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Prenatal exposure to endocrine disrupting chemicals and risk of being born small for gestational age: Pooled analysis of seven European birth cohorts

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ABSTRACT

Background and aims: There is evidence that endocrine disrupting chemicals (EDCs) have developmental effects at environmental concentrations. We investigated whether some EDCs are associated with the adverse birth outcome Small for Gestational Age (SGA).

Methods: We used PCB 153, *p,p'*-DDE, HCB, PFOS and PFOA measured in maternal, cord blood or breast milk samples of 5446 mother-child pairs (subset of 693 for the perfluorinated compounds) from seven European birth cohorts (1997–2012). SGA infants were those with birth weight below the 10th percentile for the norms defined by gestational age, country and infant's sex. We modelled the association between measured or estimated cord serum EDC concentrations and SGA using multiple logistic regression analyses. We explored effect modification by child's sex and maternal smoking during pregnancy.

Results: Among the 5446 newborns, 570 (10.5%) were SGA. An interquartile range (IQR) increase in PCB 153 was associated with a modestly increased risk of SGA (odds ratio (OR) of 1.05 [95% CI: 1.04–1.07]) that was stronger in girls (OR of 1.09 [95% CI: 1.04–1.14]) than in boys (OR of 1.03 [95% CI: 1.03–1.04]) (*p*-interaction = 0.025). For HCB, we found a modestly increased odds of SGA in girls (OR of 1.04 [95% CI: 1.01–1.07] per IQR increase), and an inverse association in boys (OR of 0.90 [95% CI: 0.85–0.95]) (*p*-interaction = 0.0003). Assessment of the HCB-sex-smoking interaction suggested that the increased odds of SGA associated with HCB exposure was only in girls of smoking mothers (OR of 1.18 [95% CI: 1.11–1.25]) (*p*-interaction = 0.055). Higher concentrations of PFOA were associated with greater risk of SGA (OR of 1.64 [95% CI: 0.97–2.76]). Elevated

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PFOS levels were associated with increased odds of SGA in newborns of mothers who smoked during pregnancy (OR of 1.63 [95% CI: 1.02–2.59]), while an inverse association was found in those of non-smoking mothers (OR of 0.66 [95% CI: 0.61–0.72]) (*p*-interaction = 0.0004). No significant associations were found for *p,p'*-DDE.
Conclusions: Prenatal environmental exposure to organochlorine and perfluorinated compounds with endocrine disrupting properties may contribute to the prevalence of SGA. We found indication of effect modification by child's sex and smoking during pregnancy. The direction of the associations differed by chemical and these effect modifiers, suggesting diverse mechanisms of action and biological pathways.

1. Introduction

A suboptimal intra-uterine environment can affect fetal growth and contribute to the risk of developing adult diseases (Barker, 1998). The fetus depends on an accurate hormone balance for its development (Diamanti-Kandarakis et al., 2009). Concern has risen since several endocrine disrupting chemicals (EDCs), particularly those with estrogenic activity, are suspected of disrupting the programming of endocrine signaling pathways during development (Newbold, 2011). Maternal exposure to EDCs has been associated with fetal growth (de Cock and van de Bor, 2014; Tang-Peronard et al., 2011). During gestation, fetuses are exposed to the accumulated maternal body burden of persistent organic pollutants with endocrine properties, including: polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (*p,p'*-DDE), hexachlorobenzene (HCB), perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). Despite regulatory measures and due to their long half-lives, these compounds are still ubiquitous in the environment and detected in a variety of human tissues and fluids (Malisch and Kotz, 2014). The human elimination half-lives of PCB 153, *p,p'*-DDE, HCB, PFOS and PFOA are > 10 years (Ritter et al., 2011), ~5 years (Ferreira et al., 2011), ~6 years (To-Figueras et al., 2000), ~5 years (Olsen et al., 2007), and 3.5 years (Olsen et al., 2007), respectively. Due to their high lipophilicity (organochlorine compounds) or amphoteric properties (perfluorinated compounds) these compounds are transported via the placenta to the fetus and can also reach the infant through maternal milk (Stefanidou et al., 2009; WHO/UNEP, 2013).

