PBDEs. The two most robust prospective studies of PBDEs found no associations with T2D after lipid adjustment (Lee et al., 2010; Magliano et al., 2021). Exposure to ∑PBDEs, based on dietary estimates, had a positive, non-linear association with T2D risk (Ongono et al., 2019). Animal studies suggest that PBDEs may increase diabetes risk, possibly involving the PPARγ receptor (Alimu et al., 2021). Consistent with our findings, PBDE 47 was shown *in vivo* to increase fasting glucose (Zhang et al., 2016). More research on PBDEs and T2D risk is warranted.

In our study, mixtures approaches were useful for comparison purposes but did not contribute significantly to our conclusions beyond what was indicated by single pollutant analyses. It is difficult to contextualize our findings in the literature as only two such studies have been conducted. Gasull and colleagues (2012) found a positive, linear association between a PCB mixture and diabetes prevalence using Bayesian Kernel Machine Regression (BKMR) modeling (Gasull et al., 2012). Using Weighted Quantile Sum (WQS) regression models, Reina-Pérez and colleagues (2023) found a positive association between a mixture of PCBs and OCPs and the prevalence of metabolic syndrome, driven by OCPs including HCB (Reina-Pérez et al., 2023). Neither of the existing mixtures studies evaluated PBDEs, and their methods, BKMR and WQS, cannot be employed in time-to-event analysis (Gasull et al., 2012; Reina-Pérez et al., 2023). Notwithstanding, it remains difficult to explain our overwhelmingly null findings relative to positive associations in mixtures and single pollutant studies.

The long follow-up period after POP measurement may have obscured a relationship between POPs and diabetes. Although a longer follow-up time has numerous advantages, the value of a single baseline serum concentration may decrease with an increasing follow-up duration, thus reducing our chances of uncovering an association (Lee et al., 2018). Exposure measurement error may increase over time as menopausal changes in adiposity affect serum concentrations of lipophilic POPs. Studying T2D risk among menopausal and post-menopausal women over a 19-year period, Wu et al. (2013) found null associations for PCBs and DDT metabolites and a positive association for HCB (Wu et al., 2013). This somewhat aligns with our findings. Furthermore, we considered that effect size may decrease as time increases between serum collection and diagnosis, but our ability to evaluate potential differences in effect size by follow-up time was impaired by low case counts (Charles et al., 2022).

Differences in exposure distributions across studies may not fully account for incongruent results, nevertheless they limit our ability to draw rigorous conclusions regarding dose-response dynamics. SWAN MPS had higher POP concentrations than NHANES 1999–2004 (Centers for Disease Control and Prevention, n.d.). Our findings could be explained in part by the possibility that diabetes risk increases more linearly for POPs in the low-dose range compared to the high-dose range (Lee et al., 2018). However, low-dose and high-dose are somewhat study-specific. Lee et al. (2010) reported PCB and OCP concentrations similar to SWAN concentrations and found trans-nonachlor to be associated with increased T2D risk. Although exposure levels were similar, our findings differed. Wu et al. (2013), a similar prospective midlife study, reported higher levels of PCB 180 and HCB and lower levels of PCB 118, 138, and 153 compared to SWAN. These differences may be due to geography and participant age. Wu et al. (2013) found null associations for PCBs that suggest non-linearity, null associations for DDT metabolites, and a positive association for HCB. Here, although exposure levels differed, our findings were somewhat aligned. Exposure distribution is one of many factors that may account for discrepancies in results across studies.

4.2 Strengths and Limitations

This is the first prospective study of POPs and diabetes to employ a mixtures approach. Our study is one of few to analyze PBDEs in addition to PCBs and OCPs. We employ QBGC, a rigorous, outcome-based mixtures method that can account for co-pollutant confounding and interactions in a highly correlated mixture. QBGC does not assume directional homogeneity, linearity, or additivity of mixture components. The study leveraged SWAN's original design to understand metabolic changes throughout the menopausal transition. The prospective design enabled time-to-event analysis over 18 years and the use of IPW at multiple timepoints to account for selection bias. Our study represents women from multiple urban areas with a focus on Chinese and Japanese women who have been historically underrepresented in U.S. studies.

This study is primarily limited by the small number of diabetes cases and the single measure of serum POPs. A larger sample would have given us the power to stratify by potential mechanistic characteristics such as menopausal status or obesity. With a larger sample we could have investigated the interaction of race/ethnicity with POPs or study site. Robust analysis of time-varying hazard ratios was prohibited by small case numbers at early follow-up visits. Furthermore, different timing of serum collection with respect to diabetes diagnosis could have affected risk estimates. These findings may only be generalizable to populations similar to U.S. midlife women residing in greater metropolitan areas. Finally, in the single pollutant analyses, we did not address multiple comparisons.

