Received: 23 January 2024 | Revised: 23 February 2025 | Accepted: 28 February 2025

DOI: 10.1002/oby.24284

ORIGINAL ARTICLE

Epidemiology/Genetics

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

Grandmaternal perinatal serum polychlorinated biphenyls and prevalence of obesity in adult daughters and granddaughters

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Funding information
National Institute of Child Health and Human Development, Grant/Award Number: HHSN275201100020C; California Breast Cancer Research, Grant/Award Numbers: 15ZB-0186, 22UB-5411; National Institute of Environmental Health Sciences, Grant/Award Numbers: R00 ES019919, R01ES01376, R01ES017024, U01 ES019471

Abstract

Objective: We investigated in utero exposure to polychlorinated biphenyl (PCB) 138, PCB 153, and PCB 180 and obesity at reproductive age in a three-generation human cohort, i.e., the Child Health and Development Studies.

Methods: We used logistic models to estimate associations of PCBs in grandmothers' (F0) archived perinatal serum with obesity in daughters (F1) at age 30 years and granddaughters (F2) at age 26 years, accounting for family clustering ($n = 258$ triads). In order to reflect mixture exposures, we modeled PCBs as a ratio of the sum of PCB 138 + PCB 180 to PCB 153 (i.e., "PCB ratio").

Results: An increase in the PCB ratio from the first to the third tertile corresponded to a 1.73 (95% CI: 1.06–2.82) increase in the odds of F1 obesity and a 1.96 (95% CI: 1.12–3.42) increase in the odds of F2 obesity. The association with F2 obesity differed by F0 BMI (p value for interaction = 0.08). F1 obesity was also associated with F2 obesity (odds ratio, 4.12, 95% CI: 1.95–8.72).

Conclusions: Grandmothers' perinatal serum levels of mixtures of PCBs may have triggered a multigenerational cycle of obesity in daughters and granddaughters. Resultant obesity among women of reproductive age could further perpetuate obesity in subsequent generations.

INTRODUCTION

Environmental obesogens, i.e., pollutants that contribute to the rise of obesity worldwide, were proposed in 2002 [1] following reports of pharmaceutical obesogens [2]. Reviews have documented this field [3–5]. A lack of multigenerational human studies, beginning in utero, has limited public health response [6].

Ubiquitous, persistent industrial pollutants, i.e., polychlorinated biphenyls (PCBs), are obesogens in experimental studies [7]. There are more than 200 PCB congeners that are often intercorrelated, creating a significant challenge in assessing health risks of individual congeners [8]. PCB 138, PCB 153, and PCB 180 increase the amount of lipids stored in adipocytes through distinct, independent mechanisms in experimental studies and may act together as obesogens in humans [9]. Yu and colleagues [9] reported that PCB 180 increases the proliferation and differentiation of preadipocytes in murine and human cell lines via mechanisms distinct from those previously observed with PCB 138 [10] and PCB 153 [11]. These three PCBs are persistent pollutants stored in fat of animals and humans at high concentration (information available at the following link: https://www.epa.gov/pcbs/learn-about-polychlorinated-biphenyls-pcbs) and are among those monitored in human blood samples in the United States;

as late as 2001 to 2004, they were detected in 71% of women of childbearing age (information available at the following link: https://www.epa.gov/sites/default/files/2015-05/documents/biomonitoring-pcbs.pdf). However, PCB levels in humans have been declining in the United States following a ban on their manufacture and use in 1979 [12], such that exposures to women in the 1960s are much higher than current exposures.

In the present three-generation human study, we tested the following two hypotheses: 1) Serum levels of mixtures of PCB 138, PCB 153, and PCB 180 during grandmothers' (F0) pregnancy expose daughters (F1) as embryos and granddaughters (F2) as ova, directly increasing risk of developing obesity at reproductive age in both generations; 2) Resultant F1 obesity at reproductive age further sustains transmission of risk of developing obesity to F2 (Figure 1). These hypotheses are grounded by evidence from experimental studies of developmental obesogens, including obesity itself, which can induce adult obesity phenotypes in multiple subsequent generations via epigenetic alterations [13]. Human pregnancy cohorts with necessary decades-long follow-up of multiple generations are rare. We address this gap using data uniquely available from the Child Health and Development Studies (CHDS), a multigenerational pregnancy cohort. Herein, we describe the relationship of exposure to PCBs measured in F0 perinatal serum to risk of developing obesity in F1 and F2 at reproductive age.

Study Importance

What is already known?

- Noncoplanar polychlorinated biphenyl (PCB) 138, PCB 153, and PCB 180 independently increase lipids stored in adipocytes through distinct mechanisms, and their enzyme induction profiles, nuclear receptor activation, and signaling pathways are congener-specific.
- Fetal life is a window of susceptibility to environmental obesogens, with consequences for obesity over the life course.

What does this study add?

- Relative amounts of PCB 138, PCB 153, and PCB 180 in grandmaternal perinatal serum associated prospectively and independently with obesity in daughters and granddaughters of reproductive age.
- Grandmaternal and maternal obesity also independently associated with obesity in daughters and granddaughters of reproductive age.
- Susceptibility of the developing fetus to environmental obesogens and a cycle of subsequent maternal obesity could explain and perpetuate increasing prevalence of obesity.

How might these results change the direction of research or the focus of clinical practice?

- Discovery of mechanisms and actionable biomarkers of grandmaternal and maternal transmission of obesity risk across generations could lead to prevention opportunities.
- Women of reproductive age are a critical target population for reducing exposure to suspected obesogens and may benefit from precautionary counseling, even when human data are lacking. Support for clinician education will be essential to implement this strategy.

