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Original Article

Associations between Exposure to Persistent Organic Pollutants in Childhood and Overweight up to 12 Years Later in a Low Exposed Danish Population

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Key Words

POPs · PCBs · Overweight · Obesity

Abstract

Background: Persistent organic pollutants (POPs) have metabolic disrupting abilities and are suggested to contribute to the obesity epidemic. We investigated whether serum concentrations of POPs at 8–10 years of age were associated with subsequent development of overweight at age 14–16 and 20–22 years. **Methods:** The study was based on data from the European Youth Heart Study, Danish component (1997). Concentrations of several polychlorinated biphenyls (PCBs) and the organochlorine pesticides p,p-dichlorodiphenyldichloroethylene (DDE) and hexachlorobenzene (HCB) were measured in serum from children aged 8–10 years (n = 509). Information on BMI z-scores, waist circumference and % body fat were collected at clinical examinations at ages 8–10, 14–16 and 20–22 years. Multiple linear regression analyses were performed taking potential confounders into account. **Results:** Overall, POP serum concentrations were low: median ΣPCB 0.18 µg/g lipid, DDE 0.04 µg/g lipid and HCB 0.03 µg/g lipid. POPs were generally not associated with weight gain at 14–16 and 20–22 years of age, except for an inverse association among the highest exposed girls at 20–22 years of age, which might possibly be explained by multiple testing or residual confounding. **Conclusion:** This study suggests that, in a low exposed population, childhood serum concentrations of PCB, DDE, and HCB are not associated with subsequent weight gain. © 2015 S. Karger GmbH, Freiburg

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Introduction

While excess caloric consumption and a sedentary lifestyle in interaction with genetic heritage are well-recognized risk factors for obesity, the cause of the obesity epidemic remains unclear and evidence for effects of several ‘non-traditional’ putative environmental contributors is emerging [1, 2]. A proposed alternative environmental risk factor is exposure to chemicals with endocrine disrupting abilities (EDCs) [3]. Persistent organic pollutants (POPs) include chemicals such as polychlorinated biphenyls (PCBs) and the organochlorine pesticides hexachlorobenzene (HCB) and p,p-dichlorodiphenyldichloroethylene (DDE) (major metabolite of DDT) – a part of a group of chemicals considered as EDCs and hypothesized to have obesogenic properties [4]. Because of their lipophilicity and long half-lives, they accumulate in the food chain, and the general population is still exposed to low doses of these substances [5] despite a ban (PCBs, HCB) or restriction (DDT) on the production and use since the 1970s by the Stockholm agreement [6]. Epidemiologic studies, have reported associations between PCBs, DDE, HCB and obesity [7–10] as well as other metabolic disorders such as insulin resistance, type 2 diabetes and metabolic syndrome [11–13]. However, there are few longitudinal studies of POP exposure and subsequent weight gain among children.

The association between exposure to POPs and body weight is proposed to be inversely U-shaped, and POPs thus potentially associated with weight gain at environmentally relevant low concentrations and weight loss or no association at higher concentrations [9, 14], which may explain the disparity of findings across studies. However, high- or low-dose ranges are not yet established [14, 15]. We have previously reported an association between prenatal exposure to POPs (PCBs, DDE) and obesity [16] among moderately exposed girls with overweight mothers from the Faroese Islands examined at age 5 and 7 years. An inverse association between serum insulin and PCB exposure was recently observed in a low exposed population of Danish children aged 8–10 years of age [17], and we here examine, in the same cohort, whether exposure to POPs was associated with weight development at 6 and 12 years of follow-up.

Material and Methods

Subjects and Sampling

The data were derived from the Danish part of the European Youth Heart Study (EYHS). The subjects were recruited in 1997 through a two-stage cluster sampling from 25 different schools in the municipality of Odense and stratified according to location and socioeconomic character. They participated as 8- to 10-year-old 3rd grade children, in the follow-up study in 2003 as 14- to 16-year-old 9th grade adolescents, and in the second follow-up study in 2009 as 20- to 22-year-old young adults. The study design, sampling, and methods have been described in more detail elsewhere [18, 19]. 590 of 771 recruited 3rd grade children participated in EYHS-I; 509 had adequate amounts available for POP analyses. A total of 384 of these children were re-examined as 9th grade students (14–16 years), and 309 children as 20- to 22-year-old adults, corresponding to 49.8% and 40.1% of the original sample frame, respectively. Puberty was furthermore assessed at the age of 12 years. The present report is based on the cohort members who were examined at 8–10 years of age and participated in follow-up examination(s) at 14–16 years and/or at 20–22 years of age and who provided information on the chemicals PCBs, DDE, HCB, and covariates. In total, overall clinical data were available for 278 children (123 boys) and 236 adults (106 men).