5. Conclusion

This study examined incident diabetes and exposure to POPs individually and as a mixture. Overall, we conclude that exposure to a mixture of serum POPs was not associated with incident diabetes in midlife U.S. women, although some individual POPs demonstrated positive yet inconsistent associations with diabetes risk. In this study, mixtures analyses did not contribute substantial information beyond the single pollutant approach. Nevertheless, a mixtures approach is valuable to validate and contextualize single pollutant findings and is necessary to evaluate the overall effect of a mixture. Additional studies are needed on the effects of PBDEs on insulin resistance. We recommend repeated POP measures and a larger study sample to elucidate this relationship and provide insight into mechanisms of action.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Centers: *University of Michigan, Ann Arbor – Carrie Karvonen-Gutierrez, PI 2021 – present, Siobán Harlow, PI 2011 – 2021, Mary Fran Sowers, PI 1994–2011; Massachusetts General Hospital, Boston, MA – Joel Finkelstein, PI 1999 – present; Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Howard Kravitz, PI 2009 – present; Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Ellen Gold, PI; University of California, Los Angeles – Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY – Carol Derby, PI 2011 – present, Rachel Wildman, PI 2010 – 2011; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004; and the University of Pittsburgh, Pittsburgh, PA – Karen Matthews, PI.*

NIH Program Office: *National Institute on Aging, Bethesda, MD – Rosaly Correa-de-Araujo 2020 - present; Chhanda Dutta 2016- present; Winifred Rossi 2012–2016; Sherry Sherman 1994 – 2012; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers.*

Central Laboratory: *University of Michigan, Ann Arbor – Daniel McConnell* (Central Ligand Assay Satellite Services).

NIA Biorepository: *Rosaly Correa-de-Araujo 2019 – Present*; SWAN Repository: *University of Michigan, Ann Arbor – Siobán Harlow 2013 – 2018; Dan McConnell 2011 – 2013; MaryFran Sowers 2000 – 2011.*

Coordinating Center: *University of Pittsburgh, Pittsburgh, PA – Maria Mori Brooks, PI 2012 - present; Kim Sutton-Tyrrell, PI 2001 – 2012; New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001.*

Steering Committee: Susan Johnson, Current Chair Chris Gallagher, Former Chair

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Data Availability

SWAN provides access to public use datasets that include data from SWAN screening, the baseline visit and follow-up visits (https://agingresearchbiobank.nia.nih.gov/). To preserve participant confidentiality, some, but not all, of the data used for this manuscript are contained in the public use datasets. A link to the public use datasets is also located on the SWAN web site: http://www.swanstudy.org/swan-research/data-access/. Investigators who require assistance accessing the public use dataset may contact the SWAN Coordinating Center at the following email address: swanaccess@edc.pitt.edu.

References

Agency for Toxic Substances and Disease Registry, 2017. Toxicological Profile for Polybrominated Diphenyl Ethers (PBDEs). Agency for Toxic Substances and Disease Registry.

Agency for Toxic Substances and Disease Registry, 2000. Toxicological Profile for Polychlorinated Biphenyls (PCBs). Agency for Toxic Substances and Disease Registry.

Alimu A, Abudureman H, Wang Y-Z, Li M-Y, Wang J-S, Liu Z-L, 2021. Decabromodiphenyl ether causes insulin resistance and glucose and lipid metabolism disorders in mice. World J. Diabetes 12, 1267–1281. 10.4239/wjd.v12.i8.1267 [PubMed: 34512892]

Barrett JR, 2013. POPs vs. Fat: Persistent Organic Pollutant Toxicity Targets and Is Modulated by Adipose Tissue. Environ. Health Perspect 121, a61. 10.1289/ehp.121-a61 [PubMed: 23380189]

Barrios-Rodríguez R, Pérez-Carrascosa FM, Gómez-Peña C, Mustieles V, Salcedo-Bellido I, Requena P, Martín-Olmedo P, Jiménez-Moleón JJ, Arrebola JP, 2021. Associations of accumulated selected

persistent organic pollutants in adipose tissue with insulin sensitivity and risk of incident type-2 diabetes. Environ. Int 155, 106607. 10.1016/j.envint.2021.106607 [PubMed: 33971459]

Billings LK, Florez JC, 2010. The genetics of type 2 diabetes: what have we learned from GWAS?: Genetics of type 2 diabetes. Ann. N. Y. Acad. Sci 1212, 59–77. 10.1111/j.1749-6632.2010.05838.x [PubMed: 21091714]

Blüher M, 2010. The distinction of metabolically 'healthy' from 'unhealthy' obese individuals. Curr. Opin. Lipidol 21, 38–43. 10.1097/MOL.0b013e3283346ccc [PubMed: 19915462]

Bonefeld-Jørgensen EC, Ghisari M, Wielsøe M, Bjerregaard-Olesen C, Kjeldsen LS, Long M, 2014. Biomonitoring and Hormone-Disrupting Effect Biomarkers of Persistent Organic Pollutants *In Vitro* and *Ex Vivo*. Basic Clin. Pharmacol. Toxicol 115, 118–128. 10.1111/bcpt.12263 [PubMed: 24797035]

Centers for Disease Control and Prevention, 2023. Diabetes Infographics.

