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Early-Life Exposures to Persistent Organic Pollutants in Relation to Overweight in Preschool Children

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Abstract

Current knowledge on obesogenic effects of persistent organic pollutants (POPs) is equivocal. We therefore evaluated the associations between early-life POP exposures and body mass index (BMI) in 444 Faroese children born in 2007–2009. POPs were measured in maternal 2-week postpartum serum and child age-5 serum. Linear regression and generalised linear models assessed the associations with continuous and dichotomous BMI z-scores, respectively, at ages 18 months and/or 5 years. Maternal serum concentrations of HCB, PFOS and PFOA were associated with increased BMI z-scores and/or overweight risk (i.e. BMI z-score 85th WHO percentile). No clear association was found for maternal serum-PCBs, *p,p'*-DDE, PFHxS, PFNA and PFDA. In cross-sectional analyses, we observed a pattern of inverse associations between child serum-POPs and BMI z-scores at age 5, perhaps due to reverse causation that requires attention in future prospective analyses. Findings in this recent cohort support a role of maternal exposure to endocrine disruptors in the childhood obesity epidemic.

Keywords

developmental toxicity; childhood obesity; endocrine disruptors; perfluoroalkyl substances; persistent organic pollutants; DOHaD

1. Introduction

The increasing global obesity trends noted in the past four decades constitute a major public health concern (1, 2). If the current trends continue, 70 million preschool children are

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estimated to be overweight or obese by 2025 (3). Childhood obesity is associated with increased risks later in adulthood of obesity and chronic diseases, such as diabetes and cardiovascular disease, thus contributing to the leading causes of global morbidity and mortality (1, 4, 5). The multifactorial etiology of obesity likely involves an interplay between genetic, lifestyle (e.g. diet and physical activity) and environmental factors. Growing evidence suggests that exposure to endocrine disruptors during critical windows of development may play a role (6–9). Many persistent organic pollutants (POPs), including organochlorine compounds (OCs) and perfluoroalkyl substances (PFASs), are known to act as endocrine disruptors (10) and are currently hypothesized to be obesogenic.

OCs, such as dichlorodiphenyltrichloroethane (DDT, and its major metabolite DDE) and hexachlorobenzene (HCB), have been widely used as pesticides and in industrial applications, until their use was gradually banned in developed countries, starting in the 1970s (11). PFASs are emerging contaminants with oil and water repellent properties used in many consumer products and industrial applications (12). Human exposure to POPs occurs mainly via ingestion of contaminated food (13, 14), with PFAS exposure also likely occurring from ingestion of contaminated water and releases from consumer products (e.g. cookware and waterproofed textiles) (12). The half-lives of POPs in adult serum are estimated to be 3 to 15 years for OCs (15), 3 to 5 years for legacy PFASs (i.e. perfluorooctanesulfonic acid [PFOS] and perfluorooctanoic acid [PFOA]), and 8.5 years for perfluorohexanesulfonate (PFHxS) (12), while the half-lives of other emerging PFASs, such as perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA), are probably similar though uncertain at this point. Human POP exposures begin during early development as the mother shares her POP exposures with her child via transplacental transfer and breast milk (16–18), and accumulate throughout the lifespan.

Prenatal exposure to DDE has been associated with an elevated body mass index (BMI) in infancy and childhood in more than 12 prospective studies, although a few other studies reported no clear association (reviewed in (19)). Positive, negative or null associations have been reported between prenatal exposure to polychlorinated biphenyls (PCBs) and children's BMI (19–26), while evidence for the potentially obesogenic role of HCB is more limited (20, 24, 26–28). Very few of the previous studies also accounted for OC exposures measured postnatally (23, 29). The associations of PFAS exposures with weight gain are supported by experimental studies (30, 31), but epidemiologic studies have only recently evaluated this hypothesis, with inconsistent findings (19, 32–38).

Prenatal exposure to PFOS has been associated with higher weight-for-age in 20-month-old girls (35), with lower BMI z-scores in 12-month-old boys (37), and elevated waist-to-height ratio in children aged 5–9 years (38), while two other studies reported no association with BMI and/or overweight in mid-childhood (33, 36). Prenatal exposure to PFOA has been positively associated with child's BMI gain and body fat (36), and with higher risk of obesity in Danish women at 20 years of age (32), whereas one other study, with exposure estimates based on residential history and proximity to chemical plants, found no association with obesity risk in adulthood (34). Only two studies have evaluated so far exposures to emerging PFASs, such as PFHxS and PFNA, and reported non-significant associations with childhood obesity (35, 36).

Because the evidence from prospective studies for the suspected obesogenic effects of POPs is limited, in particular for emerging PFASs, and because studies assessing POP exposures during different windows of development are currently lacking, we evaluated the associations of both maternal and child serum-POP concentrations with the risk of childhood overweight in a prospective birth cohort study.

2. Methods

2.1 Study population and data collection

A cohort of 490 mother-child pairs was recruited at childbirth, at the National Hospital of the Faroe Islands, during an 18-month period between 2007 and 2009, and followed at child ages 18 months and 5 years (39, 40). The Faroese are a marine population of mainly Scandinavian and Irish origin, with high seafood intakes that contribute to elevated POP exposures (41, 42).