The Danish part of the European Youth Heart Study adhered to the Helsinki Declaration and was approved by the local ethics committee [19].

Anthropometric Measurements

All measurements were carried out using standardized methods, which have been described in detail elsewhere [18, 19].

Height and weight were assessed by standard anthropometric procedures. Height was measured to the nearest mm using a stadiometer, and weight was measured to the nearest 100 g using a beam-scale-type weight [19]. BMI was calculated as weight (in kg) / (height² (in m²)) and converted to sex-specific BMI-for-age z-scores (child value minus mean value for sex and age divided by standard deviation for sex and age) using WHO standards (WHO, 2007). Waist circumference was measured twice with a metal anthropometric tape midway between the lower rib margin and the iliac crest. The mean value of the two measurements was used for analysis. Skinfold thickness (SFT) was measured at age 8–10 years, 14–16 years and 20–22 years using a Harpenden fat caliper (John Bull; British Indicators Ltd, Birmingham, UK) over the triceps brachii and biceps brachii muscles, subscapularly, and superior to the anterior superior iliac spine [20], and finally expressed as the sum of the four skinfold thicknesses (Σ SF). The calculation of % body fat (% BF) was estimated from the measurements of SFT using the equations given by Slaughter et al. [20].

Measurement of Exposure

PCBs, DDE, and HCB were analyzed from the enrolment blood samples (at age 8–10 years), by use of solid-phase extraction and sample concentration. Separation of the congeners and quantitation was performed by gas chromatography using a dual capillary column system with microelectron capture detection. The analyses were carried out at the Department of Environmental Medicine, University of Southern Denmark. The quality assurance of this analysis was verified by regular participation in international quality assurance programs [21]. The results were standardized by blood lipids [21] and reported as μ g/g lipid. The median limit of quantification was 0.06 ng/ml for PCBs, DDE, and HCB. The limit of detection (LOD) was 0.03 ng/ml which, at a mean lipid concentration of 6 g/l, corresponds to 0.005 μ g/g lipid. Values under LOD were imputed to $\text{LOD}/2 = 0.0025 \mu\text{g/g}$ lipid for two individuals [22]. The inter-batch repeatability ranged between 3 and 11%, whereas the between-batch reproducibility ranged between 2 and 9%. The accuracy reported as bias ranged between –15.0 and 8.3%. To avoid problems with congeners not assessed and concentrations below the LOD, a simplified concentration of the sum of PCBs (Σ PCB) was calculated as the sum of the three primary congeners with the longest half-lives (PCB138, PCB153, PCB180) multiplied by two [23], given that they make up approximately 50% of all PCB congener concentration in serum.

Measurement of Covariates

Information on the covariates breastfeeding, maternal educational level (socioeconomic status; SES), and maternal smoking was obtained through questionnaires at baseline. Follow-up questionnaires were used if information was missing from baseline. Maternal BMI was calculated from self-reported information on height and weight. Pubertal status was assessed by the investigators from a scale of pictures according to Tanner (1962) – girls according to breast development and pubic hair growth and boys according to genital development and pubic hair growth [24]. Physical fitness was determined by a maximal work test (wattmax test), performed as a progressive maximal cycle ergometer test (cycle ergometer Monark ergomedi 839; Monark Exercise AB, Vanobro, Sweden), and calculated as the maximal power output (wattmax). Dietary intake of the children at 8–10 years of age was assessed using a 24-hour recall face-to-face interview supported by a parent-assisted food record. The dietary information was computed (intake of total energy, total fat, monounsaturated fat, polyunsaturated fat, protein, carbohydrate, n-3 fatty acid, and n-6 fatty acid) in a database, by which it was possible to calculate nutrient information on the individual food items or whole meals and diets via the Danish national food composition tables [25].