Centers for Disease Control and Prevention, 2022. By the Numbers: Diabetes in America. National Diabetes Statistics Report.

Centers for Disease Control and Prevention, 2021. Diabetes Report Card 2021. Centers for Disease Control and Prevention.

Centers for Disease Control and Prevention, n.d. Chemical Factsheets (National Biomonitoring Program). Center for Disease Control and Prevention.

Centers for Disease Control and Prevention, n.d. Serum PCBs and Persistent Pesticides. Organic Toxicology Branch, Division of Laboratory Sciences, National Center for Environmental Health.

Centers for Disease Control and Prevention, n.d. Diabetes Risk Factors, Diabetes.

Centers for Disease Control and Prevention, n.d. National Report on Human Exposure to Environmental Chemicals: Biomonitoring Data Tables for Environmental Chemicals. Center for Disease Control and Prevention.

Charles D, Berg V, Nøst TH, Bergdahl IA, Huber S, Ayotte P, Wilsgaard T, Averina M, Sandanger T, Rylander C, 2022. Longitudinal changes in concentrations of persistent organic pollutants (1986–2016) and their associations with type 2 diabetes mellitus. Environ. Res 204, 112129. 10.1016/j.envres.2021.112129 [PubMed: 34597662]

Chatterjee S, Khunti K, Davies MJ, 2017. Type 2 diabetes. The Lancet 389, 2239–2251. 10.1016/S0140-6736(17)30058-2

Crawford SE, Brinkmann M, Ouellet JD, Lehmkuhl F, Reicherter K, Schwarzbauer J, Bellanova P, Letmathe P, Blank LM, Weber R, Brack W, van Dongen JT, Menzel L, Hecker M, Schüttrumpf H, Hollert H, 2022. Remobilization of pollutants during extreme flood events poses severe risks to human and environmental health. J. Hazard. Mater 421, 126691. 10.1016/j.jhazmat.2021.126691 [PubMed: 34315022]

Dirinck E, Dirtu AC, Jorens PG, Malarvannan G, Covaci A, Van Gaal LF, 2015. Pivotal Role for the Visceral Fat Compartment in the Release of Persistent Organic Pollutants During Weight Loss. J. Clin. Endocrinol. Metab 100, 4463–4471. 10.1210/jc.2015-2571 [PubMed: 26469381]

Dirtu AC, Dirinck E, Malarvannan G, Neels H, Van Gaal L, Jorens PG, Covaci A, 2013. Dynamics of Organohalogenated Contaminants in Human Serum from Obese Individuals during One Year of Weight Loss Treatment. Environ. Sci. Technol 47, 12441–12449. 10.1021/es400657t [PubMed: 24074050]

Enan E, Liu P, Matsumura F, 1992. TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) causes reduction in glucose uptake through glucose transporters on the plasma membrane of the guinea pig adipocyte. J. Environ. Sci. Health Part B 27, 495–510. 10.1080/03601239209372797

Erickson TB, Brooks J, Nilles EJ, Pham PN, Vinck P, 2019. Environmental health effects attributed to toxic and infectious agents following hurricanes, cyclones, flash floods and major hydrometeorological events. J. Toxicol. Environ. Health Part B 22, 157–171. 10.1080/10937404.2019.1654422

Fan Y, Wang R, Ding L, Meng Z, Zhang Q, Shen Y, Hu G, Liu M, 2020. Waist Circumference and its Changes Are More Strongly Associated with the Risk of Type 2 Diabetes than Body Mass Index and Changes in Body Weight in Chinese Adults. J. Nutr 150, 1259–1265. 10.1093/jn/nxaa014 [PubMed: 32006008]

Gasull M, Pumarega J, Téllez-Plaza M, Castell C, Tresserras R, Lee DH, Porta M, 2012. Blood Concentrations of Persistent Organic Pollutants and Prediabetes and Diabetes in the General Population of Catalonia. Environ. Sci. Technol 46, 7799–7810. 10.1021/es300712g [PubMed: 22681243]

Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT, 2015. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr. Rev 36, E1–E150. 10.1210/er.2015-1010 [PubMed: 26544531]

Grant-Alfieri A, Devasurendra A, Batterman S, Karvonen-Gutierrez C, Park SK, 2024. Changes in adipose tissue and circulating concentrations of persistent organic pollutants in midlife women. Environ. Health 10.1021/envhealth.3c00159