Information about sociodemographic characteristics, family medical history, maternal prepregnancy BMI and lifestyle factors during pregnancy (including alcohol intake and smoking habits) was collected through self-administered questionnaires completed two weeks after childbirth. Additional information was extracted from the medical records and duration of breastfeeding and the child's seafood intakes were reported by the mothers at later examinations. Biological samples and physical examination information were obtained in connection with clinical follow-ups.

This study was approved by the Faroese ethical review committee and the Institutional Review Board at Harvard T.H. Chan School of Public Health. All mothers provided written informed consent at enrolment and at subsequent clinical examinations.

2.2 Exposure assessment of POPs

Serum-POP concentrations were measured in maternal samples collected at 2 weeks after childbirth and in the child's serum obtained at age 5 years. Samples were stored at -80°C until analyses were performed at the University of Southern Denmark.

OC concentrations were measured using gas chromatography with electron capture detection as detailed elsewhere (43) and included: HCB, *p,p'*-DDE and nine major PCB congeners. The limit of detection (LOD) for all OCs was 0.03 ng/mL. Concentrations below the LOD were substituted by a value equal to half of the LOD. We calculated the sum of PCBs in serum (ΣPCBs) as the sum of PCB congeners 138, 153 and 180 multiplied by 2, because these are the most commonly detected congeners and represent close to 50% of the total serum-PCB concentrations (44). Because OCs are highly lipophilic, concentrations were divided by the serum lipid content and expressed in terms of $\mu\text{g/g}$ lipid. The lipid content was calculated from cholesterol and triglyceride serum contents (45) as determined by a kit-based analysis on a Konelab 20 Clinical Chemistry Analyzer (Thermo Fischer Scientific, Waltham, MA, USA).

Maternal serum-PFASs concentrations (in ng/mL) were analyzed using liquid chromatography with mass spectrometry, as previously described (17). The quantitated

substances were PFOS, PFOA, PFHxS, PFNA and PFDA. Concentrations below LOD (<0.03 ng/mL) were substituted by half of the LOD.

In a subset of births from this cohort ($N=50$), we measured POP concentrations also in cord blood, and these concentrations correlate closely with the maternal 2-week postpartum serum concentrations (Spearman $r>0.83$ for all measured POPs). Thus, the maternal postpartum serum concentrations analysed are considered a proxy of both fetal and early postnatal exposures.

2.3 Child anthropometry

The child's body weight and height were measured at ages 18 months and 5 years by the pediatrician of the research team following standard protocols (25). Body weight was measured in light clothing using an electronic scale (to the nearest 0,1 kg). Recumbent length was measured at 18 months, and standing height was measured without shoes at age 5 years (to the nearest 0,1 cm). We divided weight by the squared height to calculate BMI (in kg/m^2). Because physical size varies according to age and sex, we calculated age- and sex-specific z-scores for BMI using the World Health Organization (WHO) Growth Standards (46, 47). Child overweight was classified as a BMI z-score at or above the 85th WHO percentile (46, 47).

2.4 Statistical analysis

We analysed 444 mother-child pairs (91% of the original cohort) with measured POP concentrations in maternal serum and available BMI of the child at age 18 months. The analyses of maternal serum-POPs and child's BMI at age 5 years included fewer observations ($N=371$, 76% of the original cohort) due to follow-up losses. The cross-sectional analysis at age 5 included only those children who provided a blood sample sufficient for serum-POP analysis ($N=349$, 71% of the original cohort).

POP concentrations were log10-transformed to normalize the right-skewed distributions. Generalized additive models (GAMs) assessed the linearity of dose-response relationships between the continuous POP concentrations and outcome variables. Associations between maternal serum concentrations of some POPs (i.e. Σ PCBs, PFNA and PFDA) and child's BMI z-scores at 18 months and/or 5 years appeared to be nonlinear (defined as a $p\text{-gain}<0.10$ in the GAM models) (48), and we therefore report effect estimates both for continuous POP concentrations and per tertile of POP concentrations.

The associations between POP concentrations and continuous BMI z-scores were assessed using linear regression models, and associations with overweight were analyzed using generalized linear models (49). We report effect estimates from both unadjusted and fully adjusted models.

We considered a wide range of covariates based on previous findings in the literature: maternal nationality, age at delivery, prepregnancy BMI status (defined using the WHO cutoffs for adults (50)), gestational weight gain, parity history, maternal smoking, alcohol consumption and fish intake during pregnancy, gestational diabetes (based on medical registry), type of delivery, and child sex, year of birth, gestational length, preterm birth (i.e.

gestational length < 37 weeks), birth weight, exclusive breastfeeding duration and fish intake at age 5 years. We built multivariable-adjusted models including a set of covariates defined by directed acyclic graphs (DAGs). These initial adjusted models for maternal serum-POP concentrations included maternal nationality, age at delivery, prepregnancy BMI, gestational weight gain, parity, maternal smoking and fish intake during pregnancy, child sex and birth weight. The initial adjusted model for the child's 5-year serum-POP concentrations included maternal nationality, age at delivery, prepregnancy BMI, maternal smoking during pregnancy, child sex, exclusive breastfeeding duration and the child's fish intake at age 5 years. We then evaluated additional potential confounders in the associations of maternal serum-POP concentrations (gestational diabetes, maternal alcohol consumption, type of delivery, year of birth) or child serum-POP concentrations (year of birth) and the study outcomes in the initial adjusted models using forward selection (i.e., adding one variable at the time in the model). From those covariates, only the type of delivery changed the coefficients for the associations of maternal serum- Σ PCBs, p,p' -DDE, PFHxS and PFNA with child's BMI by more than 10%, and it was therefore retained in all maternal serum-POP models. The type of delivery is associated with childhood obesity (51) and it could conceivably be associated with the maternal postpartum serum-POP concentrations, as cesarean compared to vaginal delivery is associated with delayed or unsuccessful initiation of breastfeeding (52), which is an important route of POP exposure elimination for the mother (17), and increased blood loss that is compensated by blood transfusion of the mother in about 4% of cesarean sections (53).