Statistical Analysis

Σ PCB, DDE and HCB were divided into tertiles, and differences in characteristics of the population according to sex and tertiles of POPs were tested as appropriate by ANOVA or chi-square tests. Descriptive statistics were given as means and standard deviations or proportions. Exposure parameters were log-transformed to obtain normally distributed residuals with a homogeneous variance. Linear regression analyses were performed to examine the association between POP concentration at 8–10 years of age and BMI z-scores, waist circumference or % BF at 14–16 and 20–22 years of age. Based on previous epidemiological findings, covariates at baseline and at 14–16 and 20–22 years were defined from a priori considerations of relevant factors that might influence the outcome variables and were excluded stepwise if they did not affect the beta estimates by more than 10%. Accordingly, adjustment was made for SES (low/medium/high), breast-feeding status (<1 / \geq 1 month), fitness (based on maximal power output (W) per kg (continuous)), maternal BMI (continuous), and maternal smoking (yes/no). Fitness was not adjusted for in the analyses of the 20- to 22-year-olds because of missing values (n = 112); however, it was included in a sensitivity analysis.

Table 1. Child and maternal characteristics according to tertiles of ΣPCB at 8–10 years of age. Mean, EYHS cohort

Population characteristics	Tertiles of ΣPCB* (µg/g lipid)							
	girls (n = 214)				boys (n = 178)			
	<0.16	0.16–0.28	>0.28	p value	<0.14	0.14–0.25	>0.25	p value [†]
BMI z-score								
8–10 years	0.63 (1.0)	0.26 (1.0)	–0.24 (0.8)	<0.001	0.89 (1.1)	0.17 (0.9)	–0.03 (0.9)	<0.001
14–16 years	0.58 (1.0)	0.11 (0.7)	–0.19 (0.7)	<0.001	0.28 (1.0)	0.02 (1.0)	–0.09 (0.8)	0.16
20–22 years	0.94 (1.0)	0.53 (0.8)	0.02 (0.7)	<0.001	1.06 (1.1)	0.57 (1.1)	0.50 (1.0)	0.04
Waist circumference, cm								
8–10 years	60.4 (6.1)	57.6 (6.0)	56.3 (4.0)	<0.001	61.2 (6.6)	57.5 (4.4)	57.2 (4.9)	0.001
14–16 years	76.5 (8.9)	71.8 (5.7)	71.1 (4.9)	<0.001	77.4 (10.0)	75.3 (8.0)	73.6 (4.8)	0.07
20–22 years	79.0 (9.8)	74.8 (7.9)	74.3 (7.1)	0.01	87.2 (13.5)	85.2 (11.5)	81.0 (9.5)	<0.05
% BF								
8–10 years	22.0 (6.9)	19.7 (6.9)	15.6 (4.7)	<0.001	20.7 (7.9)	16.4 (5.1)	14.6 (4.3)	<0.001
14–16 years	28.1 (6.2)	24.3 (4.9)	22.9 (3.8)	<0.001	19.8 (9.0)	18.4 (8.4)	15.8 (4.6)	0.04
20–22 years	33.2 (10.2)	29.8 (8.0)	29.2 (7.2)	0.05	30.5 (15.1)	27.6 (11.7)	24.3 (8.2)	0.06
Tanner 8–10 years (1–2/3), %	59/41	70/30	83/17	0.01	100/0	100/0	100/0	NA
Tanner 12 years (1–2/3), %	31/69	38/62	42/58	0.87	61/39	67/33	76/24	0.23
Breastfed, %	83.3	91.2	97.1	0.02	74.1	81.4	100	<0.001
SES (low/medium/high), %	24/54/22	18/35/47	8/32/60	<0.001	37/44/19	26/42/32	14/35/51	0.004
Fitness, W/kg	2.6 (0.6)	2.9 (0.5)	3.1 (0.4)	<0.001	3.1 (0.5)	3.3 (0.5)	3.5 (0.4)	<0.001
Maternal BMI, kg/m ²	23.8 (3.6)	23.1 (3.9)	22.4 (2.7)	0.07	24.9 (3.7)	23.9 (4.1)	22.9 (3.2)	0.02
Maternal smoking, %	47.1	42.2	22.1	0.005	42.9	37.9	15.5	0.003

PCBs = Polychlorinated biphenyl(s); SES = socioeconomic status (maternal educational level).

*PCB concentration in µg/g lipid, measured in child serum at age 8–10 years (PCB concentration is based on sum of PCB congeners 138, 153 and 180).