Gray SL, Shaw AC, Gagne AX, Chan HM, 2013. Chronic exposure to PCBs (Aroclor 1254) exacerbates obesity-induced insulin resistance and hyperinsulinemia in mice. J. Toxicol. Environ. Health A 76, 701–715. 10.1080/15287394.2013.796503 [PubMed: 23980837]

Gregg EW, Cheng YJ, Narayan KMV, Thompson TJ, Williamson DF, 2007. The relative contributions of different levels of overweight and obesity to the increased prevalence of diabetes in the United States: 1976–2004. Prev. Med 45, 348–352. 10.1016/j.ypmed.2007.07.020 [PubMed: 17889292]

Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, Nadal A, Palanza P, Panzica G, Sargis R, Vandenberg LN, vom Saal F, 2017. Metabolism disrupting chemicals and metabolic disorders. Reprod. Toxicol 68, 3–33. 10.1016/j.reprotox.2016.10.001 [PubMed: 27760374]

International Diabetes Federation, 2021. Diabetes Around the World 2021. IDF Diabetes Atlas.

Joo SH, Liang Y, Kim M, Byun J, Choi H, 2021. Microplastics with adsorbed contaminants: Mechanisms and Treatment. Environ. Chall 3, 100042. 10.1016/j.envc.2021.100042

Keil A, 2022. qgcomp: Quantile G-Computation.

Keil Alexander P, Buckley Jessie P, O'Brien Katie M, Ferguson Kelly K, Zhao Shanshan, White Alexandra J., 2020. A Quantile-Based g-Computation Approach to Addressing the Effects of Exposure Mixtures. Environ. Health Perspect 128, 047004. 10.1289/EHP5838 [PubMed: 32255670]

Kraft M, Rauchfuss K, Fromme H, Grün L, Sievering S, Köllner B, Chovolou Y, 2021. Inhalation Exposure to PCB from Contaminated Indoor Air—How Much Is Absorbed into the Blood? Pollutants 1, 181–193. 10.3390/pollutants1030015

La Merrill M, Emond C, Kim MJ, Antignac J-P, Le Bizec B, Clément K, Birnbaum LS, Barouki R, 2013. Toxicological Function of Adipose Tissue: Focus on Persistent Organic Pollutants. Environ. Health Perspect 121, 162–169. 10.1289/ehp.1205485 [PubMed: 23221922]

Lamat H, Sauvant-Rochat M-P, Tauveron I, Bagheri R, Ugbolue UC, Maqdasi S, Navel V, Dutheil F, 2022. Metabolic syndrome and pesticides: A systematic review and meta-analysis. Environ. Pollut 305, 119288. 10.1016/j.envpol.2022.119288 [PubMed: 35439599]

Lee D-H, Porta M, Jacobs DR, Vandenberg LN, 2014. Chlorinated Persistent Organic Pollutants, Obesity, and Type 2 Diabetes. Endocr. Rev 35, 557–601. 10.1210/er.2013-1084 [PubMed: 24483949]

Lee D-H, Steffes MW, Sjödin A, Jones RS, Needham LL, Jacobs DR, 2011. Low Dose Organochlorine Pesticides and Polychlorinated Biphenyls Predict Obesity, Dyslipidemia, and Insulin Resistance among People Free of Diabetes. PLoS ONE 6, e15977. 10.1371/journal.pone.0015977 [PubMed: 21298090]

Lee D-H, Steffes MW, Sjödin A, Jones RS, Needham LL, Jacobs DR, 2010. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. Environ. Health Perspect 118, 1235–1242. 10.1289/ehp.0901480 [PubMed: 20444671]

Lee Y-M, Jacobs DR Jr., Lee D-H, 2018. Persistent Organic Pollutants and Type 2 Diabetes: A Critical Review of Review Articles. Front. Endocrinol 9, 712. 10.3389/fendo.2018.00712

Lind PM, Lind L, 2018. Endocrine-disrupting chemicals and risk of diabetes: an evidence-based review. Diabetologia 61, 1495–1502. 10.1007/s00125-018-4621-3 [PubMed: 29744538]

Magliano DJ, Rancière F, Slama R, Roussel R, Kiviranta H, Coumoul X, Balkau B, Botton J, 2021. Exposure to persistent organic pollutants and the risk of type 2 diabetes: a case-cohort study. Diabetes Metab. 47, 101234. 10.1016/j.diabet.2021.101234 [PubMed: 33515717]

McLaughlin T, 2007. Heterogeneity in the Prevalence of Risk Factors for Cardiovascular Disease and Type 2 Diabetes Mellitus in Obese Individuals: Effect of Differences in Insulin Sensitivity. Arch. Intern. Med 167, 642. 10.1001/archinte.167.7.642 [PubMed: 17420421]