METHODS

Study population

The CHDS is a population-based, multigenerational cohort with more than 60 years of follow-up [14]. Nearly all (98%) women seeking obstetric care at the Kaiser Foundation Health Plan in the San Francisco East Bay Area in California enrolled between 1959 and 1967 [14]. Women completed in-person interviews at enrollment during early pregnancy, provided permission to access medical records for themselves and their children, and gave blood samples at each trimester and in the near postpartum period, generally within 3 days of delivery. Archived serum samples drawn during pregnancy and the postpartum period from grandmothers (F0) make it possible to examine associations of environmental obesogens with health in three generations: the grandmother generation exposed during pregnancy (F0), the daughter generation exposed in utero (F1), and the granddaughter generation exposed in ovum (F2). The timing of pregnancies in the early 1960s coincides with high use of legacy pesticides and industrial chemicals (e.g., dichlorodiphenyltrichloroethane [DDT], PCBs) [15, 16]. F0 are now mostly in their 80s, F1 are mostly in their 60s, and F2 are mostly in their late 20s and early 30s. Thus, the CHDS offers a unique opportunity to test the relationship of ancestral exposures to the health of current human populations.

The present study is based on F1 and F2 participating in the Three Generations of Breast Cancer (3Gs) Study, conducted from 2010 to 2013 [17–19]. Daughters (F1) born into the CHDS who were surviving at the time of study recruitment and were phone locatable were eligible to participate in the telephone interview phase of the study ($n = 5003$). F1 known to be incarcerated or institutionalized, have a severe mental illness, have requested "not to be contacted," and/or be eligible for follow-up studies already in progress were excluded from eligibility. Sixty percent of eligible F1 completed the telephone interview ($n = 3003$). Owing to budget constraints, a subset was targeted for a home visit, recruited from three groups: daughters of mothers with breast cancer, daughters who had participated in an earlier study on breast density, and a random sample of daughters [20]. Of the 1879 eligible, 1194 completed a home visit (64%). F1 were asked to invite their daughters (F2, granddaughters) to also participate in the home visit, using snowball recruitment. In total, 729 F2

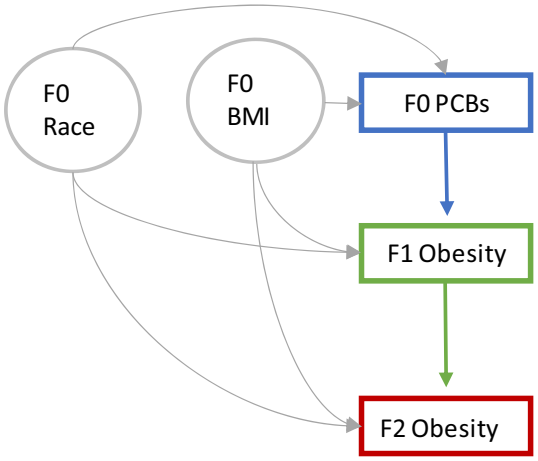

FIGURE 1 Proposed model. Blue = exposure; green = mediator; red = outcome; and gray = covariates. F0 represents grandmothers; F1 represents daughters; and F2 represents granddaughters. F0 race indicates individuals who self-identified as Black versus not Black; F0 BMI indicates BMI ≥ 25 kg/m^2 versus <25 kg/m^2.

participated in the home visit, and 356 F2 completed a questionnaire. The distribution of F0 characteristics by participation type (interview vs. home visit vs. questionnaire) for F1 and F2 was highly comparable (Table S1), suggesting that participation bias is unlikely [17]. For example, F1 and F2 who participated in the home visit are similar to those who did not participate on key characteristics such as F0 race.

For this analysis, we included F2 who completed a questionnaire, participated in a home visit, had PCB measures available from F0 archived serum, and had information available on body mass index (BMI) for all three generations (n = 258 triads; Figure S1). This same sample was the basis of our previous report on the association between F0 DDTs and F2 obesity [17].

The institutional review board of the Public Health Institute approved the protocols for this research. At enrollment, F0 provided verbal consent, as was customary in the 1960s, for themselves and their children. F1 and F2 who participated in the 3Gs Study provided verbal consent before completing the telephone interview or questionnaire and written consent before participating in the home visit.

Measures

As illustrated in Figure 1, we hypothesized that F0 PCBs influence F2 obesity, directly as an ovum and indirectly by F1 obesity at reproductive age. We provide additional detail subsequently on relevant measures for each of the three generations.

Measurement of F0 PCBs, BMI, and race

We measured PCBs in nonfasting archived serum, preferentially assaying samples collected from F0 in the near postpartum period (1–3 days after delivery), as previously described [17, 21, 22]. Postpartum samples account for 86% of PCBs measured in this study, third-trimester samples account for 12%, and second-trimester samples account for 2%. Previous research has demonstrated measurement reliability over time and correspondence in levels across gestation for these chemicals owing to their long half-lives, supporting the assumption that timing of sample collection during the perinatal period represents pregnancy exposures [23]. In addition, including trimester of collection as a covariate in models did not affect associations observed between F0 PCBs and F2 obesity, nor was trimester of collection itself associated with F0 PCBs or F2 obesity (not shown).

PCBs were measured in three laboratories using gas chromatography with electron capture detection (GC/ECD) fit with a capillary column, GC/ECD fit with dual columns, or GC coupled with a triple quadrupole mass spectrometer. We previously reported that combining organochlorine assay results from laboratories with these different methods, as was done for PCBs in this study, does not result in meaningful misclassification for chemicals detected in ≥85% of samples [21]. Table S2 provides the limits of detection for PCBs and minimum concentrations at each laboratory. Minimum concentrations are well above limits of detection, and individual variability was at least threefold greater than the variability owing to measurement error.