[†]P values were determined by using ANOVA and Pearson's chi-square tests of differences across tertiles of ΣPCB.

Obesity measures at baseline were considered as obligatory covariates and were furthermore included in all adjusted analyses, as was baseline BMI z-score in the analyses of waist circumference as an outcome. The covariates birth weight, start of puberty at 8–10 and 12 years (yes / no), maternal alcohol consumption during pregnancy (yes / no), and ethnicity (Danish / non-Danish) were not adjusted for, as they did not affect the beta estimate by more than 10%. To examine dose-response relationships, POPs were divided into tertiles. Further, to assess whether sex interacted with the association between POPs and adiposity measures, a multiplicative term with the exposure variable was included in the analyses. Additionally, in sensitivity analyses, the same procedure was applied to assess possible effect modification from baseline BMI and daily intake of nutrients, (p < 0.1 used to define significant interactions).

Statistical significance was assumed when p < 0.05 (two-sided). All analyses were performed using STATA software, version 12 (STATA Corp., College Station, TX, USA).

Results

A total of 278 (123 boys) were initially examined at 8–10 years of age and followed up at 14–16 years of age; 236 (106 boys) were examined at 8–10 years of age and followed up at 20–22 years of age; 207 (95 boys) participated in all 3 examinations (supplemental fig. 1 (supplemental material available at <http://content.karger.com/ProdukteDB/produkte.asp?doi=438834>)). Among girls, the median for ΣPCB was 0.18 µg/g (range 0.04–1.11 µg/g), for DDE 0.04 µg/g (range 0.01–0.72 µg/g), and for HCB 0.03 µg/g (range 0.01–0.10 µg/g); among boys the respective values were 0.20 µg/g (range 0.02–1.15 µg/g), 0.04 µg/g (range 0.01–0.72 µg/g), 0.03 µg/g (range 0.00–0.21 µg/g), respectively.

The characteristics of the population according to tertiles of Σ PCB and sex are shown in table 1. Compared to children from the lowest tertile, those from the highest tertile had significantly lower BMI, waist circumference and % BF at 8–10, 14–16 and 20–22 years of age. Moreover, the frequency of breastfeeding was higher, they were from a higher social class, they had a better fitness score, their mothers had a lower BMI, and fewer of their mothers were smokers. In addition, compared to girls from the lowest tertile, fewer girls from the highest exposure tertile had started their puberty at 8–10 years of age. Results were essentially similar for DDE and HCB (data not shown).

Interactions were observed for sex that modified the associations between Σ PCB or DDE and BMI at 20–22 years of age ($p = 0.05$ or $p = 0.02$, respectively) as well as between Σ PCB and waist circumference or body fat % BF at 14–16 years of age ($p = 0.04$ and $p = 0.03$, respectively). The results of the multivariate analyses are therefore presented for girls and boys separately.

In the crude analyses between tertiles of Σ PCB at 8–10 years of age and the measurements of adiposity at 14–16 and 20–22 years of age, a lower BMI z-score, waist circumference and % BF was observed for those in the highest tertile of Σ PCB (table 2). After adjustment for baseline obesity, breastfeeding, SES, fitness, maternal BMI and maternal smoking, the majority of the observed inverse associations were generally attenuated, but the inverse association between Σ PCB and change in BMI persisted among those in the highest (mean $0.4 \mu\text{g/g}$ lipid) compared to the lowest exposure tertile (mean $0.1 \mu\text{g/g}$ lipid) among the 20- to 22-year-old women (BMI z-scores -0.44 ; 95% CI $-0.80, -0.08$; $p = 0.02$). Similar findings were seen for the individual PCB congeners, DDE and HCB (supplemental tables 1, 2 (supplemental material available at <http://content.karger.com/ProdukteDB/produkte.asp?doi=438834>)). Also, DDE was related to a change in % BF and both DDE and HCB to a change in waist circumference. Further analyses including only those with complete information at all three surveys (207 individuals) gave essentially similar results (data not shown).