Mendes V, Ribeiro C, Delgado I, Peleteiro B, Aggerbeck M, Distel E, Annesi-Maesano I, Sarigiannis D, Ramos E, 2021. The association between environmental exposures to chlordanes, adiposity and diabetes-related features: a systematic review and meta-analysis. Sci. Rep 11, 14546. 10.1038/s41598-021-93868-4 [PubMed: 34267268]

O'Brien KM, Upson K, Cook NR, Weinberg CR, 2016. Environmental Chemicals in Urine and Blood: Improving Methods for Creatinine and Lipid Adjustment. Environ. Health Perspect 124, 220–227. 10.1289/ehp.1509693 [PubMed: 26219104]

Ongono JS, Dow C, Gambaretti J, Severi G, Boutron-Ruault M-C, Bonnet F, Fagherazzi G, Mancini FR, 2019. Dietary exposure to brominated flame retardants and risk of type 2 diabetes in the French E3N cohort. Environ. Int 123, 54–60. 10.1016/j.envint.2018.11.040 [PubMed: 30496982]

Reina-Pérez I, Artacho-Cordón F, Mustieles V, Castellano-Castillo D, Cardona F, Jiménez-Díaz I, López-Medina JA, Alcaide J, Ocaña-Wilhelmi L, Iribarne-Durán LM, Arrebola JP, Olea N, Tinahones FJ, Fernández MF, 2023. Cross-sectional associations of persistent organic pollutants measured in adipose tissue and metabolic syndrome in clinically diagnosed middle-aged adults. Environ. Res 115350. 10.1016/j.envres.2023.115350 [PubMed: 36709023]

Rignell-Hydbom A, Lidfeldt J, Kiviranta H, Rantakokko P, Samsioe G, Agardh C-D, Rylander L, 2009. Exposure to p,p'-DDE: a risk factor for type 2 diabetes. PloS One 4, e7503. 10.1371/journal.pone.0007503 [PubMed: 19838294]

Rignell-Hydbom A, Rylander L, Hagmar L, 2007. Exposure to persistent organochlorine pollutants and type 2 diabetes mellitus. Hum. Exp. Toxicol 26, 447–452. 10.1177/0960327107076886 [PubMed: 17623770]

Ruzzin J, Petersen R, Meugnier E, Madsen L, Lock E-J, Lillefosse H, Ma T, Pesenti S, Sonne SB, Marstrand TT, Malde MK, Du Z-Y, Chavey C, Fajas L, Lundebye A-K, Brand CL, Vidal H, Kristiansen K, Frøyland L, 2010. Persistent Organic Pollutant Exposure Leads to Insulin Resistance Syndrome. Environ. Health Perspect 118, 465–471. 10.1289/ehp.0901321 [PubMed: 20064776]

Sharma A, Kumar V, Shahzad B, Tanveer M, Sidhu GPS, Handa N, Kohli SK, Yadav P, Bali AS, Parihar RD, Dar OI, Singh K, Jasrotia S, Bakshi P, Ramakrishnan M, Kumar S, Bhardwaj R, Thukral AK, 2019. Worldwide pesticide usage and its impacts on ecosystem. SN Appl. Sci 1, 1446. 10.1007/s42452-019-1485-1

Sims EA, 2001. Are there persons who are obese, but metabolically healthy? Metabolism 50, 1499–1504. [PubMed: 11735101]

Sowers M, Crawford S, Sternfeld B, Morganstein D, Gold E, Greendale G, Evans D, Neer R, Matthews K, Sherman S, Lo A, Weiss G, Kelsey J, 2000. SWAN: A Multicenter, Multiethnic, Community-Based Cohort Study of Women and the Menopausal Transition. Menopause: Biology and Pathobiology.

Suarez-Lopez JR, Lee D-H, Porta M, Steffes MW, Jacobs DR, 2015. Persistent organic pollutants in young adults and changes in glucose related metabolism over a 23-year follow-up. Environ. Res 137, 485–494. 10.1016/j.envres.2014.11.001 [PubMed: 25706918]

Tan Q, Wang M, Yu L, Liang R, Liu W, Dong C, Zhang Y, Li M, Ye Z, Wang B, Zhou M, Chen W, 2022. Associations of polychlorinated biphenyls exposure with plasma glucose and diabetes in general Chinese population: The mediating effect of lipid peroxidation. Environ. Pollut 308, 119660. 10.1016/j.envpol.2022.119660 [PubMed: 35738522]

The Aspen Institute, 2017. Glossary for Understanding the Dismantling Structural Racism/Promoting Racial Equity Analysis, The Roundtable on Community Change.

