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Article

Changes in Adipose Tissue and Circulating Concentrations of Persistent Organic Pollutants in Midlife Women

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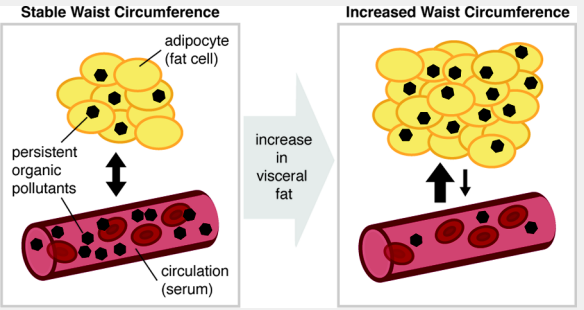
ABSTRACT: Polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs) are persistent organic pollutants (POPs) that bioaccumulate in adipose tissue. We investigated the relationship between change in central adiposity and changes in circulating concentrations of POPs over a 12-year period during the midlife. Serum concentrations of 34 PCBs and 19 OCPs were measured at four time points (1999/2000, 2002/03, 2005/06, 2009/11) in a cohort of midlife women, the Study of Women's Health Across the Nation. Linear mixed models were used to test the association between a change in waist circumference and a change in serum POP concentrations. Sixty-five women contributed 181 PCB observations. Fifty-nine women contributed 151 OCP observations. After adjustment for covariates (study site, race and ethnicity, age at baseline, parity), a one-inch (2.54 cm) increase in the change in waist circumference between visits was associated with a 4.9% decrease in the change in serum concentration of PCB 194 (95% CI: −8.0%, −1.6%). No associations were observed for other PCB congeners or the presence of OCPs. An increase in the difference in waist circumference over time was not associated with a change in the difference in serum concentrations of PCBs and OCPs except for PCB 194, possibly due to the high lipophilicity.



KEYWORDS: *persistent organic pollutants, PCBs, pesticides, adipose tissue, women, midlife*

INTRODUCTION

Persistent organic pollutants (POPs) include polyhalogenated organic compounds that can confer harmful health effects including neurological, immunological, hepatic, reproductive, and developmental toxicity as well as carcinogenesis.[1,2] Two important classes of POPs are polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs). PCBs encompass 209 congeners with between 1 and 10 chlorine atoms on a biphenyl (two benzene ring) structure.[1] PCBs were heavily produced in the United States (U.S.) from the 1930s until 1979 and used as dielectric, coolant, and heat-transfer fluids as well as paint and plastic additives. Many OCPs are defined by chlorine-substituted aliphatic or aromatic rings and other structures. Most uses of OCPs were banned by many high-income countries, including the U.S., in the 1970s and 1980s due to harmful ecological and neurological effects and possible carcinogenic effects.[3] Other countries later adopted regulations on OCPs such as Mexico, which banned DDT in 2000.[4] Due to rising food demands and pesticide resistance, the use of pesticides including OCPs has risen in countries across Asia as well as in parts of Europe and Africa, although the contribution of OCPs relative to total pesticide burden is difficult to determine.[4]

POPs persist in the environment and animals, especially in adipose tissue, and act as endocrine disrupting chemicals. The main pathway of human exposure to POPs is diet, through consumption of animal-based fatty foods.[1] Indoor air is another important exposure source of PCBs, settling on surfaces and accumulating in household dust.[5] Due to their lipophilic nature and very low elimination rates, even after external exposure ceases, POPs stored in adipose tissue continue to serve as an internal source of exposure.[6] The capacity and duration of POP storage in adipose tissue may vary by tissue type and POP lipophilicity.[7] Highly chlorinated PCBs are more likely to bioaccumulate than less-chlorinated PCBs. Obesity and weight change affect the sequestration of POPs and their circulation in blood, and in turn, may affect health outcomes.[8,9]

There is limited evidence regarding the temporal trends in POPs. In the U.S. there are two longitudinal studies of general

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background exposure to PCBs and/or OCPs measured in serum at multiple time points.[10,11] Results are inconsistent. Sjödin and colleagues measured *p,p′*-DDE and 6 PCBs annually from 2009 to 2011 and found a decreasing trend ($p < 0.05$) for PCB 99 in mothers and for PCB 99, 118, 138/158, 153, and 180 in children. Marek and colleagues measured 209 PCBs in 2008/09 and 2009/10 and found that the median concentration of ∑PCBs increased by 6 ng/g of lipid (5th−95th percentile: −115 to 164). Given the persistence and slow elimination of many POPs, with half-lives ranging from days to 30 years or more in the case of DDT metabolites and some PCBs,[12] multiple measurements may be necessary to characterize within-person changes over time. Most cohort studies with repeat serum measurements have focused on historically highly exposed populations, e.g., anglers and residents near contaminated industrial sites, and thus do not reflect background exposure levels of the broader U.S. population.[13−17] Longitudinal studies of longer duration have been conducted elsewhere, all in northern Europe, and found decreasing serum concentrations of OCPs and PCBs since the late 1980s with some OCPs exhibiting more stable trends.[18−20] Cross-sectional studies corroborate these findings and suggest that exposure to OCPs and PCBs will continue to wane in large part thanks to global efforts to ban or reduce production of these chemicals; yet, among older, and thus more highly exposed, individuals, serum concentrations of some PCBs and OCPs have been shown to increase with age.[21] Overall, there is insufficient evidence to support conclusions about intra-individual trends in serum concentrations of POPs and how trends may be influenced by changes in adiposity.