Discussion

We found no evidence for associations between Σ PCB, DDE and HCB at age 8–10 years of age and subsequent 6- and 12-year development in overall or abdominal obesity. Before adjustment, a higher Σ PCB, DDE, and HCB exposure at age 8–10 years of age was inversely associated with subsequent 6- and 12-year change in BMI, change in waist circumference, and change in % BF at both 14–16 and 20–22 years of age; however, after adjustment for relevant confounders, the majority of the associations were attenuated and no longer statistically significant, except for a change in BMI among 20- to 22-year-old women. Although some POPs display estrogenic effects that may explain the diverging findings among the two sexes, we regard the findings of inverse associations among the 20- to 22-year-old women as spurious and more likely explained by multiple testing or residual confounding. As such, we performed many analyses, and, according to a calculated Bonferroni-adjusted significance level ($p \leq 0.002$), the inverse associations were no longer significant. Alternatively, it may be related to residual confounding. Indeed, we did not adjust for differences in fitness at age 20–22 years because of many missing values ($n = 112$), which may add to explain the inverse association. However, sensitivity analyses performed for those with measures of fitness gave essentially similar results, making residual confounding from fitness less likely. It may also be that a low exposure to POPs has a protective effect in regard to obesity development; however, considering the fact that EDCs target many different endpoints [26], this explanation seems unlikely. Finally, it could be argued that POPs may have a toxic effect leading to weight loss. However, the low exposure level in our population argues against this explanation.

Table 2. Associations between ΣPCB (µg/g lipid) at age 8–10 years in tertiles and continuous and measurements of adiposity at age 14–16 and 20–22 years according to sex, EYHS cohort

PCB in tertiles [‡]	Girls, regression coefficient [†]					
	14–16 years (n = 155)			20–22 years (n = 130)		
	crude		adjusted*	crude		adjusted*
	estimate (95% CI)	p value	estimate (95% CI)	p value	estimate (95% CI)	p value
<i>BMI z-score</i>	reference		reference		reference	
1st tertile	-0.47 (-0.76, -0.17)	0.002	0.05 (-0.18, 0.28)	0.67	-0.41 (-0.76, -0.07)	0.02
2nd tertile	-0.76 (-1.06, -0.47)	<0.001	0.08 (-0.18, 0.33)	0.55	-0.92 (-1.26, -0.58)	<0.001
3rd tertile		<0.001		0.55		<0.001
p-trend		<0.001		0.74		<0.001
Continuous	-0.61 (-0.78, -0.43)	<0.001	0.03 (-0.14, 0.20)	0.74	-0.73 (-0.95, -0.50)	<0.001
<i>Waist circumference</i>	reference		reference		reference	
1st tertile	-4.72 (-7.12, -2.32)	<0.001	-0.04 (-2.05, 1.97)	0.97	-4.28 (-7.69, -0.87)	0.01
2nd tertile	-5.34 (-7.75, -2.94)	<0.001	0.11 (-2.07, 2.28)	0.92	-4.71 (-8.07, -1.36)	0.006
3rd tertile		<0.001		0.91		0.007
p-trend		<0.001		0.17		<0.001
Continuous	-4.61 (-6.07, -3.14)	<0.001	-1.03 (-2.50, 0.44)	0.17	-4.41 (-6.67, -2.16)	<0.001
<i>% BF</i>	reference		reference		reference	
1st tertile	-3.87 (-5.68, -2.07)	<0.001	-0.86 (-2.53, 0.81)	0.31	-3.44 (-6.98, 0.09)	0.06
2nd tertile	-5.24 (-7.04, -3.43)	<0.001	-0.33 (-2.15, 1.50)	0.72	-3.98 (-7.45, -0.52)	0.03
3rd tertile		<0.001		0.83		0.03
p-trend		<0.001		0.66		0.002
Continuous	-4.02 (-5.12, -2.92)	<0.001	-0.27 (-1.49, 0.95)	0.66	-3.75 (-6.08, -1.42)	0.002