The additional covariates included in the statistical models presented missing values in less than 6% of observations (Table 1 shows the results for the analysis of 18-month outcomes and Table S1 for the analysis of 5-year outcomes). We first performed complete-case analyses (i.e. excluding subjects with missing values from the models). To maximise the sample size, we also repeated the analyses after creating a "missing" category in the breastfeeding duration covariate, which was the only covariate of those retained in the fully adjusted models with missing information. Because the coefficients were similar in magnitude and significance to those obtained from the complete-case analyses, we present only the results from the analyses using a "missing" category in the covariate of breastfeeding.

Previous studies have reported associations of POP exposures with child BMI to be modified by child sex (19, 20, 23–25, 26), exclusive breastfeeding duration (24, 26) and maternal prepregnancy BMI (20, 24, 25). Thus, we evaluated effect modification by these factors by introducing interaction terms (POP exposure*modifier) in the fully adjusted models and stratifying models according to potential modifiers.

In sensitivity analyses we reran the statistical models after substituting the lipid-corrected OC concentrations (in ng/g lipid) by OC concentrations in ng/mL and including the serum lipid content as a separate covariate. Because elimination of POPs in the mother occurs during pregnancy through transplacental transfer and accumulation of exposure to the tissues of the fetus (16), we considered birth weight as a possible determinant of the maternal serum concentration measured after delivery. However, birth weight may likely mediate the associations between maternal exposure during pregnancy (that is reflected by the maternal

postpartum serum concentrations) to at least some of the POPs and child BMI, and in sensitivity analyses we therefore excluded birth weight from the fully adjusted models. Further, we repeated the analyses after excluding the 3.2% of the children who were preterm births (i.e. <37 weeks of gestation; n=14) and/or had low birth weights (i.e. <2500 gr; n=5), as those children would be more prone to catch-up growth during infancy (21). Finally, we compared the main characteristics between included and excluded from analysis mother-child pairs to evaluate the likelihood of selection bias.

Statistical significance level for all associations, including the evaluation of effect modifiers, was set as a two-sided p-value less than 0.05. DAGs were drawn using DAGitty version 2.3 (54). All statistical analyses were conducted using STATA 14.

3. Results

The prevalence of overweight (including obesity) was 15% at age 18 months and 19% at age 5 years. Overweight compared to normal weight children at age 18 months had higher average birth weights (3890 versus 3674 grams) and also higher weights (21.5 versus 19.1 kg) and heights (112 versus 110 cm) at age 5 years (Table 1). Mothers of overweight infants were somewhat younger at the time of delivery (28.8 versus 30.3 years), and more likely to have consumed alcohol during pregnancy (10% versus 4%). By the age of 5 years, children who were overweight compared to normal weight children (Table S1) were more likely to have breastfed for a shorter period (67% versus 50%), and their mothers had gained on average more weight during pregnancy (16.3 versus 14.5 kg) and were more likely to have smoked during pregnancy (23% versus 14%). Other characteristics did not significantly differ according to overweight status at either 18 months or 5 years of age.

The OCs detected in the highest concentrations in both maternal and child serum were the major PCB congeners and *p,p'*-DDE, and the most highly detected PFASs were PFOS and PFOA (Table 2). Comparable OC concentrations were detected in maternal and child serum, whereas all PFASs occurred in higher concentrations in child serum compared to maternal serum, except from PFOS for which concentrations were almost twice as high in maternal serum collected five years earlier. In regard to maternal serum concentrations, Pearson correlation coefficients ranged from 0.62 to 0.83 among the OCs, with the highest correlation shown between Σ PCBs and *p,p'*-DDE, and from 0.40 to 0.85 among the PFASs, with the highest correlation shown between PFNA and PFDA (Table S2). In regard to child serum concentrations, Pearson correlation coefficients ranged from 0.81 to 0.90 among the OCs, and from 0.28 to 0.74 among the PFASs (Table S2). Pearson correlation coefficients between maternal and child serum POP concentrations were the lowest for PFDA ($r=0.25$) and the highest for *p,p'*-DDE ($r=0.69$) (Table S2).