Weight and fat loss are associated with increased serum concentrations of POPs.[11,22−30] However, most studies assessed adults with obesity before and after a weight loss program (e.g., dietary intervention), bariatric surgery, or gastroplasty.[23,26−30] Few studies went further to include control individuals who were not obese and did not undergo weight loss, which would allow for greater discrimination of effects due to weight loss.[24,25] To our knowledge, only two studies represent general, nonobese, nonpatient populations; one was conducted among the elderly in Sweden and the other among children in the U.S.[11,22] Studies are limited by a maximum of two serum POP samples and a lack of representativeness of individuals without obesity.

To better understand the relationship between POPs and adiposity, we must evaluate long-term trends in exposure during a life stage characterized by changes in the body composition. The menopausal transition is widely understood as a time of rapid increases in fat mass and redistribution of adipose tissue.[31] The Study of Women's Health Across the Nation (SWAN) is one of the most carefully phenotyped populations with respect to the timing of the menopausal transition and various heath markers. This study investigated whether changes in waist circumference (WC), a measure of central adiposity, were associated with changes in serum concentrations of POPs among U.S. midlife women in a longitudinal substudy of the SWAN.

METHODS

Study Population

Participants were from the Study of Women's Health Across the Nation (SWAN) Multipollutant Study (MPS), which is ancillary to the larger SWAN. SWAN is fully detailed in a previous study.[32] SWAN is a multisite, multiethnic cohort study launched in 1996 to follow 3,302 premenopausal women between the ages of 42 and 52 through the menopausal transition. By design, women were recruited from seven clinical sites (Oakland, CA; Los Angeles, CA; Chicago, IL; southeast, MI; Pittsburgh, PA; Boston, MA; and Newark, NJ). Each site recruited a White sample and a site-specific sample of Black, Chinese, Hispanic, or Japanese women. Additional eligibility criteria included having an intact uterus and ovary, reporting a menstrual period within the past three months, and not using hormone medications in the last three months. Across a total of 17 follow-up visits from 1996 to the present day, SWAN has collected data on metabolic and reproductive biomarkers and health outcomes, in addition to sociodemographic, lifestyle, and other risk factors. The institutional review board at each participating site approved the study protocol, and all participants provided written, signed informed consent at each study visit.

The SWAN MPS characterizes longitudinal environmental exposure in a subset of SWAN women. The sample design of the SWAN MPS is detailed in Supplemental Figure A.1. Environmental exposure data was collected from biobanked specimens from 1999/2000 at SWAN Visit 3 (V03 or baseline). After further excluding participants with insufficient serum or urine samples, the final MPS study totaled 1,400 women at V03 (1999/2000). A subset of 75 women were analyzed for serum concentrations of POPs at three additional time points for a total of 300 samples across four visits: V03 (1999/2000), Visit 6 (V06, 2002/03), Visit 9 (V09, 2005/06), and Visit 12 (V12, 2009/11). The substudy sampling procedure is detailed in Supplemental Figure A.2. Due to limited resources, three study sites were selected in attempts to best capture racial/ethnic and geographic variations: Boston, MA, southeast MI, and Oakland, CA. To maximize representativeness, we conducted random sampling to attain an equal distribution of women with above-, below-, or at-average WC change (ΔWC) over the study period, after omitting those in the top and bottom 2% of ΔWC. We oversampled certain racial and ethnic groups to attain a composition of 50% White women, 25% Black women, and 25% Chinese women. The substudy is a unique longitudinal cohort designed to assess environmental exposures over time in relation to the changing WC, a proxy for central adiposity. We analyzed POP observations for individuals with a minimum of two time points that met POP quality assurance criteria. Consequently, PCB data were available for 65 women for a total of 181 observations, and the OCP data were available for 59 women for a total of 151 observations.

POP Measurements

Serum concentrations of PBDEs, PCBs, and OCPs were measured using fasting blood samples collected from the 75 women in the SWAN MPS substudy at V03 (1999/2000), V06 (2002/03), V09 (2005/06), and V12 (2009/11). PCB, PBDEs, and OCPs are major types of POPs; they are all lipophilic and are often measured together in serum. The SWAN MPS identified PBDEs as a focus of its research because they are less studied relative to PCBs and OCPs. Serum samples were processed by the Organic Chemistry Lab in the Department of Environmental Health Sciences at the University of Michigan, Ann Arbor, Michigan, USA, for 34 PCBs, 14 PBDEs, and 19 OCPs including DDT metabolites, chlordanes, and hexachlorobenzene (HCB) (see Supplemental Table A.1 for the complete list). Typically, the more chlorinated PCB homologues are more persistent,[1] whereas PBDE congeners with higher numbers reflect lower bromination and lesser persistence.[33]

Target analyte concentrations (ng/g of sample) were measured by gas chromatography−mass spectrometry (GC/MS) using the following procedures. Two vials of serum, nominally slightly over 0.5 mL each, were withdrawn from the SWAN repository. The samples had been previously stored at −80 °C for 8−20 years after sample collection. Given the stability of the analytes at this temperature, loss of sample integrity was not expected to be an issue. The two samples were combined to obtain a larger volume desired for analysis, weighed, and spiked with surrogate standards $^{13}C_{12}$-PCB-208 and $^{-13}C_{12}$-BDE-139 prepared at 10 ng/mL, and 1 mL of 6 M hydrochloric acid was added. Liquid−liquid extractions used