We identified F0 BMI and F0 race a priori as covariates that may be associated with F0 PCBs, F1 obesity, and F2 obesity (Figure 1). F0 BMI was previously observed to be associated with both F0 PCBs [24] and F2 obesity [17] in the CHDS and in other populations [25]. F0 BMI in early pregnancy was calculated from weight (in kilograms) divided by height (in meters squared) as measured at the first prenatal visit or reported during the interview at enrollment. Weight was adjusted to compensate for variation in the timing of measurement by regressing weight on gestational age using the locally weighted scatterplot smoothing technique [26]. Adjusted weight was imputed as the fitted mean weight at day 101 of gestation (median day of interview) plus the residual from the regression. F0 BMI was dichotomized as overweight or obesity versus lean (≥25 vs. <25 kg/m^2) because fewer F0 had obesity compared with F1 and F2 at about the same age (Table 1). We considered F0 race (Black vs. non-Black) as a social construct related to multigenerational racism, as well as inequalities in income, educational attainment, and exposure to legacy pesticides and industrial chemicals (information available at the following link: https://indigo.uic.edu/articles/report/Best_Practices_for_Using_Race_in_Public_Health_Research/15159393?file=29123847). F0 race was also previously observed to be associated with F0 BMI and F0 organochlorine exposures in the CHDS [24].

Measurement of F1 BMI

F1 BMI at age 30 years was calculated from weight (in kilograms) divided by height (in meters squared) as reported during the telephone interview; the telephone interview included questions regarding weight and height at younger ages (median age of 49 years at the time of the interview). We chose to examine F1 BMI at age 30 years

TABLE 1 Distribution of study characteristics among three CHDS generations: grandmothers (F0), daughters (F1), and granddaughters (F2)

	Grandmothers (F0), $n = 258$				Daughters (F1), $n = 258$				Granddaughters (F2), $n = 258$			
		Percentile				Percentile				Percentile		
	Mean (SD)	25th	50th	75th	Mean (SD)	25th	50th	75th	Mean (SD)	25th	50th	75th
Year of birth	1936 (6.6)	1931	1937	1941	1962 (1.8)	1961	1962	1964	1989 (3.6)	1987	1990	1993
Year of interview	1962 (1.8)	1961	1962	1964	2011 (0.7)	2011	2012	2012	2013 (0.0)	2013	2013	2013
Age, y	26 (6.0)	22	25	31	49 (2.0)	48	49	51	26 (4.4)	22	26	29
Weight, kg	62.9 (14.0)	53.7	59.3	69.0	70.8 (16.4)	59.0	65.8	77.1	76.9 (23.4)	61.0	70.05	89.0
Height, m	1.62 (0.07)	1.57	1.63	1.68	1.66 (0.07)	1.60	1.65	1.70	1.66 (0.07)	1.62	1.66	1.71
BMI, kg/m^2	23.9 (5.1)	20.9	22.5	25.6	25.8 (5.6)	22.0	23.9	29.2	28.0 (8.4)	21.8	25.1	32.9
Age at menarche, y	12.7 (1.4)	12	13	13	12.8 (1.8)	12	13	14	12.4 (1.6)	11	12	13
Parity	1.8 (2.0)	0	1	3								
Year of blood draw	1962 (1.8)	1961	1962	1964								
PCB 138, ng/mL	0.59 (0.34)	0.39	0.50	0.67								
PCB 153, ng/mL	0.76 (0.40)	0.52	0.66	0.88								
PCB 180, ng/mL	0.50 (0.26)	0.34	0.44	0.60								
(PCB 138 + PCB 180)/PCB 153	1.46 (0.16)	1.37	1.46	1.53								
Race and ethnicity, *n* (%)												
Black	78 (30)				84 (33)				73 (33)[b]			
Asian	6 (3)				4 (2)				12 (5)[b]			
Hispanic	13 (5)				17 (6)				17 (8)[b]			
White	153 (59)				146 (56)				117 (53)[b]			
Other/mixed	8 (3)				7 (3)				3 (1)[b]			
Education, *n* (%)												
Less than high school	53 (22)[a]				12 (4)				13 (6)[c]			
High school	89 (37)[a]				31 (12)				48 (22)[c]			
Some college	52 (22)[a]				105 (41)				115 (54)[c]			
≥College	44 (19)[a]				110 (43)				38 (18)[c]			
BMI, *n* (%)												
Lean (<25 kg/m^2)	182 (71)				153 (59)				129 (50)			
Overweight (≥25–<30 kg/m^2)	52 (20)				47 (18)				47 (18)			
Obesity (≥30 kg/m^2)	24 (9)				58 (23)				82 (32)			

Abbreviations: CHDS, Child Health and Development Studies; PCB, polychlorinated biphenyl.
[a]F0 missing on education ($n = 20$).
[b]F2 missing on race and ethnicity ($n = 36$).
[c]F2 missing on education ($n = 44$).

because that was near the age of F1 when they gave birth to F2, and their obesity likely represents in utero exposure for F2 and/or a marker of genetic risk. We dichotomized F1 BMI as obesity versus overweight or lean (≥30 vs. <30 kg/m^2).

Measurement of F2 BMI

F2 BMI was calculated from weight (in kilograms) divided by height (in meters squared) as measured during the home visit and using standardized protocols (median age of 26 years at the time of the home visit) [18]. We dichotomized F2 BMI as obesity versus overweight or lean (≥30 vs. <30 kg/m^2) [27].