Maternal 2-week postpartum serum-HCB concentrations were associated with increased child's BMI z-scores at 18 months (adjusted β per log₁₀-unit HCB increase: 0.15; 95%CI: 0.01, 0.30) and at 5 years (adjusted β per log₁₀-unit HCB increase: 0.19; 95%CI: 0.04, 0.34) (Table 3). Associations between maternal serum-HCB concentrations and child's risk of overweight were in the same direction as the associations with BMI z-scores but did not reach statistical significance (Table 3). Maternal serum-PFOS concentrations were positively

associated with BMI z-scores (adjusted β per log10-unit PFOS increase: 0.23; 95%CI: 0.04, 0.42) and overweight risk (adjusted RR per log10-unit PFOS increase: 1.29; 95%CI: 1.01, 1.64) at age 18 months, but no association was observed at age 5 years. Marginally significant associations in the same direction as those for PFOS were seen for continuous PFOA and PFHxS concentrations in regard to the child's BMI z-scores at age 18 months. Further, maternal serum concentrations of PFOA, and less clearly for PFHxS, were associated with the child's risk of overweight at age 5 years (adjusted RR per log10-unit PFOA increase: 1.50; 95% CI: 1.01, 2.24). Other POPs were not significantly associated with the child's BMI z-scores or overweight risk at either age, with some evidence of non-linear inverse associations between maternal serum concentrations of PFNA and PFDA with the child's overweight risk at age 5. The adjusted associations for all POPs (Table 3) were in the same direction to those obtained from the unadjusted models (Table S3), and in particular for PFASs, the inclusion of additional covariates in the models tended to increase the magnitude of the associations.

The cross-sectional analyses at age 5 years revealed a pattern of inverse associations between most of the POPs measured in child serum and BMI z-scores or overweight risk, both in the unadjusted (Table S4) and in the fully adjusted models (Table 4). In fully adjusted models simultaneously adjusted for maternal and child serum POP concentrations (data not shown), the prospective and cross-sectional POP associations with child BMI z-scores or overweight at 5 years did not change substantially from those shown in the single time-point exposure models.

Child sex, exclusive breastfeeding duration or maternal prepregnancy BMI did not modify the associations of either maternal or child serum POP concentrations and child BMI z-scores (p for interactions tested in all models >0.20). In sensitivity analyses, associations between OCs and child BMI z-scores remained robust when OCs were expressed in terms of ng/mL and lipid concentrations were included as a separate covariate in the models (data not shown). Further, effect estimates for the associations of maternal serum-POP concentrations and child's BMI or overweight risk did not change substantially after omitting birth weight from the statistical models, or after excluding preterm births and/or children with low birth weights (data not shown). The mothers of children included compared to those excluded from the 5-year examination analyses were older at pregnancy (30.5 versus 27.2 years), gained less weight during pregnancy (14.9 versus 16.6 kg), and were less likely to be nulliparous (27% versus 40%). However, included and excluded children did not differ according to maternal prepregnancy BMI, birth weight and other characteristics (Table S5).

4. Discussion

In this prospective birth cohort study from the Faroe Islands, we evaluated a wide range of POP exposures and observed positive associations between maternal postpartum serum concentrations of HCB, PFOS and PFOA in regard to the child's BMI z-scores at ages 18 months and/or 5 years. Maternal serum-HCB concentrations were associated with increases in the child's risk for overweight at either age, although not reaching statistical significance, and maternal serum concentrations of PFOS and PFOA were significantly associated with increased risks for overweight at age 18 months and 5 years, respectively. Other measured

POPs (*p,p'*-DDE, Σ PCBs, PFHxS, PFNA and PFDA) were more weakly correlated with child BMI z-scores and/or overweight risk. Associations were not found to be influenced by child sex, duration of breastfeeding, and maternal prepregnancy BMI. In addition, they remained robust after adjustment for the child's serum-POP concentrations at age 5. Contrary to the positive associations shown for maternal serum, the cross-sectional analyses at age 5 showed a pattern of mainly inverse associations between child serum-POP concentrations and the concomitant BMI z-scores or overweight risk.

Cord serum-POP concentrations measured in a subset of births from this cohort were highly correlated to maternal 2-week postpartum serum concentrations, and high correlations have been also reported between POP concentrations in early pregnancy maternal serum and cord serum (18, 55). Therefore, the maternal postpartum serum concentrations in our study likely reflect early developmental exposure levels. Our findings are consistent with those of some previous birth cohort studies, though not all. Prenatal HCB exposure has been associated with the risk for overweight at 14 months (24), at 4 years (20) and 6.5 years of age (27) in previous studies with higher concentrations detected in maternal and/or cord serum. However, two other studies have reported no association between prenatal HCB exposures and obesity outcomes in childhood (26, 28). Differences in the levels of exposure could explain, at least in part, the inconsistencies in findings across studies. In the previous Faroese Cohort 3 (N=656), prenatal PCB and *p,p'*-DDE exposures were associated with increased BMI z-scores at ages 5–7 years in girls of overweight mothers, though not in boys or children of mothers with normal prepregnancy BMIs (25). The lack of replication in this most recent Faroese Cohort could be due to the decreased ranges and lower averages of OC exposures and/or the smaller sample size that reduces power for detecting significant associations, and in particular interactions.

The positive association we found between maternal serum-PFOS concentrations and child BMI z-scores at 18 months is in agreement with the positive association reported for prenatal PFOS exposure and weight-for-age in 20 month-old British girls (35). In our study, this association did not persist at age 5, which is in agreement with the findings of three previous studies that did not observe significant associations with child BMI and/or overweight risk at mid- and late- childhood (33, 36, 38). Further, two of these studies found no clear association between prenatal exposure to PFOA and childhood overweight (33, 38), while the other study showed a positive association between PFOA and the child's BMI (36), in agreement with the positive association with overweight risk at age 5 years reported in the present study. Although the moderate to high correlations shown between PFOS and PFOA in this and other studies do not allow us to identify their relative contributions to the associations, the findings of this study may suggest that PFOS associations with obesity primarily appear in early childhood, while PFOA associations become apparent at later ages. The continuous follow-up of the Faroese cohort will hopefully permit us to elucidate whether the associations persist at later life stages. Other emerging PFASs (PFHxS and PFNA) have been assessed in only two previous prospective studies reporting non-significant associations with child obesity outcomes (35, 36), which is in agreement with our findings.