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sequential additions of 6 mL of methanol−isopropanol (1:1), 6 mL of hexane/methyl t-butyl ether (1:1), and 3 mL of hexane/MTBE to the sample, followed by cleanup using a column packed with 0.1 g of silica (top layer) and 1 g of silica (lower layer). The column was eluted with hexane/DCM (8 mL, 1:1 v/v) and concentrated to 0.5 mL under nitrogen flow, dissolved with 0.5 mL of *n*-nonane, evaporated to 0.25 mL, and transferred to a conical insert placed in a GC-vial. The cleaned extracts were spiked with 15 μL of an internal standard containing 11 OCPs, 10 BDEs, and 21 PCBs, all labeled compounds at a concentration of 7.5 ng/mL, then the vial sealed and placed into the autosampler for analysis. Surrogate and internal standards were from Cambridge Isotope Laboratories (Andover, MA, USA). Analytes were identified and quantified by GC/MS (5890/5973, Agilent Industries, Palo Alto, CA, USA) using 2 μL of splitless injections, a capillary DB-5MS column (30 m length, 0.25 mm ID, 0.25 μm film thickness, J&W Scientific, Folsom, CA, USA), negative chemical ionization, the two most abundant ions, and separate runs for OCPs, BDEs, and PCBs with GC temperature programs optimized to separate compounds. Calibrations used authentic standards that spanned the expected concentration range of the target analytes. If individual peaks could not be identified (several PCBs fell into crowded windows), a mixture was reported and not used in the analysis.

Quality control/quality assurance measures performed in each analytical sequence included the use of ^{13}C labeled internal and surrogate standards, blank checks, drift checks, recovery checks, and performance checks using a standard reference material (SRM 1957 "Organic contaminants in non-fortified human serum", NIST, Gaithersburg, MD, USA). Acceptance criteria for drift checks were variation less than 10% and $r^2 > 0.999$ for linearity. Spike recoveries ranged from 88−95%. PCB surrogate recoveries ranged from 76% to 103%. Method detection limits (MDLs), based on 7 replicate low concentration measurements, ranged from 0.0062 to 0.092, 0.0041 to 0.513, and 0.072 to 0.462 ng/mL for OCPs, PCBS, and PBDEs, respectively.

POPs congeners detected in at least 70% of the samples at all four visits and were included in analyses of individual congeners. Concentrations below the MDL were replaced with $MDL/\sqrt{2}$. PBDEs were not included due to their low detection frequencies. PBDEs with relatively high detection frequencies (20−50%) were PBDE 47, 153, and 154. Detection frequencies for OCPs, PCBs, and PBDEs are presented in Supplemental Table A.1.

Lipid-standardized POP concentrations are preferable to wet weight concentrations because POPs are lipophilic, circulate bound to serum lipids, and distribute in the body mainly according to a tissue's lipid content.[34,35] Serum lipids including total cholesterol and triglycerides for lipid standardization of POP concentrations were measured by enzymatic methods using a Hitachi 747-200 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). The total lipid concentration was imputed using linear regression to replace missing observations of total cholesterol (n = 1) and triglycerides (n = 10). Supplemental Figure A.3 illustrates the relationships among adipose tissue, serum lipids, and serum POPs.

Standardizing serum POP concentrations by serum lipid levels has been the most common method employed in studies of serum POPs. We compared two methods of lipid standardization: traditional standardization (Method 1) and covariate-adjusted standardization (Method 2).[36] Method 1 eliminates the influence of recent fat intake on serum lipids and facilitates comparisons of exposure between individuals. O'Brien and colleagues recommended traditional standardization in addition to model adjustment for serum lipids when serum POPs are the exposure of interest. However, in our study, it is the outcome. Serum lipid levels are affected by the gain or loss of adipose tissue, which is our exposure of interest. Method 2 allows for between-person variation in adiposity-based serum lipids due to participant characteristics. Method 2 is preferred over Method 1 because standardizing serum POPs with serum lipids may lead to a spurious association between adipose tissue loss and gain and lipid-standardized serum POP levels. We further compared Methods 1[37] and 2, shown below, to models of wet weight serum POPs (Method 3).

Method 1:

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

$$OTL = (2.27 \times TC) + TG + 62.3$$

Method 2:

$$AS = C/(OTL/FTL)$$

where S is the lipid-standardized serum POP concentration (ng/g lipid); C is the wet weight serum POP concentration (ng/g); OTL is the observed total lipid concentration (mg/dL); TC is total cholesterol (mg/dL); TG is triglycerides (mg/dL); AS is the covariate-adjusted standardized serum POP concentration (ng/g); and FTL is the fitted concentration of total lipids (ng). A linear mixed model was used to calculate the natural-log-transformed FTL adjusting for WC, age, study site, and race and ethnicity with a random effect for each woman.

Our outcome of primary interest is the proportional change in the POP concentration between visits (ΔPOP) using the natural log transformation to normalize the distributions. As shown below,

$$\Delta \ln POP = \ln(POP_{v+1}/POP_v)$$

where POP_v is the POP concentration (ng/g lipid) at visit v and POP_{v+1} is the POP concentration at the next available time point.

Waist Circumference (WC)

WC is a marker of central (visceral) adiposity assessed at each study visit by a trained technician. WC was measured to the nearest 0.1 cm at the narrowest part of the torso. We converted the units from centimeters to inches to aid interpretation. ΔWC between visits was calculated.