Statistical analysis

We used logistic regression models to examine the association between F0 PCBs and F2 obesity. We also examined the association between F0 PCBs and F1 obesity, and we report associations with F2 obesity before and after adjustment for F1 obesity. Because PCBs are highly correlated (Table S3, Figure S2), we used a linear combination or a ratio of PCB 138 + PCB 180 to PCB 153 (hereafter referred to as "PCB ratio"). We chose a ratio based on experimental literature demonstrating that these three PCBs have distinct, independent mechanisms [9], in addition to results of models including the following: 1) all PCBs dichotomized at the sample median (PCB 138, 0.50 ng/mL; PCB 153, 0.66 ng/mL; PCB 180, 0.44 ng/mL); 2)

PCB 153 and PCB 180 dichotomized at the sample median; and 3) PCB 138 and PCB 153 dichotomized at the sample median (Table S4). These models indicated a positive association of PCB 138 and PCB 180 with F2 obesity but a negative association with PCB 153, consistent with the observation that F0 have varying relative amounts of PCBs in their serum (Table 1). Therefore, the PCB ratio more accurately reflects mixture exposures and builds upon prior observations in the CHDS that mixtures of different compounds in the same chemical class are associated with multiple health outcomes [15, 22, 28–32].

We modeled the PCB ratio as a continuous variable, log-transformed (base 2) to reduce the influence of outliers. Linear combinations were then used to estimate an odds ratio (OR) for the median of the PCB ratio in Tertile 2 (1.47) minus the median in Tertile 1 ($1.47 - 1.33 = 0.14$), as in our prior studies of DDTs [15, 17, 22]. Similarly, we estimated an OR for the median of the PCB ratio in Tertile 3 minus the median in Tertile 1, equivalent to the inter-tertile range ($1.60 - 1.33 = 0.27$). All models included F0 BMI (≥25 vs. <25 kg/m^2) and F0 race (Black vs. non-Black), as described earlier.

We also evaluated confounding by the following: 1) F0 *o,p'*-DDT, as we previously reported an association with F2 obesity in this same analytic sample [17]; 2) F0 total cholesterol and triglycerides because PCBs are lipophilic (total cholesterol and triglycerides were measured at the Clinical and Epidemiologic Research Laboratory at Boston Children's Hospital, using methods previously described [33]; and 3) F0 education (less than high school, high school diploma or General Educational Development [GED], and some college or more) and family income (less than vs. greater than or equal to the median income in Oakland, California, in 1960, i.e., $6303) to determine whether associations may be accounted for by these aspects of inequality while recognizing that many other inequalities are not available for analysis.

Sensitivity analyses

In sensitivity analyses, we modeled the PCB ratio as tertiles (Tertile 1 [reference category], ≤1.40; Tertile 2, >1.40 and ≤1.50; and Tertile 3, >1.50) and as a dichotomous variable at the sample median (≤1.46 vs. >1.46). We also compared results of models with the PCB ratio based on molar units versus nanograms per milliliters.

Secondary analysis

We estimated associations with each PCB in traditional single-pollutant models and then in multiple-pollutant models that were mutually adjusted for all three PCBs. Multiple-pollutant models included a model with each of the three PCBs and a model with PCB 153 and PCB 138+ PCB 180. In all of these models, each PCB was modeled as a continuous variable and log-transformed (base 2).

The institutional review board of the Public Health Institute approved the protocols for this research. At enrollment, F0 provided verbal consent, as was customary in the 1960s, for themselves and their children. F1 and F2 who participated in the 3Gs Study provided

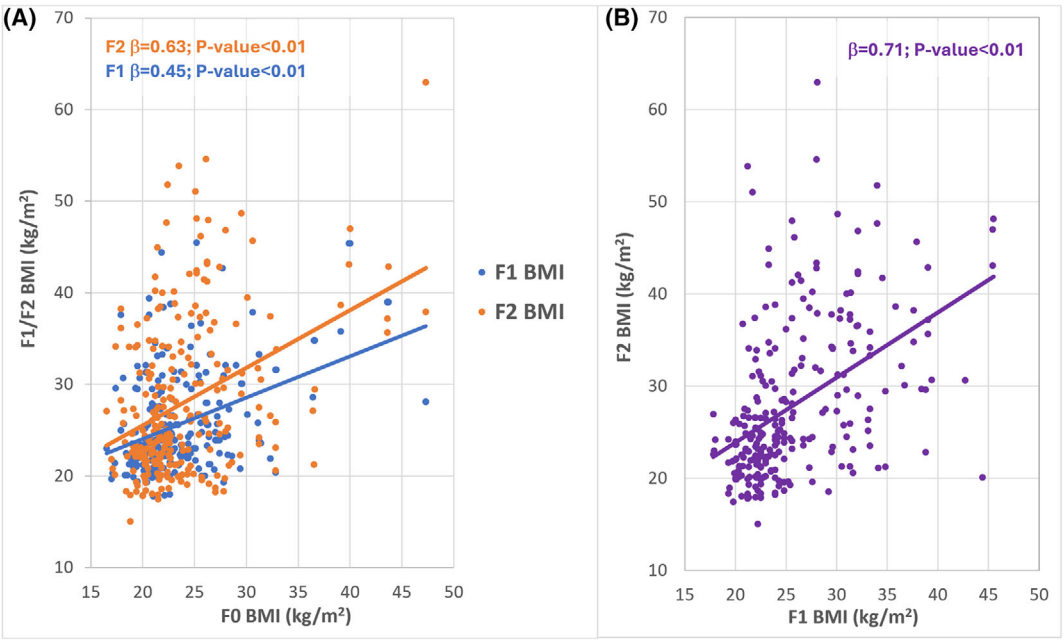

FIGURE 2 Correlation of BMI in three generations ($n = 258$ triads). (A) Correlation of grandmothers' (F0) BMI in early pregnancy (mean age of 26 years) with daughters' (F1) BMI at age 30 years and granddaughters' (F2) BMI at age 26 years. Panel A illustrates correlation of F0 BMI in early pregnancy with BMI in two subsequent generations, as well as an increase in BMI from F0 to F1 to F2. Notably, F2 have the highest BMI. (B) Correlation of F2 BMI at age 26 years with each mother's (i.e., F1) BMI at age 30 years.

verbal consent before completing the telephone interview or questionnaire and written consent before participating in the home visit.