The child's age-5 serum-POP concentrations were not associated with increases in child BMI and did not affect the associations of maternal serum-POP concentrations, thus suggesting that exposure during fetal and/or perinatal life may be the most critical window of susceptibility. The inverse cross-sectional associations observed for POPs and child BMI z-scores at age 5 years may likely be due to reverse causation associated with the expanded distribution volumes in obese compared to lean children, or unmeasured confounding and the lack of adequate adjustment for child's dietary habits and physical activity. One previous study similarly reported postnatal PCB153 exposure, estimated based on pharmacokinetic models, to be negatively associated with child growth at age 2 years, while null associations were reported for prenatal PCB153 exposure (29). The differences in findings between maternal and child serum concentrations in our study highlight that conclusions based on cross-sectional associations involve caveats, as the findings may not reflect prospective associations. As the children are growing older, the prospective evaluation of the associations between the measured child's serum-POP concentrations and subsequent changes in children's BMI at later ages may help to broaden the understanding of the role of postnatal POP exposures on children's growth.

The maternal serum-OC concentrations in this Faroese population were generally lower than those reported in previous birth cohort studies (23, 26, 27). The decrease in OC concentrations throughout recent decades is likely due to the decreased use of OCs in Western countries since the 1970s (11). Similarly, maternal serum-PFOA and serum-PFOS concentrations were lower than those reported in some previous studies (32, 33, 35, 36). Maternal serum-PFHxS concentrations were also somewhat lower in our study compared to the concentrations reported previously in US and British pregnant women (35, 36), while PFNA concentrations were higher in the Faroese population than those reported previously in a Danish birth cohort (32). Increasing trends of PFNA and PFHxS concentrations from 1999 to 2008 have been noted in a previous study using data from the National Health and Nutrition Examination Survey (NHANES) (56). Therefore, prospective evidence on the health effects of these emerging PFASs is currently much needed.

The high participation rate at the follow-up examinations, the wide variety of POPs measured in serum of both the mothers and their children, and the minimal influence of numerous evaluated confounders, are important strengths of this study. One other strength is the low detection limits of the analytical methods for the quantification of serum POPs, which allowed almost complete quantification of the concentrations of all POPs, including those of emerging PFASs (>93% of analysed samples). The Faroese population is fairly homogeneous in regard to nationality and socioeconomic factors, and the likelihood of residual confounding is therefore reduced compared to other settings. Regardless of the differences in maternal age, gestational weight gain and parity, included and excluded children did not differ in regard to major determinants of child's BMI, such as maternal BMI status and birth weight, and any important selection bias is therefore unlikely. However, we cannot rule out the possibility that correlated exposures to other unmeasured prenatal and/or postnatal endocrine disruptors may confound the associations. Study limitations include the somewhat modest sample size that reduces the power, and the lack of detailed information on child's diet and physical activity that may have confounded the cross-sectional associations shown at age 5 years. However, the associations were robust after controlling

for maternal and child's fish consumption that represents a major source of POP exposures in the Faroe Islands (41, 42) and may also affect the child's growth. Finally, the possibility of chance findings due to multiple comparisons may need to be considered.

5. Conclusions

In this Faroese birth cohort born in 2007–2009, we found positive prospective associations between maternal serum concentrations of HCB, PFOS and PFOA and BMI z-scores and/or overweight risk in preschool children. Other measured POPs (*p,p'*-DDE, PCBs, PFHxS, PFNA and PFDA) were not significantly associated with child's BMI or risk for overweight. These findings support the suspected contribution of early-life exposures to endocrine disruptors in the global obesity epidemic. The pattern of inverse associations between serum-POP concentrations and BMI z-scores observed in cross-sectional analyses at age 5 years highlight the importance of evaluating these associations in prospective cohort studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	Body Mass Index
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
HCB	Hexachlorobenzene
OCs	Organochlorine Compounds
PCBs	Polychlorinated Biphenyls
PFASs	Perfluoroalkyl Substances
PFDA	Perfluorodecanoic Acid
PFHxS	Perfluorohexanesulfonate
PFNA	Perfluorononanoic Acid
PFOA	Perfluorooctanoic Acid
PFOS	Perfluorooctanesulfonic Acid
POPs	Persistent Organic Pollutants

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Table 1

Characteristics of the mother-child pairs from the Faroe Islands Cohort, overall and by child BMI status at age 18 months.