Covariates

Potential confounders of the relationship between ΔPOP and ΔWC were selected a priori and included age at baseline (1999/2000), study site, race and ethnicity, and parity. Age is important given that bans and phase-outs of many POPs have increased the likelihood that older women have a greater body burden.[18,38] Study sites included Oakland, CA, Boston, MA, and southeast MI. Race and ethnicity included Black, Chinese, and White. Race is not used as a proxy for biological or genetic differences yet is included because it is implicit in systems, policies, and institutions that shape individuals' environments and experiences. Study site and race and ethnicity can influence lifestyle and access to resources (i.e., diet, built environment) that affect both POPs exposure and WC. Furthermore, historical contamination differs by site.[39] Differences in lifestyle, resources, and past contamination may result from structural racism (institutional or systemic 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."[40] Parity is also important to consider because breastfeeding is an elimination route of POPs,[41] and parity may be associated with adiposity changes later in life.[42,43] Parity was defined as nulliparous or parous based on live births and stillbirths. Uniform protocols were used to collect covariate data across the study sites.

Statistical Analysis

The distributions of 34 PCB congeners and 19 OCPs were characterized by using the median and interquartile range (IQR). We reported concentrations using traditional lipid-standardization to facilitate comparison with previous studies. An intraclass correlation coefficient (ICC) was calculated to assess how much temporal variability in serum POP measurements exists between subjects. A high ICC indicates that the intersubject variability exceeds within-subject variability. We examined time-dependent and time-independent participant characteristics. *t* tests and ANOVAs were performed to analyze the WC and serum POP concentrations by participant characteristics.

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Linear mixed models were constructed with random intercepts for each participant to examine the association between a change in WC and a change in serum POP concentrations. We fit a crude model of ΔPOP that included ΔWC and the visit (V03 serving as the reference) to capture time trends and other visit effects. Serum concentrations of POPs were transformed by using the natural log to approximate a normal distribution. In the final model, we adjusted for age at baseline, race and ethnicity, study site, parity, and number of visits elapsed between observations.

As a sensitivity analysis, we assessed the impact of additional adjustment for the serum concentration of POPs at the first available time point.

We compared models using traditional POP lipid-standardization with those using wet weight concentrations and covariate-adjusted standardization. Ultimately, we used covariate-adjusted standardization in crude and adjusted models, as shown below,

$$\Delta\ln(POP)_{ij} = \beta_0 + \beta_1\Delta WC + \beta_2 V06_i + \beta_3 V09_i + \beta_4 V12_i + \beta_5 Chinese_i + \beta_6 White_i + \beta_7 Parous_i + \beta_8 Oakland_i + \beta_9 Michigan_i + \beta_{10} Age_i + \beta_{11} T_i + b_{0j} + \varepsilon_{ij}$$

where $\Delta\ln(POP)_{ij}$ is the proportional change in POP concentration between visits (ng/g) for the *ith* subject with the *jth* observation; ΔWC is the change in WC (inches) between visits; $V06$ is 2002/03, $V09$ is 2005/06, and $V12$ is 2009/11; Age is age at baseline (years); and T is the number of visits elapsed between observations. Statistical analyses were conducted using Rstudio (2022.12.0.353), Integrated Development Environment for R, Posit Software, PBC, Boston, MA.

RESULTS

Participant Characteristics

The characteristics of SWAN women at baseline (or first available time point, in the case of sociodemographic characteristics) are presented in Table 1. Characteristics vary slightly depending on the POP type (and therefore sample) for which data is available at two or more time points. The median age at baseline was 49 years (IQR: 47−50). Most women were from Oakland, CA, followed by Boston, MA. In terms of race and ethnicity, approximately half were White women. Black and White women were recruited from Boston, MA, and southeast MI whereas Chinese and White women were recruited from Oakland, CA. The median WC at baseline was approximately 32 in. (81.28 cm) (IQR: 30−37). Few women (17%) were nulliparous.

Table 1. Characteristics of Participants in the SWAN MPS Longitudinal Substudy (N = 65 for PCBs; N = 59 for the OCPs)[a]

	PCBs (N = 65)	OCPs (N = 59)
Study Site		
Boston, MA	19 (29%)	18 (31%)
Oakland, CA	31 (48%)	28 (47%)
SE Michigan	15 (23%)	13 (22%)
Race and Ethnicity		
Black	15 (23%)	13 (22%)
Chinese	17 (26%)	16 (27%)
White	33 (51%)	30 (51%)
Age at baseline (yr)	49 (47−50)	49 (47−50)
Waist Circumference at Baseline (in)	32.56 (30.31−37.40)	32.32 (30.24−37.42)
Parous (Y/N)	54 (83%)	49 (83%)

[a]Note: Characteristics at baseline or the first available visit for women with at least two observations of serum POPs. Median (IQR: 25th−75th percentile) or Frequency (%).

The ΔWC between visits is reported in Table 2. Among women with available PCB data, the average ΔWC was positive between time points up to Visit 9 and negative for intervals that included Visit 12. For example, the mean ΔWC was 0.52 in. (1.32 cm) (range: −2.48, 5.39) from Visit 3 to 6 and −0.77 in. (−1.96 cm) (range: −4.65, 3.35) from Visit 9 to 12. Among women with available OCP data, the average ΔWC showed similar trends. The sample size and composition of the OCP and PCB subgroups differed slightly.