All analyses were conducted in SAS version 9.4 (SAS Institute Inc.). We used the procedure "GENMOD" with the repeated option to adjust the covariance matrix for correlation within families.

RESULTS

Characteristics of the study population are shown in Table 1. PCB 153 (mean [SD], 0.76 [0.40] ng/mL) was most abundant in F0, followed by PCB 138 (0.59 [0.34] ng/mL) and PCB 180 (0.50 [0.26] ng/mL). All three PCBs were detected in all F0.

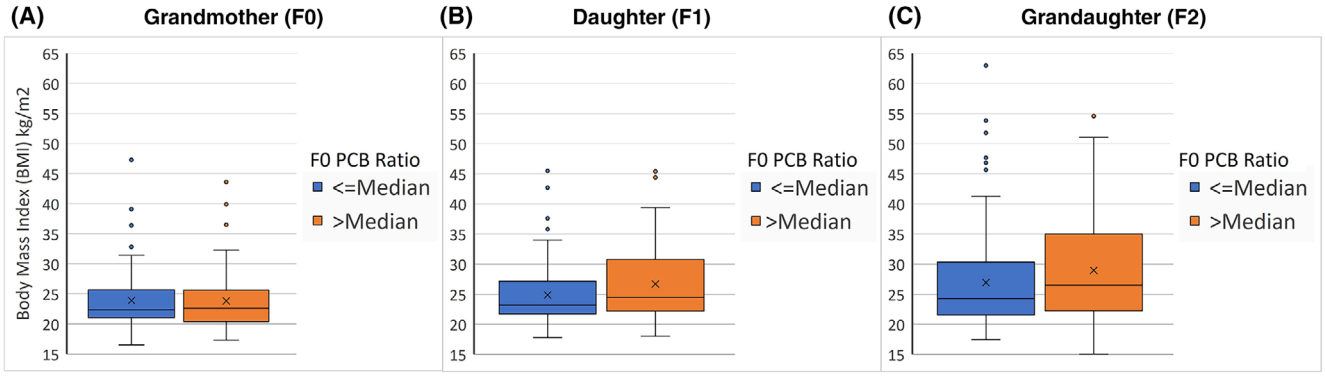

FIGURE 3 Box plots for BMI in three generations by the polychlorinated biphenyl (PCB) ratio (PCB 138 + PCB 180 to PCB 153) in grandmothers' (F0) perinatal serum ($n = 258$ triads). (A) BMI for grandmothers (F0) in early pregnancy (mean age of 26 years). (B) BMI for daughters (F1) at age 30 years. (C) BMI for granddaughters (F2) at age 26 years. The PCB ratio is dichotomized at the sample median (1.46): less than or equal to median (blue) and greater than median (orange). A PCB ratio greater than median in F0 perinatal serum is associated with higher BMI at reproductive age in both F1 and F2, but not for F0. BMI increased over each generation, resulting in higher prevalence of overweight and obesity (BMI ≥ 25 kg/m^2) for F1 compared with F0 and F2 compared with F1.

TABLE 2 Associations of grandmothers' (F0) perinatal serum levels of the ratio of PCB 138 + PCB 180 to PCB 153 ("PCB ratio") with obesity (BMI ≥ 30 vs. <30 kg/m^2) in daughters (F1) and granddaughters (F2), $n = 258$ triads.

	Outcome and generation					
	Obesity at age 30 y in F1 (daughters)			Obesity at age 26 y in F2 (granddaughters)		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Model 1						
F0 PCB ratio, Tertile 1	1.00			1.00		
F0 PCB ratio, Tertile 2	1.33	1.03–1.71	0.03	1.42	1.06–1.89	0.02
F0 PCB ratio, Tertile 3	1.73	1.06–2.82	0.03	1.96	1.12–3.42	0.02
F0 Black (vs. non-Black)	1.66	0.77–3.56	0.19	2.65	1.42–4.95	<0.01
F0 BMI (≥25 vs. <25 kg/m^2)	2.66	1.28–5.55	0.01	3.94	2.06–7.53	<0.01
Model 2						
F0 PCB ratio, Tertile 1				1.00		
F0 PCB ratio, Tertile 2				1.32	0.97–1.78	0.07
F0 PCB ratio, Tertile 3				1.70	0.95–3.05	0.07
F0 Black vs. other				2.53	1.31–4.88	0.01
F0 BMI (≥25 vs. <25 kg/m^2)				3.13	1.57–6.22	<0.01
F1 BMI (>30 vs. <30 kg/m^2)				4.12	1.95–8.72	<0.01

Note: Associations are estimated as OR from models with the PCB ratio as a continuous variable and log-transformed (base 2), adjusted for clustering within families. Models 1 and 2 included the PCB ratio, F0 race (Black vs. non-Black), and F0 BMI in early pregnancy (≥25 kg/m^2 vs. <25 kg/m^2). Model 2 was additionally adjusted for F1 BMI (≥30 vs. <30 kg/m^2) at age 30 years, which was based on self-report (see *Methods* section for details). F2 obesity was based on measured weight and height when F2 were a median age of 26 years. OR for Tertile 2 versus Tertile 1 was estimated for the median of the PCB ratio in Tertile 2 minus the median of Tertile 1 ($1.47 - 1.33 = 0.14$). OR for Tertile 3 vs. Tertile 1 was estimated for the median of the PCB ratio in Tertile 3 minus the median of Tertile 1 ($1.60 - 1.33 = 0.27$), equivalent to the inter-tertile range.
Abbreviations: OR, odds ratio; PCB, polychlorinated biphenyl.