Turyk M, Anderson HA, Knobeloch L, Imm P, Persky VW, 2009. Prevalence of diabetes and body burdens of polychlorinated biphenyls, polybrominated diphenyl ethers, and p,p′-diphenyldichloroethene in Great Lakes sport fish consumers. Chemosphere 75, 674–679. 10.1016/j.chemosphere.2008.12.035 [PubMed: 19157498]

U.S. Environmental Protection Agency, 2023. DDT: A Brief History and Status.

Vargas-Vázquez A, Bello-Chavolla OY, Ortiz-Brizuela E, Campos-Muñoz A, Mehta R, Villanueva-Reza M, Bahena-López JP, Antonio-Villa NE, González-Lara MF, Ponce de León A, Sifuentes-Osornio J, Aguilar-Salinas CA, 2021. Impact of undiagnosed type 2 diabetes and pre-diabetes on severity and mortality for SARS-CoV-2 infection. BMJ Open Diabetes Res. Care 9, e002026. 10.1136/bmjdrc-2020-002026

Vasiliu O, Cameron L, Gardiner J, DeGuire P, Karmaus W, 2006. Polybrominated Biphenyls, Polychlorinated Biphenyls, Body Weight, and Incidence of Adult-Onset Diabetes Mellitus. Epidemiology 17, 352–359. 10.1097/01.ede.0000220553.84350.c5 [PubMed: 16755267]

Wahlang B, 2018. Exposure to persistent organic pollutants: impact on women's health. Rev. Environ. Health 33, 331–348. 10.1515/reveh-2018-0018 [PubMed: 30110273]

Wang S-L, Tsai P-C, Yang C-Y, Leon Guo Y, 2008. Increased Risk of Diabetes and Polychlorinated Biphenyls and Dioxins: A 24-year follow-up study of the Yucheng cohort. Diabetes Care 31, 1574–1579. 10.2337/dc07-2449 [PubMed: 18487481]

Wang X, Karvonen-Gutierrez CA, Mukherjee B, Herman WH, Park SK, 2020. Urinary metals and adipokines in midlife women: The Study of Women's Health Across the nation (SWAN). Environ. Res 110426. 10.1016/j.envres.2020.110426 [PubMed: 33157106]

Wolf K, Bongaerts BWC, Schneider Alexandra, Huth C, Meisinger C, Peters A, Schneider Andrea, Wittsiepe J, Schramm K-W, Greiser KH, Hartwig S, Kluttig A, Rathmann W, 2019. Persistent organic pollutants and the incidence of type 2 diabetes in the CARLA and KORA cohort studies. Environ. Int 129, 221–228. 10.1016/j.envint.2019.05.030 [PubMed: 31132656]

World Health Organization, 2022. Diabetes.

Wu H, Bertrand KA, Choi AL, Hu FB, Laden F, Grandjean P, Sun Q, 2013. Persistent organic pollutants and type 2 diabetes: a prospective analysis in the nurses' health study and meta-analysis. Environ. Health Perspect 121, 153–161. 10.1289/ehp.1205248 [PubMed: 23131992]

Yau ET, Mennear JH, 1977. The inhibitoty effect of DDT on insulin secretion in mice. Toxicol. Appl. Pharmacol 39, 81–88. 10.1016/0041-008X(77)90179-X [PubMed: 320718]

Yu GW, Laseter J, Mylander C, 2011. Persistent Organic Pollutants in Serum and Several Different Fat Compartments in Humans. J. Environ. Public Health 2011, 1–8. 10.1155/2011/417980

Zhang Z, Li S, Liu L, Wang L, Xiao X, Sun Z, Wang X, Wang C, Wang M, Li L, Xu Q, Gao W, Wang S-L, 2016. Environmental exposure to BDE47 is associated with increased diabetes prevalence: Evidence from community-based case-control studies and an animal experiment. Sci. Rep 6, 27854. 10.1038/srep27854 [PubMed: 27291303]

Highlights

- Relations of persistent organic pollutants and incident diabetes were examined in midlife women.
- Exposure to polychlorinated biphenyl (PCB) 123, hexachlorobenzene, and polybrominated diphenyl ether (PBDE) 47 may increase diabetes risk.
- Exposure to a mixture of persistent organic pollutants was not linked to incident diabetes.
- Non-linear and non-monotonic dose-response dynamics deserve further exploration.

Table 1.

Characteristics of SWAN MPS Participants Free of Diabetes at Baseline, 1999/2000.