Longitudinal Trends of Serum POPs Concentrations 1999−2011

Serum concentrations of POPs across follow-up visits are displayed in Table 3 for compounds with detection frequencies >70%. PCBs were detected at the highest frequencies with many congeners detected in all samples across the four visits. For OCPs, only trans-chlordane, *p,p′*-DDE, and *p,p′*-DDD were detected at frequencies greater than 70% across all visits. Detection frequencies for all compounds are presented in Supplemental Table A.1.

Median concentrations of POPs were relatively stable over the four time points. Across most congeners, the median concentrations of OCPs and PCBs increased from visit 3 to 6, decreased from visit 6 to 9, and then increased slightly from visit 9 to 12. This trend must be interpreted carefully because many women do not have POP observations at all time points. Intraclass correlation coefficients were low (range: 0.01−0.32), indicating low similarity and highly variable concentrations for a woman over time.

Changes in Waist Circumference and Serum POPs

After adjusting for confounding factors, a 1 in. (2.54 cm) increase in the difference in WC between visits was associated with a 4.9% decrease in the difference in a serum concentration of PCB 194 (95% CI: −8.0%, −1.6%) (see Figure 1). No associations were observed for other PCB congeners, all of which have a lower degree of lipid solubility,[44−46] or for the OCPs (*p,p′*-DDE, *p,p′*-DDD, or trans-chlordane). Similar findings were observed in unadjusted models [Supplemental Table A.3]. We compared our results using the three approaches to calculating serum POPs concentrations: wet weight (ng/g serum), traditional lipid-standardization (ng/g lipid), and covariate-adjusted lipid-standardization (unitless) [Supplemental Table A.4]. The effect estimate for PCB 194 was smallest when using wet weight POP concentrations [−4.0% (95% CI: −7.2%, −0.58%)], whereas it was largest when using traditional lipid-standardization [−5.5% (95% CI: −8.6%, −2.3%)]. Regardless of the standardization method, our conclusions for PCBs and OCPs remain unchanged. Furthermore, additional adjustment for first-available POP concentration did not impact associations in any consistent direction [Supplemental Table A.5]; although the inverse association detected for PCB 194 was attenuated slightly, it remained statistically significant, which affirmed our original conclusions.

DISCUSSION

This study contributes valuable information about changes in circulating concentrations of POPs in women as they undergo changes in adiposity throughout the midlife. Fluctuations in WC detected across the four study visits (1999−2011)

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Table 2. Average and Range of Waist Circumference Change (inches) between Visits in the SWAN MPS (N = 181 for PCBs; N = 151 for OCPs)[a]

	Visit 3 (1999/2000)−Visit 6 (2002/03)	Visit 6 (2002/03)−Visit 9 (2005/06)	Visit 9 (2005/06)−Visit 12 (2009/11)	Visit 3 (1999/2000)−Visit 9 (2005/06)	Visit 3 (1999/2000)−Visit 12 (2009/11)	Visit 6 (2002/03)−Visit 12 (2009/11)
PCB Group	N = 26	N = 24	N = 35	N = 18	N = 4	N = 9
	0.52 (−2.48, 5.39)	0.49 (−3.27, 4.72)	−0.77 (−4.65, 3.35)	1.38 (−4.92, 8.15)	−0.61 (−5.31, 4.09)	−2.12 (−7.83, 1.50)
OCP Group	N = 17	N = 15	N = 25	N = 19	N = 4	N = 12
	0.58 (−2.24, 5.39)	0.54 (−3.27, 4.72)	−0.49 (−4.65, 3.35)	1.80 (−4.92, 8.15)	−2.27 (−5.31, 3.50)	−1.98 (−7.83, 1.50)

[a]Note: Included women with at least two observations of serum POPs. Mean (Range). One inch = 2.54 cm.

reinforce our decision to leverage repeat measures available at all visits as opposed to an overall trend.

Changes in Waist Circumference and Serum POPs

Overall, an increase in ΔWC was associated with a diminished change in the serum concentration of PCB 194. No statistically significant relationship was detected for other PCBs and OCPs. Previous epidemiological studies suggest that adipose tissue is a reservoir for POPs which when gained or lost may sequester or release POPs, respectively.[11,22−25,29]

Lipid solubility may explain why associations were seen for PCB 194 and not for other congeners. POPs with higher degrees of lipophilicity, or chlorination in the case of PCBs, have had stronger inverse associations with adipose tissue gain.[23,24,47] Of the POPs present in this analysis, PCB 194 has the highest lipid solubility (logK_{ow} of 7.80, Table 3).[44] POPs may be stored preferentially in visceral, compared to subcutaneous, adipose tissue which means that weight loss may prompt larger releases of POPs from visceral fat compartments and subsequent distribution patterns may depend on lipophilicity.[26,48] Animal studies highlight the importance of this research, demonstrating that fat loss leads to elevated POP concentrations in blood and lipid-rich tissue like the brain and liver, which can have toxic effects.[48,49]

Our analyses utilized several modeling strategies, including traditional lipid-standardized (Method 1), covariate-adjusted standardized (Method 2), and wet weight POPs (Method 3). When comparing results for these different approaches, we found that associations for some higher-chlorinated PCBs were strongest and closest to reaching statistical significance when using Method 1 and weakest when using wet weight concentrations (Supplemental Table A.4). This may suggest that serum lipids suppress the true effect of change in WC and that failure to account for predictors of serum lipids may overestimate the true effect. On the other hand, it is possible that using covariate-adjusted lipid standardized serum POP concentrations may have led to model overadjustment. Methods 2 and 3 do not account for within-subject variation; however, the use of fasting serum samples may sufficiently reduce measurement error due to recent dietary fat intake. Although none of these approaches fully addressed these issues, our findings were consistent regardless of modeling techniques.