BMI increased across generations, resulting in a higher prevalence of overweight and obesity (BMI ≥ 25 kg/m^2) for F1 (41%) compared with F0 (29%) and for F2 (50%) compared with F1 (41%; Table 1). F0 BMI was correlated with F1 BMI and F2 BMI (Figure 2) [17], and F1 BMI and F2 BMI were higher for F0 with a PCB ratio greater than the sample median (1.46; Figure 3).

In adjusted models, the PCB ratio was statistically significantly associated with obesity in F1 and F2 (Table 2). Specifically, an increase in the PCB ratio from the median of Tertile 1 to the median of Tertile 3 corresponded to a 1.73 (95% confidence interval [CI]: 1.06–2.82) increase in the odds of F1 obesity and a 1.96 (95% CI: 1.12–3.42) increase in the odds of F2 obesity. After adjustment for F1 obesity, an increase in the PCB ratio from the median of Tertile 1 to the median of Tertile 3 corresponded to a 1.70 (95% CI: 0.95–3.05) increase in the odds of F2 obesity. F1 obesity was also associated with F2 obesity (OR, 4.12, 95% CI: 1.95–8.72). These associations were robust to additional adjustment for F0 *o,p'*-DDT (Table S5), F0 total cholesterol and triglycerides (Table S6), F0 education and family income (Table S7), and laboratory results (Table S8). In addition, modeling the PCB ratio as tertiles (Table S9), as a dichotomous variable at the sample median (Table S10), and based on molar units (Table S11) produced similar results.

As shown in Table 3, the association between F0 PCBs and F2 obesity differed by F0 BMI (p value for interaction = 0.08). Specifically, an increase in the PCB ratio from the median of Tertile 1 to the median of Tertile 3 corresponded to a 3.24 (95% CI: 1.38–7.58) increase in the odds of F2 obesity, but only for F0 without overweight or obesity in early pregnancy. There was no association between the PCB ratio and F2 obesity for F0 with overweight or obesity in early pregnancy (OR, 1.11, 95% CI: 0.56–2.21).

Table 4 provides results from traditional single-pollutant models and multiple-pollutant models. F0 PCBs were associated with F2 obesity in multiple-pollutant models, consistent with mixture exposures and the PCB ratio (modeled as a continuous variable: OR, 12.08, 95% CI: 1.54–94.66). For example, PCB 138 and PCB 180 corresponded to a 3.54 (95% CI: 0.87–14.37) and 3.02 (95% CI: 0.87–10.5) increase in the odds of F2 obesity, whereas PCB 153 corresponded to a 0.08 (95% CI: 0.01–0.69) decrease in the odds of F2 obesity.

TABLE 3 Associations of grandmothers' (F0) perinatal serum levels of the ratio of PCB 138 + PCB 180 to PCB 153 ("PCB ratio") and obesity (BMI ≥ 30 vs. <30 kg/m^2) in granddaughters (F2), according to F0 BMI (≥25 vs. <25 kg/m^2)

F0 without overweight or obesity in early pregnancy (BMI < 25 kg/m^2), n = 182 triads			
	OR	**95% CI**	***p* value**
Model 1			
F0 PCB ratio, Tertile 1	1.00		
F0 PCB ratio, Tertile 2	1.84	1.18–2.86	0.01
F0 PCB ratio, Tertile 3	3.24	1.38–7.58	0.01
F0 Black (vs. non-Black)	3.99	1.87–8.53	<0.01
Model 2			
F0 PCB ratio, Tertile 1	1.00		
F0 PCB ratio, Tertile 2	1.74	1.09–2.79	0.02
F0 PCB ratio, Tertile 3	2.92	1.18–7.23	0.02
F0 Black (vs. non-Black)	3.37	1.49–7.63	<0.01
F1 BMI (≥30 vs. <30 kg/m^2)	5.00	1.84–13.62	<0.01
F0 with overweight or obesity in early pregnancy (BMI ≥ 25 kg/m^2), n = 76 triads			
	OR	**95% CI**	***p* value**
Model 1			
F0 PCB ratio, Tertile 1	1.00		
F0 PCB ratio, Tertile 2	1.06	0.74–1.51	0.76
F0 PCB ratio, Tertile 3	1.11	0.56–2.21	0.76
F0 Black (vs. non-Black)	1.44	0.52–4.01	0.49
Model 2			
F0 PCB ratio, Tertile 1	1.00		
F0 PCB ratio, Tertile 2	1.00	0.70–1.42	1.00
F0 PCB ratio, Tertile 3	1.00	0.51–1.97	1.00
F0 Black (vs. non-Black)	1.55	0.53–4.57	0.43
F1 BMI (≥30 vs. <30 kg/m^2)	2.99	1.01–8.86	0.05

Note: Associations are estimated as OR from models with the PCB ratio as a continuous variable and log-transformed (base 2), adjusted for clustering within families. Models 1 and 2 included the PCB ratio, F0 race (Black vs. non-Black), and F0 BMI in early pregnancy (≥25 kg/m^2 vs. <25 kg/m^2). Model 2 was additionally adjusted for F1 BMI (≥30 vs. <30 kg/m^2) at age 30 years, which was based on self-report (see *Methods* section for details). F2 obesity was based on measured weight and height when F2 were a median age of 26 years. OR for Tertile 2 versus Tertile 1 was estimated for the median of the PCB ratio in Tertile 2 minus the median of Tertile 1 (1.47 − 1.33 = 0.14). OR for Tertile 3 versus Tertile 1 was estimated for the median of the PCB ratio in Tertile 3 minus the median of Tertile 1 (1.60 − 1.33 = 0.27), equivalent to the inter-tertile range. *P* value for interaction (PCB ratio × F0 BMI ≥ 25 kg/m^2 vs. <25 kg/m^2) = 0.11 in Model 1 and 0.08 in Model 2.
Abbreviations: OR, odds ratio; PCB, polychlorinated biphenyl.