Characteristics	Overall N=444		Normal weight N=376 (85%)		Overweight N=68 (15%)		P-value ^d
	N	% or mean $\pm$ SD	N	% or mean $\pm$ SD	N	% or mean $\pm$ SD	
<i>Maternal characteristics</i>							
Faroes nationality							
No	18	4.0	15	4.0	3	4.4	
Yes	426	96.0	361	96.0	65	95.6	0.87
Age at delivery (years)	444	30.1 $\pm$ 5.4	376	30.3 $\pm$ 5.5	68	28.8 $\pm$ 5.7	0.04
BMI status							
Underweight/Normal weight	288	64.9	248	66.0	40	58.8	
Overweight	112	25.2	94	25.0	18	26.5	
Obese	44	9.9	34	9.0	10	14.7	0.31
Gestational weight gain (kg)	444	15.2 $\pm$ 5.7	376	15.1 $\pm$ 5.7	68	15.7 $\pm$ 5.8	0.39
Parity (number of previous births)							
0	126	28.4	104	27.7	22	32.3	
1	162	36.5	138	36.7	24	35.3	
2	156	35.1	134	35.6	22	32.3	0.72
Smoking during pregnancy							
No	374	84.2	321	85.4	53	77.9	
Yes	70	15.8	55	14.6	15	22.1	0.12
Alcohol intake during pregnancy							
No	421	95.8	360	95.7	61	89.7	
Yes	22	5.0	15	4.0	7	10.3	0.03
Missing	1	0.2	1	0.3	0	0.0	
Fish intake in pregnancy (dinners per week)							
1	182	38.5	97	41.4	85	40.5	
1–2	143	33.4	75	32.0	68	32.4	
>2	119	28.1	62	26.5	57	27.1	0.97
Gestational diabetes							

Characteristics	Overall N=444		Normal weight N=376 (85%)		Overweight N=68 (15%)		P-value ^d
	N	% or mean ± SD	N	% or mean ± SD	N	% or mean ± SD	
No	433	97.5	366	97.3	67	98.5	
Yes	10	2.3	9	2.4	1	1.5	0.63
<i>Missing</i>	1	0.2	1	0.3	0	0.0	
Type of delivery							
Vaginal	386	86.9	329	87.5	57	83.8	
Cesarean	58	13.1	47	12.5	11	16.2	0.41
Child characteristics							
Child sex							
Boy	231	52.0	191	50.8	40	58.8	
Girl	213	48.0	185	49.2	28	41.2	0.22
Preterm birth							
No	428	96.4	363	96.5	65	95.6	
Yes	14	3.2	11	3.0	3	4.4	0.52
<i>Missing</i>	2	0.4	2	0.5	2	0.95	
Birth weight (g)	444	3707±529	376	3674±532	68	3890±483	0.002
Gestational length (weeks)	444	39.7±1.5	376	39.7±1.5	68	39.7±1.4	0.89
Breastfeeding duration (months)							0.45
0–5	242	54.5	203	54.0	39	57.4	
>5–12	190	42.8	164	43.6	26	38.2	0.48
<i>Missing</i>	12	2.7	9	2.4	3	4.4	
At age 18 months							
Exact age at examination (months)	444	18.1±0.7	376	18.1±0.66	68	18.0±0.59	0.20
Weight (kg)	444	11.8±1.3	376	11.5±1.1	68	13.2±1.2	<0.001
Length (cm)	444	81.6±2.9	376	81.6±2.8	68	81.5±2.9	0.90
BMI z-score	444	1.15±0.9	376	0.9±0.7	68	2.5±0.5	<0.001
At age 5 years							
Exact age at examination (months)	361	59.9±0.8	306	60.0±0.8	55	59.8±0.7	0.12
<i>Missing</i>	83	18.7	70	18.6	13	19.2	
Weight (kg)	360	19.5±2.5	306	19.1±2.4	54	21.5±2.2	<0.001

Characteristics	Overall N=444		Normal weight N=376 (85%)		Overweight N=68 (15%)		P-value ^a
	N	% or mean ± SD	N	% or mean ± SD	N	% or mean ± SD	
<i>Missing</i>	84	18.9	70	18.6	14	20.6	
Height (cm)	360	110.6±4.4	306	110±4.4	54	112±4.0	0.03
<i>Missing</i>	84	18.9	70	18.6	14	20.6	
BMI z-score	360	0.4±0.8	306	0.23±0.8	54	1.23±0.7	<0.001
<i>Missing</i>	84	18.9	70	18.6	14	20.6	
Fish intake (dinners per week)							
1	139	31.3	118	31.4	21	30.9	
1-2	168	37.8	139	37.0	29	42.7	
>2	54	12.1	49	13.0	5	7.3	0.36
<i>Missing</i>	83	18.7	70	18.6	13	19.1	

^aStudent's t test for continuous covariates (normally distributed) and chi-square test for categorical variables.

Table 2

Concentrations of POPs in maternal and child serum.

POP		Maternal 2-week postpartum serum							Child 5-year serum						
Compound	Unit	%<LOD ^a	GM	Min	Percentiles			Max	%<LOD ^a	GM	Min	Percentiles			Max
					25	50	75					25	50	75	
HCB	µg/g-lipid	0.8%	0.02	0.00	0.01	0.02	0.02	0.12	0%	0.02	0.01	0.02	0.02	0.03	0.09
	ng/mL	0.8%	0.14	0.02	0.10	0.14	0.21	1.00	0%	0.13	0.03	0.09	0.13	0.18	0.48
ΣPCBs	µg/g-lipid	0%	0.42	0.02	0.25	0.42	0.78	2.96	0%	0.40	0.02	0.22	0.48	0.88	3.50
	ng/mL	0%	3.48	0.12	2.02	3.56	6.57	23.6	0%	2.11	0.10	1.16	2.50	4.61	18.7
p,p'-DDE	µg/g-lipid	0%	0.13	0.01	0.07	0.13	0.29	1.52	0%	0.19	0.01	0.08	0.20	0.39	2.60
	ng/mL	0%	1.09	0.04	0.56	1.15	2.36	11.9	0%	0.97	0.07	0.44	1.05	2.10	12.6
PFOS	ng/mL	0%	8.04	1.89	6.23	8.25	10.6	24.6	0%	4.68	1.01	3.50	4.70	6.34	16.3
	ng/mL	0%	1.37	0.25	0.95	1.40	1.95	6.49	0%	2.22	0.68	1.75	2.20	2.80	13.3
PFHxS	ng/mL	2.8%	0.19	0.02	0.13	0.20	0.31	1.49	0%	0.34	0.08	0.24	0.33	0.45	3.30
PFNA	ng/mL	0%	0.67	0.18	0.52	0.66	0.86	4.30	0%	1.12	0.12	0.79	1.13	1.64	5.75
PFDA	ng/mL	0%	0.26	0.07	0.19	0.26	0.35	1.00	0.6%	0.33	0.02	0.25	0.34	0.47	1.72