	PCB Subsample	PBDE Subsample	OCP Subsample
Characteristic	**N = 838**[1]	**N = 943**[1]	**N = 1,040**[1]
Developed Diabetes	85 (10%)	92 (9.8%)	102 (9.8%)
Age at Baseline (yr)	49.0 (47.0, 51.0)	49.0 (47.0, 51.0)	49.0 (47.0, 51.0)
Race/Ethnicity			
Black	152 (18%)	169 (18%)	191 (18%)
White	441 (53%)	495 (52%)	548 (53%)
Chinese	116 (14%)	135 (14%)	141 (14%)
Japanese	129 (15%)	144 (15%)	160 (15%)
Study Site			
Boston	126 (15%)	144 (15%)	157 (15%)
Los Angeles	224 (27%)	251 (27%)	290 (28%)
Oakland	208 (25%)	236 (25%)	246 (24%)
Pittsburgh	145 (17%)	159 (17%)	180 (17%)
SE Michigan	135 (16%)	153 (16%)	167 (16%)
Educational Attainment			
High School or Less	137 (16%)	160 (17%)	179 (17%)
Beyond High School	261 (31%)	285 (30%)	316 (30%)
College	199 (24%)	231 (24%)	253 (24%)
Beyond College	241 (29%)	267 (28%)	292 (28%)
Menopause Status			
Pre-menopause or early peri-menopause	524 (63%)	590 (63%)	649 (62%)
Late peri-menopause or surgical/natural post-menopause	182 (22%)	202 (21%)	218 (21%)
Unknown	132 (16%)	151 (16%)	173 (17%)
Alcohol Consumption at Baseline			
None	425 (51%)	483 (51%)	529 (51%)
<1 drink per week	210 (25%)	227 (24%)	257 (25%)
1–7 drinks per week	145 (17%)	163 (17%)	179 (17%)
>7 drinks per week	58 (6.9%)	70 (7.4%)	75 (7.2%)
Smoking Status at Baseline			
Never	539 (64%)	604 (64%)	667 (64%)
Current	80 (9.5%)	89 (9.4%)	98 (9.4%)
Past Only	219 (26%)	250 (27%)	275 (26%)
Financial Strain, Somewhat or Very Difficult	240 (29%)	272 (29%)	303 (29%)
Physical Activity Score (3 to 15), not including work	7.8 (6.7, 8.9)	7.9 (6.7, 9.0)	7.9 (6.7, 9.0)
Parous (live or still birth)	662 (79%)	751 (80%)	826 (79%)
Total Serum Lipid Concentration (mg/dl) at Baseline	613.2 (544.9, 699.4)	610.5 (545.0, 695.9)	611.8 (545.8, 698.6)

	PCB Subsample	PBDE Subsample	OCP Subsample
Characteristic	**N = 838**[1]	**N = 943**[1]	**N = 1,040**[1]
Waist Circumference (cm)	81.3 (73.3, 93.2)	81.1 (73.0, 92.8)	81.1 (73.1, 93.2)
High Fat Dairy Consumption (weekly frequency)	10.6 (5.7, 19.0)	10.8 (5.8, 19.1)	10.8 (5.8, 19.3)
Meat Consumption (weekly frequency)	3.5 (2.0, 5.6)	3.5 (1.8, 5.6)	3.5 (2.0, 5.5)
Fish and Shellfish Consumption (weekly frequency)	1.3 (0.79, 2.5)	1.5 (0.79, 2.5)	1.5 (0.79, 2.5)

[1] Median (IQR) or Frequency (%)

Table 2.

Serum POP Concentrations (ng/g lipid) among SWAN MPS Participants Free of Diabetes at Baseline, 1999/2000

	DF (%)	P25	P33	P50	P66	P75
PCBs (n = 838)						
PCB 105	99.3	38.3	47.6	73.8	98.1	122.4
PCB 118	95.3	138.4	178.7	263.4	348.7	402.8
PCB 123	91.7	13.1	16.7	30.7	46.1	60.7
PCB 138	100.0	176.0	247.8	366.0	534.0	643.4
PCB 153	100.0	120.8	151.9	215.6	288.7	353.4
PCB 156	97.2	3.9	4.6	6.3	9.4	11.9
PCB 157	85.7	1.4	1.8	2.6	3.6	4.4
PCB 167	98.8	3.6	4.4	6.2	8.2	9.6
PCB 170	99.7	12.2	14.1	19.0	25.2	28.6
PCB 174	98.5	11.3	14.3	21.1	27.6	33.1
PCB 178	82.1	3.8	4.7	6.6	8.8	10.2
PCB 180	94.9	24.6	29.1	39.1	52.7	60.1
PCB 187	99.8	19.7	24.5	34.4	45.6	53.7
PCB 194	71.8	<LOD	3.5	4.8	6.3	7.3
PBDEs (n = 943)						
PBDE 47	72.8	<LOD	24.6	38.5	57.1	80.7
OCPs (n = 1,040)						
cis-chlordane	78.4	6.4	8.0	10.8	14.2	16.5
HCB	97.1	9.3	10.3	12.9	16.2	18.3
trans-chlordane	96.1	7.0	8.9	12.7	17.0	20.6
trans-nonachlor	72.0	<LOD	6.7	10.0	13.6	16.5
p,p'-DDT	39.6	<LOD	<LOD	<LOD	5.2	9.3
p,p'-DDD	38.9	<LOD	<LOD	<LOD	11.3	25.7
p,p'-DDE	38.8	<LOD	<LOD	<LOD	11.7	23.1

Table 3.