Our findings also suggest that midlife women exhibited a large within-person variability of serum POP concentrations between 1999 and 2011. This observation aligns in part with a previous finding of wide intraperson variation in serum PCBs and metabolites.[10] Other longitudinal studies did not report intraperson correlation.[11,22] Our findings suggest the importance of characterizing intraperson variation of serum POPs, particularly in light of changes in potential predictors of variability such as gain/loss of adipose tissue, which is rapid and common during certain life stages. Understanding intraperson variation is required to more accurately quantify POP exposure to evaluate the temporal association between POP exposure and onset of disease.

Two longitudinal studies have investigated the relationship between weight loss and serum POPs in general nonobese, nonpatient populations such as ours.[11,22] Sjödin and colleagues found that among children ages 7 to 9, a one-kilogram increase in body weight was associated with a decrease in serum PCB concentrations ranging from −0.5% to −0.7%, depending on the congener, and a 2.4% decrease in serum p,p'-DDE concentrations. Stubleski and colleagues conducted a study similar to ours, assessing the relationship between the percent change in weight and the percent change in serum POP concentrations. Increases and decreases in weight change of 1% were associated with a smaller change in the serum concentration of 14 PCBs, HCB, and trans-nonachlor among Swedish men and women from age 70 to 75. The strongest association was between a 1% difference in weight change and PCB 194 (β = −4.9, SE = 2.0, p = 0.016), which supports our finding. The inverse relationship between weight change and change in serum POPs could be explained by adiposity loss increasing serum POPs, followed by metabolism and excretion of POPs, which decrease serum levels, somewhat offsetting the prior increase.[50] Due to these counteracting processes, people who lose adiposity may experience a smaller reduction in serum POP levels than people who gain or maintain adiposity.[22]

Losing weight or fat mass has been associated with increased serum concentrations of POPs in several studies before and after weight loss regimens or surgery.[23−25,27,29] One study found increased serum OCPs but not PCBs,[28] and two studies suggested that the magnitude of the increase may differ by sex.[23,28] Weight loss studies of women observed increased serum p,p'-DDE, HCB, and PCBs, with PCB 153 displaying the greatest increase.[26,30] Increases in serum PCBs may be more pronounced in women who lose more visceral than subcutaneous fat.[26] The present study specifically investigated visceral (central) adiposity for this reason.

Our results have some inconsistencies with the literature. PCB 138, PCB 153, and p,p'-DDE were relatively abundant in this and previous studies; yet, unlike prior studies, we did not find inverse associations between serum concentrations of these compounds and ΔWC. Our finding for PCB 194 is consistent with the literature. However, caution must be taken when comparing previous findings with ours. We analyzed differences in the between-visit changes of both outcome and predictor, whereas most studies analyzed differences in a continuous outcome before and after weight loss. Additionally, a one-inch (2.54 cm) increase in ΔWC is much smaller than the ΔWC following weight loss interventions in previous studies: 15 cm[27] and 32.4 cm[23] in women after 12 months. This distinction may have limited the impact of the adiposity

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Table 3. Median (IQR) Serum POP Concentrations (ng/g lipid) in the SWAN MPS (N = 181 for PCBs; N = 151 for OCPs)[a]