Table 2 continued on next page

Table 2. Continued

PCB in tertiles [#]	Boys, regression coefficient [†]					
	14–16 years (n = 123)			20–22 years (n = 106)		
	crude		adjusted*	crude		adjusted*
	estimate (95% CI)	p value	estimate (95% CI)	p value	estimate (95% CI)	p value
<i>BMI z-score</i>	reference		reference		reference	
1st tertile	-0.26 (-0.63, 0.12)	0.18	0.15 (-0.12, 0.43)	0.27	-0.49 (-0.96, -0.01)	0.04
2nd tertile	-0.36 (-0.75, 0.02)	0.06	0.14 (-0.19, 0.46)	0.41	-0.56 (-1.03, -0.09)	0.02
3rd tertile		0.06		0.43		0.02
p-trend		0.01		0.83		0.01
Continuous	-0.33 (-0.58, -0.07)		0.02 (-0.19, 0.24)		-0.41 (-0.71, -0.11)	
					0.22 (-0.12, 0.55)	0.20
<i>Waist circumference</i>	reference		reference		reference	
1st tertile	-2.14 (-5.28, 0.99)	0.18	1.96 (-0.39, 4.30)	0.10	-2.01 (-7.13, 3.11)	0.44
2nd tertile	-3.82 (-7.05, -0.59)	0.02	0.64 (-2.13, 3.41)	0.65	-6.23 (-11.26, -1.20)	0.02
3rd tertile		0.02		0.70		0.02
p-trend		<0.001		0.45		0.004
Continuous	-4.05 (-6.13, -1.96)		-0.72 (-2.57, 1.14)		-4.87 (-8.11, -1.63)	
					0.20 (-3.84, 4.25)	0.92
<i>% BF</i>	reference		reference		reference	
1st tertile	-1.47 (-4.5, 1.56)	0.34	1.90 (-0.34, 4.15)	0.10	-2.92 (-8.18, 2.35)	0.28
2nd tertile	-4.02 (-7.13, -0.92)	0.01	1.59 (-1.04, 4.21)	0.23	-6.19 (-11.37, -1.02)	0.02
3rd tertile		0.01		0.26		0.02
p-trend		<0.001		0.49		0.006
Continuous	-4.14 (-6.14, -2.14)		0.64 (-1.18, 2.45)		-4.75 (-8.09, -1.41)	
					0.69 (-4.24, 5.62)	0.78

Σ PCB = Σ polychlorinated biphenyls.

*Adjustment made for baseline obesity outcomes, breastfed, SES, fitness, maternal BMI and maternal smoking.

[†]Regression coefficient derived from multiple linear regression model. Continuous estimated coefficients are the absolute change in adiposity measurements expected when the log-transformed PCB variable is multiplied by 2.7 (all continuous variables in this table).

[#]PCB in $\mu\text{g/g}$ lipid, log-transformed. Concentrations were measured in child serum at age 8–10 y (PCB congeners 138, 153 and 180).

Our findings of no apparent obesogenic effect of POPs do not seem in agreement with the experimental evidence that generally has reported obesogenic effects of exposure to doses of POPs considered relevant to humans [27]. The human evidence, though, is more diverse and also difficult to compare because of methodological differences between studies. Indeed, findings tend to differ according to type of POPs investigated. The evidence for obesogenic effects from the organochlorine pesticide HCB is still limited, whereas DDE generally has been found to have obesogenic effects [9]. As such, a growing body of prospective epidemiological studies has shown an association between prenatal concentration of DDE and subsequent development of obesity [9]. Similar findings have been reported in prospective studies with exposures in adults [28, 29] and in several cross-sectional studies reviewed earlier [9]. However, the human evidence for an obesogenic effect of PCBs is less clear [27]. The contrasting findings may be explained by differences in the measured PCBs. Some studies only measured PCB153 as a marker of total PCB exposure, while others [9], like in the present study, investigated the effects of a sum of different PCBs, which is generally considered more relevant [23]. In addition, associations between POPs and obesity development may not be linear or monotonous. Indeed, we recently proposed that the relationship was inversely U-shaped [9], suggesting that associations would be direct at low exposures ($<1.0 \mu\text{g/g lipid}$), but inverse or not existing at higher exposures ($>4.0 \mu\text{g/g lipid}$).

The level of exposure in our population was low (median ΣPCB $0.19 \mu\text{g/g lipid}$) and thus contradicting the hypothesis of exposure related obesogenic effects at low exposures. Compared to the study of Hertz-Picciotto et al. [30], the exposure level in the present study was lower (median ΣPCB $0.62 \mu\text{g/g lipid}$) and slightly higher than the exposure level in Verhulst et al. [10] (median ΣPCB $0.10 \mu\text{g/g lipid}$) who both found direct associations between prenatal exposure to ΣPCB and weight gain among children. However, both studies concerned prenatal exposure to ΣPCB . Because EDCs potentially have the largest impact when exposure occurs during fetal development [31], time of measurement of POPs in our cohort may attribute to the observed absence of obesogenic effects. On the other hand, other studies have found that POPs measured at age 8–10 years reflects both the pre- and postnatal exposure, and may be a good indicator also for prenatal POP exposure because of their long half-lives [32]. However, if POPs are measured after obesity onset, it may well be that the concentration of POPs has been diluted because of increased adipose tissue, and a bias may occur [27]. Serum POPs may be lower in those with a larger body mass because of a greater volume of distribution and sequestration in adipose tissue [33]. A dilution effect would result in a reverse causation phenomenon where our findings of lower adiposity measurements among the highest exposed women then would be the attributable factor to higher concentration of POPs. A further stratification by baseline BMI (8–10 years of age) as a sensitivity analysis, revealed that the inverse associations were present among the normal-weight women only, which most likely was a result of the regression towards the mean phenomenon (data not shown) [34].