^aValues below the limit of detection (LOD) are substituted by LOD/2.

GM: geometric mean

Table 3

Adjusted associations of POPs in maternal 2-week postpartum serum with child BMI z-scores and overweight at ages 18 months and 5 years.

Maternal serum POP	Child outcomes at 18 months N=444		Child outcomes at 5 years N=371	
	BMI z-score	Overweight	BMI z-score	Overweight
	β (95%CI) ^a	RR (95% CI) ^a	β (95%CI) ^a	RR (95% CI) ^a
HCB (µg/g-lipid)				
Per log ₋₁₀ unit increase	0.15 (0.01, 0.30) **	1.11 (0.92, 1.34)	0.19 (0.04, 0.34) **	1.46 (0.95, 2.24) *
<0.01	Reference	Reference	Reference	Reference
0.01–0.02	0.06 (–0.14, 0.26)	1.06 (0.83, 1.36)	0.00 (–0.20, 0.21)	0.84 (0.46, 1.52)
>0.02	0.21 (0.01, 0.41) **	1.09 (0.84, 1.40)	0.25 (0.05, 0.46) **	1.30 (0.77, 2.18)
ΣPCBs (µg/g-lipid)				
Per log ₋₁₀ unit increase	–0.01 (–0.12, 0.09)	0.98 (0.86, 1.11)	0.05 (–0.06, 0.16)	1.24 (0.92, 1.67)
<0.30	Reference	Reference	Reference	Reference
0.30–0.66	–0.14 (–0.34, 0.06)	0.90 (0.70, 1.15)	–0.01 (–0.22, 0.19)	0.82 (0.44, 1.52)
>0.66	–0.06 (–0.26, 0.15)	0.95 (0.74, 1.21)	0.10 (–0.11, 0.31)	1.59 (0.95, 2.66) *
p,p'-DDE (µg/g-lipid)				
Per log ₋₁₀ unit increase	0.01 (–0.07, 0.09)	0.97 (0.88, 1.08)	0.05 (–0.04, 0.13)	1.17 (0.93, 1.47)
<0.09	Reference	Reference	Reference	Reference
0.09–0.22	0.11 (–0.08, 0.31)	0.96 (0.76, 1.22)	0.07 (–0.13, 0.27)	0.97 (0.56, 1.67)
>0.22	0.05 (–0.15, 0.26)	1.03 (0.80, 1.31)	0.14 (–0.06, 0.35)	1.32 (0.79, 2.22)
PFOS (ng/mL)				
Per log ₋₁₀ unit increase	0.23 (0.04, 0.42) **	1.29 (1.01, 1.64) **	0.04 (–0.15, 0.22)	1.01 (0.58, 1.75)
<6.83	Reference	Reference	Reference	Reference
6.83–9.68	0.08 (–0.12, 0.28)	1.05 (0.82, 1.34)	0.06 (–0.15, 0.26)	1.13 (0.68, 1.87)
>9.68	0.20 (0.01, 0.40) **	1.24 (0.98, 1.57) *	–0.01 (–0.22, 0.19)	0.94 (0.53, 1.66)
PFOA (ng/mL)				
Per log ₋₁₀ unit increase	0.14 (–0.03, 0.31)	1.14 (0.92, 1.40)	0.16 (–0.01, 0.33) *	1.50 (1.01, 2.24) **
<1.07	Reference	Reference	Reference	Reference
1.07–1.72	0.11 (–0.09, 0.31)	1.16 (0.91, 1.47)	0.16 (–0.04, 0.37)	1.33 (0.75, 2.35)
>1.72	0.06 (–0.16, 0.28)	1.10 (0.84, 1.46)	0.11 (–0.11, 0.34)	1.88 (1.05, 3.35) **
PFHxS (ng/mL)				
Per log ₋₁₀ unit increase	0.10 (–0.01, 0.21) *	1.12 (0.97, 1.30)	0.04 (–0.07, 0.15)	1.11 (0.77, 1.59)
<0.16	Reference	Reference	Reference	Reference
0.16–0.27	–0.03 (–0.23, 0.17)	1.06 (0.82, 1.38)	–0.02 (–0.22, 0.19)	0.86 (0.47, 1.55)
>0.27	0.18 (–0.03, 0.38) *	1.24 (0.97, 1.58) *	0.07 (–0.14, 0.28)	1.22 (0.73, 2.04)
PFNA (ng/mL)				
Per log ₋₁₀ unit increase	0.01 (–0.19, 0.21)	1.02 (0.79, 1.31)	–0.00 (–0.21, 0.20)	1.15 (0.67, 1.98)
<0.57	Reference	Reference	Reference	Reference