DISCUSSION

We found evidence supporting the hypothesis that grandmothers' (F0) perinatal serum levels of mixtures of PCB 138, PCB 153, and PCB 180 are linked to risk of obesity in their daughters (F1) and granddaughters (F2). Our human data are consistent with prior observations in experimental studies [9] that these PCBs are environmental obesogens, supporting the idea that the rise in obesity worldwide may, in part, be explained by environmental obesogens in the womb. Within our three-generation cohort, obesity prevalence at reproductive age increased from 9% in grandmothers to 23% in daughters to 32% in granddaughters. Obesity in daughters also independently contributed to obesity in granddaughters, raising the possibility that intergenerational transmission of obesity, initiated in the grandmother's generation, may continue beyond the granddaughter's generation owing to ongoing maternal obesity.

Developmentally programmed traits associated with maternal obesity and a high-fat diet have been observed across multiple

generations in experimental studies and are plausible for humans, although mechanisms have been incompletely characterized because there are few multigenerational human studies [13]. Thus, mechanisms for multigeneration effects of PCBs on obesity remain unknown, and our findings point to several possibilities. First, grandmaternal PCB associations with obesity in granddaughters were particularly strong for grandmothers who did not have overweight or obesity in early pregnancy, suggesting that transmission of obesity associated with perinatal PCBs is not due to shared germline inheritance. Second, PCBs are generally known to be stored in fat and slowly released, redistributed [34, 35], and passed on through the placenta [36] and milk [37]. It is possible that the associations in offspring are caused by this transfer of PCB body burden and may reflect different rates of transfer to offspring for PCB 153 compared with PCB 138 and PCB 180. The fact that PCB 153 works through different obesogenic pathways than PCB 138 and PCB 180 in experimental studies is consistent with our findings. Third, although the three PCBs studied here belong to the class of noncoplanar PCBs, enzyme induction profiles, nuclear receptor activation, and signaling pathways are congener-specific [38], adding plausibility for contrasting associations by congener. The PCB ratio reflects the relative amounts of these PCBs within individual grandmothers in relationship to obesity in daughters and granddaughters. Variability of the ratio likely reflects differences in exposure source, metabolism, excretion, or transfer to the fetus during gestation. Finally, prenatal PCB levels have been shown to induce epigenetic changes in placenta and brain in a mouse model [39], including Wnt signaling, which is known to be involved in obesity [40].

Prior research has strongly implicated prenatal life as a critical window of susceptibility to environmental chemicals or pharmaceuticals that can function as obesogens [3, 41, 42]. In a previous three-generation study, also based on the CHDS, we observed associations of perinatal serum levels of DDTs with obesity in daughters and granddaughters [17, 18]. In the present study, the association between perinatal serum levels of PCBs and obesity in granddaughters was robust to adjustment for F0 *o,p'*-DDT, ruling out confounding and suggesting that PCBs are unlikely to be the only obesogens during development; that is, DDTs and PCBs in perinatal serum are each independently associated with obesity in granddaughters. Importantly, perinatal serum samples were collected for pregnancies occurring in 1959 to 1967, before PCBs were banned and when their concentrations were high. These ancestral exposures remain relevant to the current generation of women of reproductive age who are represented by the granddaughters in this study. Experimental studies have also firmly established the sensitivity of both the embryo and the germline to environmental obesogens [4]. Most recently, in vitro studies have provided evidence that germ cells are susceptible to alteration of differentiation and molecular programing during early development, demonstrated by effects of low levels of bisphenol A [43].

This study has several limitations. As for all observational human studies, we cannot rule out confounding by unmeasured or unknown variables, including exposure to other environmental obesogens. Other determinants of obesity across generations require a deeper investigation of inequality and racism that is beyond the scope of this report. F0 BMI may reflect both prepregnancy BMI and early pregnancy weight gain, prior to the first prenatal visit. However, it demonstrates predictive validity because it is associated with both F1 and F2 obesity. F1 BMI was self-reported, potentially introducing measurement error and the possibility that the associations between F1 obesity and F2 obesity are underestimates or potentially biased if recall was differential. However, like F0 BMI, self-reported weight in F1 demonstrated predictive validity because it was associated with F2 obesity and F0 overweight and obesity, as expected. Moreover, we observed 85% concordance for F1 obesity based on self-reported weight at age 30 years with F1 obesity based on measured height and weight at age 49 years. We were unable to investigate ancestral PCB associations with obesity in sons and grandsons at this time and did not have information on postnatal diet, body composition, or exercise. However, associations of maternal body fat with daughters' body fat

TABLE 4 Single-pollutant models and multiple-pollutant models for associations of grandmothers' (F0) perinatal serum levels of PCBs and granddaughters' (F2) obesity (BMI ≥ 30 vs. <30 kg/m^2), $n = 258$ triads.