	Visit 3 (1999/2000), N = 40		Visit 6 (2002/03), N = 31		Visit 9 (2005/06), N = 39		Visit 12 (2009/11), N = 41	
OCPs	DF (%)	ng/g lipid	DF (%)	ng/g lipid	DF (%)	ng/g lipid	DF (%)	ng/g lipid
p,p′-DDD	92.9	44.40 (12.76, 116.33)	100	65.57 (20.46, 120.57)	90.7	58.83 (15.20, 140.49)	93.0	39.67 (13.75, 120.22)
p,p′-DDE	90.5	54.15 (23.37, 85.80)	91.4	50.72 (23.32, 133.25)	83.7	32.70 (13.38, 103.59)	88.4	62.73 (24.61, 114.78)
trans-chlordane	88.1	5.30 (1.71, 9.32)	94.3	4.78 (2.43, 11.07)	81.4	4.88 (1.46, 6.66)	86.1	5.15 (2.37, 10.94)
	Visit 3 (1999/2000), N = 48		Visit 6 (2002/03), N = 37		Visit 9 (2005/06), N = 48		Visit 12 (2009/11), N = 48	
PCBs	DF (%)	ng/g lipid	DF (%)	ng/g lipid	DF (%)	ng/g lipid	DF (%)	ng/g lipid
PCB 79	100	460.10 (199.68, 1,215.12)	100	665.70 (173.61, 1,458.56)	100	289.48 (152.47, 896.86)	100	650.48 (188.44, 1,393.93)
PCB 105	88.0	43.53 (17.26, 88.61)	84.6	44.61 (15.91, 114.55)	74.0	26.70 (6.14, 67.30)	82.0	41.96 (11.19, 88.27)
PCB 118	100	424.14 (337.77, 544.01)	100	410.51 (298.22, 620.63)	100	346.64 (281.34, 485.88)	100	409.71 (265.68, 610.37)
PCB 123	100	59.66 (43.07, 83.89)	97.4	53.52 (39.94, 65.92)	96.0	47.43 (37.52, 74.40)	98.0	60.01 (41.16, 87.90)
PCB 138	100	533.52 (429.75, 706.37)	100	524.23 (403.09, 813.69)	100	435.41 (346.67, 562.35)	100	539.50 (339.58, 841.59)
PCB 153	100	160.58 (106.26, 232.52)	100	176.17 (103.59, 323.93)	94.0	122.87 (85.81, 217.67)	90.0	157.55 (83.29, 252.38)
PCB 156	100	19.42 (15.52, 24.35)	100	20.42 (15.02, 30.67)	100	15.71 (13.27, 20.86)	100	19.26 (13.22, 25.72)
PCB 157	96.0	4.15 (3.05, 5.52)	100	4.77 (3.12, 6.19)	94.0	3.64 (2.54, 5.08)	88.0	3.98 (2.72, 4.96)
PCB 167	100	9.30 (7.48, 11.74)	100	9.58 (7.42, 13.14)	100	7.52 (6.10, 10.97)	100	9.03 (6.38, 13.17)
PCB 170	100	26.61 (21.90, 35.43)	100	28.84 (24.02, 39.97)	100	23.03 (17.62, 29.55)	100	26.52 (18.56, 35.77)
PCB 174	100	31.06 (24.60, 42.31)	100	30.56 (23.30, 47.83)	100	25.14 (21.38, 33.52)	98.0	27.33 (20.09, 45.96)
PCB 178	100	9.49 (7.30, 12.24)	100	9.06 (7.42, 13.02)	98.0	7.36 (6.30, 11.08)	100	8.34 (6.48, 12.10)
PCB 180	100	54.14 (46.07, 68.60)	100	56.94 (44.87, 74.82)	100	46.61 (34.94, 63.54)	100	51.08 (37.67, 73.21)
PCB 187	100	48.21 (40.75, 63.50)	100	51.86 (38.36, 72.67)	100	40.18 (33.70, 57.89)	100	50.07 (34.99, 68.66)
PCB 194	98.0	6.36 (5.13, 9.00)	97.4	6.67 (5.10, 9.86)	92.0	5.80 (4.54, 7.69)	90.0	6.06 (4.68, 8.31)
PCB 199	90.0	10.64 (8.55, 13.29)	92.3	11.18 (8.61, 15.05)	82.0	8.81 (6.75, 11.55)	86.0	10.00 (7.49, 12.79)
PCB 202	100	10.16 (7.99, 12.16)	92.3	9.10 (7.21, 15.64)	92.0	8.14 (6.75, 11.60)	90.0	9.43 (5.99, 12.79)

[a]Note: DF = detection frequency, which is based on substudy women with POP observations that met quality assurance criteria.

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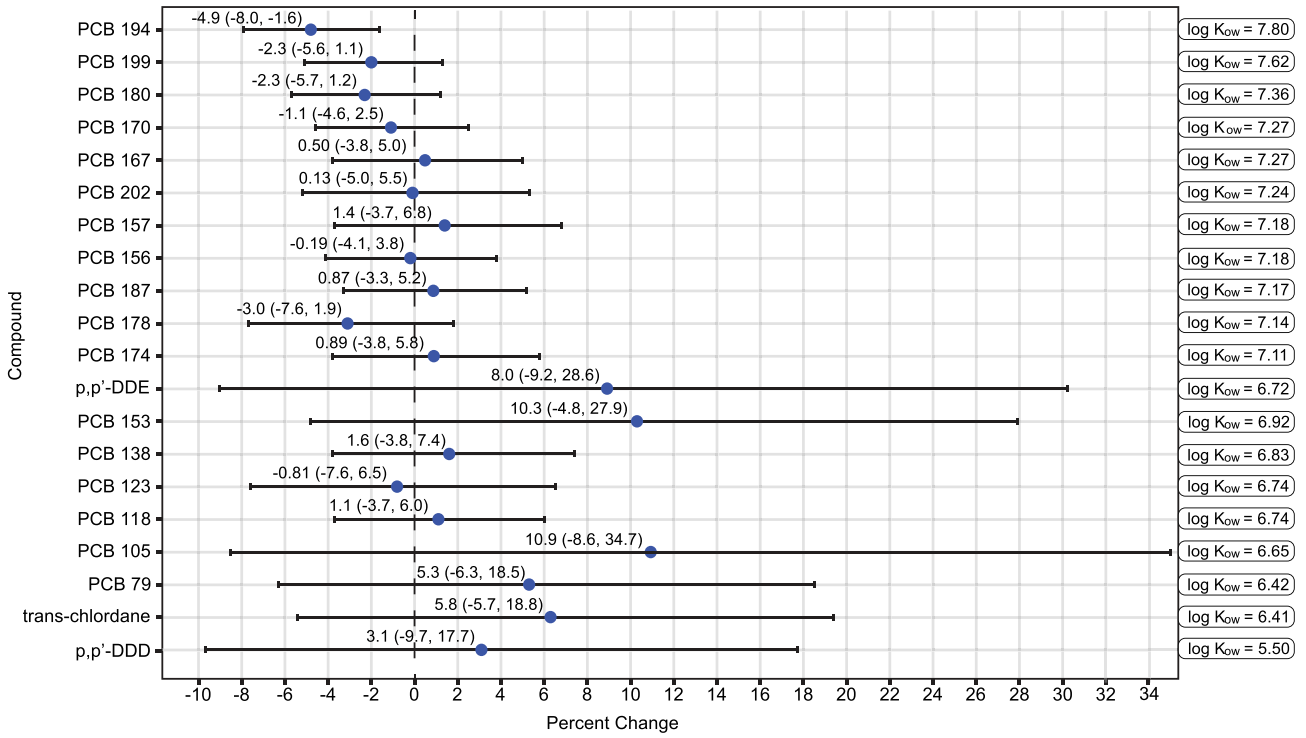