Maternal serum POP	Child outcomes at 18 months N=444		Child outcomes at 5 years N=371	
	BMI z-score	Overweight	BMI z-score	Overweight
	β (95%CI) ^a	RR (95% CI) ^a	β (95%CI) ^a	RR (95% CI) ^a
0.57–0.79	−0.13 (−0.33, 0.06)	0.80 (0.62, 1.02) *	−0.15 (−0.35, 0.05)	0.61 (0.35, 1.06) *
>0.79	0.01 (−0.19, 0.20)	1.02 (0.81, 1.28)	−0.06 (−0.26, 0.14)	1.04 (0.65, 1.66)
PFDA (ng/mL)				
Per log ₁₀ unit increase	0.09 (−0.10, 0.26)	1.14 (0.91, 1.43)	−0.04 (−0.23, 0.14)	1.02 (0.61, 1.70)
<0.22	Reference	Reference	Reference	Reference
0.22–0.32	−0.07 (−0.27, 0.13)	0.90 (0.71, 1.15)	−0.14 (−0.34, 0.06)	0.51 (0.29, 0.88) **
>0.32	0.06 (−0.14, 0.26)	1.03 (0.82, 1.31)	−0.07 (−0.27, 0.13)	0.86 (0.55, 1.36)

**
P-value<0.05;

*
P-value 0.05 and <0.10.

^a All models are adjusted for maternal nationality, age at delivery, prepregnancy BMI, gestational weight gain, parity, smoking during pregnancy, maternal fish intake during pregnancy, type of delivery, child sex and birth weight.

Table 4

Adjusted cross-sectional associations of POPs in child serum with child BMI z-scores and overweight at age 5 years.

Child serum POP	Child outcomes at 5 years N=349	
	BMI z-score	Overweight
	β (95%CI) ^a	RR (95% CI) ^a
HCB (µg/g-lipid)		
Per log ₋₁₀ unit increase	-0.26 (-0.45, -0.06) **	0.65 (0.39, 1.08)
<0.02	Reference	Reference
0.02–0.03	-0.14 (-0.36, 0.09)	0.88 (0.52, 1.48)
>0.03	-0.30 (-0.52, -0.07) **	0.56 (0.31, 1.03) *
ΣPCBs (µg/g-lipid)		
Per log ₋₁₀ unit increase	-0.13 (-0.22, -0.04) **	0.83 (0.67, 1.02) *
<0.29	Reference	Reference
0.30–0.70	-0.10 (-0.32, 0.12)	0.85 (0.49, 1.51)
>0.70	-0.39 (-0.61, -0.16) **	0.66 (0.37, 1.19)
p,p'-DDE (µg/g-lipid)		
Per log ₋₁₀ unit increase	-0.06 (-0.15, 0.03)	0.92 (0.74, 1.15)
<0.13	Reference	Reference
0.13–0.31	-0.02 (-0.24, 0.21)	0.75 (0.40, 1.39)
>0.31	-0.09 (-0.32, 0.14)	0.90 (0.52, 1.55)
PFOS (ng/mL)		
Per log ₋₁₀ unit increase	-0.21 (-0.44, 0.02) *	0.68 (0.36, 1.29)
<3.87	Reference	Reference
3.87–5.58	-0.16 (-0.38, 0.07)	0.68 (0.38, 1.21)
>5.58	-0.16 (-0.39, 0.07)	0.87 (0.51, 1.51)
PFOA (ng/mL)		
Per log ₋₁₀ unit increase	-0.27 (-0.52, -0.02) **	0.68 (0.38, 1.22)
<1.88	Reference	Reference
1.88–2.55	0.05 (-0.17, 0.27)	0.76 (0.44, 1.31)
>2.55	-0.14 (-0.36, 0.08)	0.84 (0.48, 1.44)
PFHxS (ng/mL)		
Per log ₋₁₀ unit increase	-0.15 (-0.34, 0.04)	0.73 (0.44, 1.23)
<0.28	Reference	Reference
0.28–0.39	0.07 (-0.15, 0.30)	1.00 (0.59, 1.70)
>0.39	-0.12 (-0.35, 0.11)	0.94 (0.54, 1.62)
PFNA (ng/mL)		
Per log ₋₁₀ unit increase	-0.18 (-0.34, -0.02) **	0.67 (0.45, 1.00) *
<0.91	Reference	Reference

Child serum POP	Child outcomes at 5 years N=349	
	BMI z-score	Overweight
	β (95%CI) ^a	RR (95% CI) ^a
0.91–1.44	−0.05 (−0.27, 0.17)	1.15 (0.69, 1.92)
>1.44	−0.22 (−0.44, 0.01) *	0.70 (0.38, 1.30)
PFDA (ng/mL)		
Per log ₋₁₀ unit increase	−0.18 (−0.33, −0.02) **	0.64 (0.46, 0.90) **
<0.28	Reference	Reference
0.28–0.42	−0.22 (−0.44, −0.00) **	0.53 (0.30, 0.94) **
>0.42	−0.19 (−0.41, 0.02) *	0.58 (0.34, 0.97) **

**
P-value<0.05;

*
P-value 0.05 and <0.10.

^a All models are adjusted for maternal nationality, age at delivery, prepregnancy BMI, smoking during pregnancy, child sex, exclusive breastfeeding duration and child's fish intake at age 5 years.