	Single-pollutant models[a]			Multiple-pollutant models[b]		
	OR	(95% CI)	*p* value	OR	(95% CI)	*p* value
PCB 138	0.90	0.58–1.40	0.64	3.54	0.87–14.37	0.08
PCB 153	0.78	0.49–1.23	0.29	0.08	0.01–0.69	0.02
PCB 180	0.90	0.56–1.43	0.66	3.02	0.87–10.50	0.08
PCB 138 + PCB 180				10.78	1.32–87.94	0.03
PCB 153				0.08	0.01–0.62	0.02
(PCB 138 + PCB 180)/PCB 153				12.08	1.54–94.66	0.02

Note: PCBs were modeled continuously and log-transformed (base 2). All models included F0 race (Black vs. non-Black) and F0 BMI in early pregnancy (≥25 kg/m^2 vs. <25 kg/m^2), adjusted for clustering within families.

Abbreviations: OR, odds ratio; PCB, polychlorinated biphenyl.

[a]Single-pollutant models each contain only one of the PCBs.

[b]Multiple-pollutant models are mutually adjusted for PCBs; three multiple-pollutant models are shown: a model with each of the three PCBs, a model with PCB 138 + PCB 180 and PCB 153, and a model with PCB 138 + PCB 180/PCB 153 ("PCB ratio").

in middle childhood are also observed for BMI [44]. Our analytic sample does not have substantial representation of Asian and Hispanic women, as it reflects the population in Alameda County, California, in the early 1960s. Measurement error for PCBs could have resulted in underestimation of the associations, although restricting the sample to the laboratories with the most assays and lowest measurement error did not alter results.

This study has several strengths. To our knowledge, this is the first study to examine the relationship of grandmothers' perinatal serum PCBs to the risk of developing obesity in two subsequent generations. This research was made possible by a unique 60-year follow-up of the CHDS, beginning with pregnancies that occurred in the early 1960s and well before the ban of PCBs in the United States in 1979. We considered a PCB mixture based on experimental literature implicating PCB 138, PCB 153, and PCB 180 as obesogens [9] and tested this existing mechanistic hypothesis in humans. We addressed exposure during critical developmental windows: for daughters as an embryo in relationship to grandmaternal perinatal serum levels of PCBs, and for granddaughters as an ovum in relationship to grandmaternal perinatal serum levels of PCBs. We were able to observe independent associations of grandmaternal serum levels of PCBs with both mothers' obesity and granddaughters' obesity in this unique three-generation study. Obesity in granddaughters was measured and not self-reported. Findings in granddaughters are relevant to current populations of young women of reproductive age who are experiencing an epidemic of obesity.

CONCLUSION

This three-generation study supports the hypothesis that ancestral perinatal exposures to PCBs found in high concentration in the environment, animals, and humans are associated with risk of obesity in two subsequent generations. Ancestral exposures to obesogens may initiate and sustain the cycle of multigenerational obesity. The high prevalence of obesity in the current generation of childbearing women, represented by the granddaughters in our study, suggests that their own daughters will also be at increased risk for obesity. Thus, the control of obesity and its public health impact may depend not only on interrupting the environmental initiation of the obesity cycle but also discovery of biomarkers that identify specific mechanistic pathways that can be interrupted to end the multigenerational cycle of obesity.O

AUTHOR CONTRIBUTIONS

Barbara A. Cohn and Piera M. Cirillo conceived the study. Piera M. Cirillo and Nickilou Y. Krigbaum carried out data collection and prepared analysis files. Barbara A. Cohn, Piera M. Cirillo, and Nickilou Y. Krigbaum collaborated on data analysis. Barbara A. Cohn and Michele A. La Merrill obtained funding. Barbara A. Cohn and Piera M. Cirillo wrote the first draft. Interpretation of findings, presentation of findings, and writing were a team effort involving all authors, with expertise of Michele A. La Merrill and Xin Hu on the toxicology and chemistry of PCBs, Caitlin C. Murphy on interpretation and clarity of presentation of findings, Nickilou Y. Krigbaum on validity of assay methods, and Piera M. Cirillo on interpretation and presentation of findings. All authors were involved in writing and editing the figures, tables, and text and had final approval of the submitted (and published) versions.

ACKNOWLEDGMENTS

We thank the CHDS families and acknowledge Jacob Yerushalmy and Barbara J. van den Berg, former CHDS directors, an June-Soo Park, Myrto Petreas, and Mary Wolff for measuring PCBs. Deidentified data are available by request to Barbara A. Cohn with approval of the institutional review board at the Public Health Institute. Approval requires a data use agreement.

FUNDING INFORMATION

This research was supported by grants to Barbara A. Cohn from the California Breast Cancer Research Program (grants #15ZB-0186 and #22UB-5411), the Breast Cancer Environment Research Program (grant #U01 ES019471), National Institute of Environmental Health Sciences (grant #R01ES01376), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (contract # HHSN275201100020C); a grant to Michele A. La Merrill from the National Institute of Environmental Health Sciences (#R00 ES019919) and for a subset of assays reported herein; and a grant to Pam Factor-Litvak from the National Institute of Environmental Health Sciences (#R01ES017024). Funders had no role in the conduct or reporting of this research.

CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest. Barbara A. Cohn, Piera M. Cirillo, and Nickilou Y. Krigbaum report grant support to their institutions from the Mercatus Fund. Caitlin C. Murphy reports personal consulting fees outside of the submitted work with Freenome and membership on Medical Advisory Board, Fight Colorectal Cancer (unpaid).

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How to cite this article: Cohn BA, Cirillo PM, La Merrill MA, Murphy CC, Hu X, Krigbaum NY. Grandmaternal perinatal serum polychlorinated biphenyls and prevalence of obesity in adult daughters and granddaughters. *Obesity (Silver Spring)*. 2025;33(6):1165-1175. doi:10.1002/oby.24284