Hazard Ratio (95% CI) of incident diabetes associated with serum POP concentrations, 1999–2016.

Model adjusted for age at baseline, race/ethnicity, site, education, financial strain, alcohol, smoking, parity, physical activity, high fat dairy intake, meat intake, and fish/shellfish intake, serum lipids at baseline, and joint stabilized inverse probability weights. Second and third tertiles of serum POP concentrations were analyzed relative to the first tertile.

Compound	Continuous (per doubling)	p	Tertile 2	Tertile 3	p for trend
OCPs (n = 1040)					
cis-chlordane	1.05 (0.89, 1.25)	0.5632	0.88 (0.52, 1.46)	0.96 (0.58, 1.59)	0.8713
HCB	1.07 (0.81, 1.42)	0.6298	1.67 (1.00, 2.79)	1.49 (0.84, 2.66)	0.1584
trans-chlordane	1.02 (0.88, 1.19)	0.7878	1.41 (0.84, 2.38)	1.30 (0.75, 2.24)	0.3399
trans-nonachlor	1.04 (0.86, 1.27)	0.6734	0.92 (0.55, 1.54)	1.13 (0.67, 1.89)	0.6481
PBDEs (n = 943)					
PBDE 47	1.11 (1.00, 1.24)	0.0509	0.98 (0.56, 1.72)	1.37 (0.78, 2.43)	0.2772
PCBs (n = 838)					
PCB 105	0.98 (0.85, 1.14)	0.8290	1.03 (0.59, 1.80)	0.81 (0.44, 1.48)	0.5031
PCB 118	0.92 (0.76, 1.12)	0.4052	0.91 (0.52, 1.59)	0.85 (0.47, 1.53)	0.5819
PCB 123	1.10 (0.96, 1.27)	0.1704	1.87 (1.06, 3.29) *	1.60 (0.88, 2.92)	0.1180
PCB 138	0.95 (0.81, 1.11)	0.5254	0.83 (0.48, 1.43)	0.72 (0.40, 1.28)	0.2607
PCB 153	0.92 (0.73, 1.17)	0.4990	1.05 (0.61, 1.82)	0.72 (0.39, 1.33)	0.3068
PCB 156	0.85 (0.69, 1.05)	0.1303	0.91 (0.53, 1.57)	0.68 (0.38, 1.21)	0.1881
PCB 157	0.91 (0.71, 1.17)	0.4498	0.71 (0.40, 1.23)	0.72 (0.39, 1.33)	0.2744
PCB 167	0.91 (0.70, 1.17)	0.4539	0.84 (0.50, 1.42)	0.88 (0.48, 1.62)	0.6585
PCB 170	0.92 (0.75, 1.14)	0.4593	0.95 (0.55, 1.64)	0.77 (0.43, 1.35)	0.3636
PCB 174	0.92 (0.74, 1.15)	0.4799	0.98 (0.57, 1.68)	0.77 (0.42, 1.43)	0.4111
PCB 178	0.91 (0.70, 1.19)	0.5003	0.93 (0.53, 1.61)	0.77 (0.43, 1.37)	0.3742
PCB 180	1.00 (0.85, 1.17)	0.9825	0.67 (0.38, 1.19)	0.80 (0.47, 1.38)	0.4101
PCB 187	0.97 (0.77, 1.22)	0.8033	0.98 (0.57, 1.71)	0.84 (0.47, 1.50)	0.5598
PCB 194	0.96 (0.71, 1.30)	0.7876	0.81 (0.46, 1.45)	0.96 (0.56, 1.65)	0.8687

* indicates a p-value < 0.05

Table 4.

Hazard Ratio (95% CI) of incident diabetes associated with DDT metabolites, 1999–2016.

Model adjusted for age at baseline, race/ethnicity, site, education, financial strain, alcohol, smoking, parity, physical activity, high fat dairy intake, meat intake, and fish/shellfish intake, serum lipids at baseline, and joint stabilized inverse probability weights. Moderate and high quantiles of exposure were analyzed relative to non-detection. (n = 1040)

Metabolite	Moderate Exposure	High Exposure	p for trend
p,p'-DDD	0.93 (0.53, 1.64)	0.96 (0.56, 1.65)	0.836
p,p'-DDE	0.80 (0.44, 1.45)	1.35 (0.84, 2.17)	0.381
p,p'-DDT	1.16 (0.70, 1.92)	1.11 (0.63, 1.97)	0.614