Figure 1. Percent change (95% CI) in the difference in covariate-adjusted lipid-standardized POP concentration associated with a one-inch increase in the difference in waist circumference in the SWAN MPS longitudinal substudy (N = 181 for PCBs; N = 151 for OCPs). Models were adjusted for race and ethnicity, age at baseline, parity, study site, visit, and number of visits elapsed between observations. K_{ow} is the octanol/water partition coefficient, which represents the degree of lipid solubility. All PCB log K_{ow} values are from IARC (2018).[44] Log K_{ow} values for p,p'-DDE and p,p'-DDD are from Han et al. (2011).[45] Log K_{ow} values for trans-chlordane are from Ellington and Stancil (1988).[46]

change on circulating POP concentrations. Our community-based population may also differ from the women (and men) with obesity who participate in weight loss programs or undergo surgery. This matters because the effects of adiposity loss on serum POP concentrations may differ from the effects of adiposity gain.

Less evidence is available for nonobese, nonpatient populations, although such studies drew a similar conclusion that natural weight gain is associated with decreased serum POP concentrations.[11,22] However, in contrast to our study, they identified significant effects for more congeners. For example, Sjodin and colleagues found that a one-kilogram increase in body weight was associated with decreases in serum concentrations of PCB 118, 138, 153, and 180 yet was associated with a 2.4% increase in the concentration of p,p'-DDE.[11] They attributed the large effect for p,p'-DDE to higher exposure due to the more recent phasing out of DDT in Mexico, the country of origin for many study participants. Also faced with inconsistency, Stubleski and colleagues found significant associations for many POPs except p,p'-DDE, which they attributed to the possibility that individual POPs respond differently to physiological changes.[22] It is important to note that the percent decreases detected by Sjodin and colleagues was very small (less than 1%) and that their study population (children ages seven to nine) is undergoing physiological changes very differently than midlife women. Nevertheless, it is possible that our finding of significance for only a single congener was due to random chance.

Strengths and Limitations

A study strength is the repeated measurement of serum POPs which allow us to investigate intraindividual changes in exposure over 12 years. In terms of assessing changing adiposity, 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.[26] Our models were made more robust by our careful consideration of the role of serum lipids; we compared three treatments of serum POPs using wet weight concentrations, traditional lipid-standardization, and covariate-adjusted standardization.[36] Another strength is the representation of women from multiple urban areas across the U.S. and a focus on Chinese women, who have been historically underrepresented in U.S. studies. The study leverages SWAN's original design to characterize changes throughout the menopausal transition, which include changes in adiposity. As our data suggest, one measurement of serum POPs may not be sufficient to characterize an individual's exposure, especially if adipose tissue serves as a time-varying internal source of POPs exposure.

This study is limited by its small sample. A larger sample size would enable the power necessary to perform analyses stratified by key mechanistic factors, e.g., menopausal status, obesity status, or metabolic dysfunction. In addition, the study design decision to exclude women in the top and bottom 2% of WC change could have biased results toward the null and may have reduced the generalizability of our findings. We considered adjusting for the consumption of animal-based, high-fat foods but decided not to include these dietary variables in our final models because doing so reduced the sample size by 11%, eliminating 7 participants and a total of 22 PCB observations and 18 OCP observations. Future studies should account for potential impacts of the diet. Our oversampling of Black and Chinese women expanded our

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understanding of these issues in a more diverse population, yet may not be representative of the U.S. population. A larger sample size would allow investigations of interactions between the site and race and ethnicity. Our results may not be generalizable to all SWAN women because the 75 substudy women resided in only three of seven study locations and were required to meet additional eligibility criteria. To better understand whether associations differ by race, ethnicity, or geographic location, future studies should strive to include a larger sample that reflects the diversity of the U.S. population. Finally, we did not assess the potential impact of unmeasured confounders.

CONCLUSION

In summary, among U.S. midlife women between 1999 and 2011, an increase in the ΔWC over time was not associated with a decrease in the change in serum concentrations of PCBs or OCPs with the exception of PCB 194. Future research should engage a larger study population with POPs measured at multiple time points to better understand trends within and between individuals. Last, studies should evaluate potential racial/ethnic and place-based disparities in the relationship between changes in adipose tissue and serum POPs.

ASSOCIATED CONTENT

Data Availability Statement

SWAN provides access to public use data sets 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 data sets. A link to the public use data sets is also located on the SWAN Web site: http://www.swanstudy.org/swan-research/data-access/. Investigators who require assistance accessing the public use data set may contact the SWAN Coordinating Center at the following email address: swanaccess@edc.pitt.edu.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.3c00159.

Additional Supporting Information, including the study design details, the detection frequencies and the availability of POP measures, and sensitivity analysis results (PDF)

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Author Contributions

Amelia Grant-Alfieri was responsible for data cleaning and analysis, interpretation of results, and writing−original draft, revisions, and editing. Amila Devasurendra was responsible for the measurement of POPs in serum and provided feedback on the manuscript. 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.

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Notes

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the U.S. Department of Health and Human Services.. The institutional review board at each participating study site

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