Recent cross-sectional findings performed in our cohort showed inverse associations between ΣPCB and insulin, HOMA-IR or HOMA-B at 8–10 years of age [17], which was suggested to be related to a possible damage of the beta cells [35]. Hence, it may be speculated that the low PCB concentrations in the present study were too low to influence development of obesity, but may potentially be sufficient to contribute to metabolic disturbances, eventually leading to type 2 diabetes [36].

It may be speculated that belonging to a higher social class is associated with better lifestyle, but also with a concomitant higher POP exposure. As such, fish is the most significant source of exposure to POPs [37] and is more frequently consumed in higher social classes [38]. This may explain why the inverse associations between POPs and development in adiposity generally disappeared after adjustment for social class and related covariates.

Furthermore, the social gradient in diet is not as strong among men than among women [39], which may explain the apparent and persisting gender difference for those aged 20–22 years. Because children from parents of higher social class had higher levels of POPs compared with children from those of lower social class, and because adiposity levels are lower among children from high social class parents, residual confounding from social class or other unmeasured variables cannot be excluded.

Finally, humans are not exposed to one single chemical only, but to a combination of several compounds of which some are not measured. As such, observed effects may be attributable to other chemicals than those measured, or a combination of the compounds may be the responsible factor here [40]. Hence, it may be speculated that the explanation for the observed obesogenic effects of POPs in the study of Verhulst et al. [10], with a similar level of exposure as the present study, may be attributable to some unmeasured chemicals with obesogenic properties.

Because POPs may increase the susceptibility to the effects of e.g. a high-fat diet [41], we investigated in sensitivity analyses whether a daily high intake of nutrients (intake of total energy, total fat, monounsaturated fat, polyunsaturated fat, protein, carbohydrate, n-3 fatty acid and n-6 fatty acid) either modified or confounded the association between POPs and future weight gain, but did not observe any effect modification or confounding (data not shown).

The major strength of this study is the longitudinal design with a long follow-up that enabled us to examine association between POPs at 8–10 years of age and development of obesity at 14–16 or 20–22 years of age. Moreover, the prospective design also reduces the risk of reverse causation as seen in many of the cross-sectional studies. A limitation of our study is the timing of measure of POPs in our cohort that was done at 8–10 years of age. As such, we did not have any exact measure of the prenatal exposure and may therefore have missed the critical window for POP effects on obesity. A further limitation of our study is the modest sample size, which means that modest effects may have been missed. It should be noted that part of the covariates were assessed by questionnaires and self-report, which may have introduced bias. However, as participants were unaware of their PCB levels as well as their future obesity status, we do not expect differential misclassification bias due to residual confounding, although this cannot be ruled out.

In conclusion, we found no evidence for an obesogenic effect of Σ PCB, DDE, HCB in a population of 8- to 10-year-old children with a low exposure to POPs and a follow-up time of 6–12 years. However, we did not measure POPs at the most sensitive window, e.g. prenatally, but at 9 years of age. Therefore, more studies are warranted to examine long-term potential obesogenic effects of both low and high exposures to POPs.

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Authorship

The authors' responsibilities were as follows – AG and MRL were responsible for the data collection; FN was in charge of the POP analyses; JLTP, TKJ, HRA and BLH were involved in the design of the current study; JLTP analyzed data and wrote the first draft of the manuscript; AGT and LBA provided assistance with data analysis; TKJ, HRA and BLH: supervised the work; and all authors were involved in data interpretation, revising the manuscript, and approved the final version of the manuscript.

Disclosure Statement

None of the authors had a conflict of interest.

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