Up to date, most epidemiological studies have investigated associations between EDCs and birth weight or other continuous measures like birth length, head circumference, gestational age, and most of them reported significant inverse associations, i.e. lower birth weight, birth length and head circumference for increased EDC concentrations, including HCB (Eggesbo et al., 2009), PCBs (Govarts et al., 2012) and perfluorinated compounds (Bach et al., 2015; Johnson et al., 2014). However, there is much variation in studies reporting on these associations with several studies observing no significant association (Berkowitz et al., 1996; Gladen et al., 2003; Khanjani and Sim, 2006; Longnecker et al., 2005; Wolff et al., 2007). Moreover, although birth weight is accurately measured, its interpretation is not always obvious (EURO-PERISTAT, 2013). Investigating infants born small for gestational age (SGA) has advantages since it is a clinical outcome, and therefore has clear implications for public health (Lee et al., 2013). Only a few studies, have looked at the association of EDCs and SGA (Basterrechea et al., 2014; Eggesbo et al., 2009; Lauritzen et al., 2017; Longnecker et al., 2005; Manzano-Salgado et al., 2017). Longnecker et al. (Longnecker et al., 2005) found a significant positive association of PCBs with SGA while no significant association was found for birth weight. The HUMIS cohort found a positive association close to significance of HCB with SGA (Eggesbo et al., 2009), while Basterrechea et al. (Basterrechea et al., 2014) found no significant association for HCB. In a recent Scandinavian study, prenatal exposure to PFOA, PCB 153 and HCB were significantly associated with higher odds for SGA (Lauritzen et al., 2017). Manzano-Salgado et al. (Manzano-Salgado et al., 2017) found no significant associations between some perfluorinated compounds and SGA, whereas PFOS exposure was associated with low birth weight in boys.

In the present study, we harmonized and pooled data from seven European birth cohorts with organochlorine measures and four of them with measures of the perfluorinated compounds, providing a large study sample to investigate the association between the selected EDCs and SGA. This allowed us to examine the hypothesis that EDCs influence fetal growth.

2. Methods

2.1. Description of cohorts

Within the EU-FP7 OBELIX project, five European birth cohorts were available for our pooled analysis: FLEHS I and II (FLemish Environment and Health Study), HUMIS (HUman Milk Study), LINC (LInking EDCs in maternal Nutrition to Child health) and PCB cohort of Flanders, Norway, The Netherlands and Slovakia respectively. We invited two additional cohorts, INMA (INfancia y Medio Ambiente; Environment and Childhood) (Spain) and PELAGIE (Endocrine disruptors: longitudinal study on pathologies of pregnancy, infertility and childhood) (France), resulting in seven European birth cohorts. Cohort participants were sampled from the general population and included births from 1997 to 2012. The INMA cohort was considered as two populations based upon the matrix (one available per child) used for the EDC measurements (maternal or cord serum). This makes a total of 8 study populations. Our study population sample was restricted to live-born singleton births, with available exposure levels and information on at least one birth outcome. In total, we used EDC measurements from 5446 women. Table 1 lists cohort characteristics, while Supplemental Material, Table S1 contains cohorts' descriptions and references. Each cohort study was approved by the national ethical committee. Mothers provided written informed consent prior to participation.

2.2. Exposure assessment

All cohorts provided concentrations from the selected exposure markers if available. PCB 153 was selected as a marker of overall exposure to PCBs (used in many industrial applications), since it is the most abundant congener (Hagmar et al., 2006) and highly correlated with most of the congeners, *p,p'*-DDE because it is the most persistent metabolite of the widely used insecticide DDT (Agency for Toxic Substances and Disease Registry (ATSDR), 2002), and HCB, another organochlorine pesticide widely used as fungicide. PFOS and PFOA were included as markers for exposure to the perfluorinated compounds which are used as fluorosurfactants in consumer products such as teflon, stain-resisting fabrics and fire-fighting foams. Information on chemical-analytical methods and their limits of detection/quantification (LODs/LOQs) together with the lipid analysis method of the sampled matrices is given in the Supplemental Material, p.6–7 and Table S2. Concentrations below the LOD/LOQ were replaced with LOD/LOQ divided by $\sqrt{2}$ (Hornung and Reed, 1990). Cohorts with ≥50% of samples below the LOD/LOQ for an exposure biomarker were excluded from the analysis of that exposure biomarker.

Since cord serum levels are considered the best proxy of organochlorine exposure during fetal life (Korrick et al., 2000), we estimated the equivalent concentrations in cord serum from the concentrations measured in maternal serum or breast milk.

Table 1
Characteristics of the 8 study populations.

Characteristics	FLEHS I (Belgium, 2002–2004)	FLEHS II (Belgium, 2008–2009)	HUMIS (Norway, 2002–2006)	INMA cord (Spain, 1997–2008)	INMA mat (Spain, 2004–2008)	LINC (The Netherlands, 2011–2012)	PCB cohort (Slovakia, 2002–2004)	PELAGIE (France, 2002–2006)
N[a]	1105	242	440	1287	860	84	1034	394
Small for gestational age								
Yes	113 (10.2%)	17 (7.0%)	60 (13.6%)	129 (10.0%)	91 (10.6%)	4 (4.8%)	127 (12.3%)	29 (7.4%)
No	992 (89.8%)	225 (93.0%)	380 (86.4%)	1158 (90.0%)	769 (89.4%)	80 (95.2%)	907 (87.7%)	365 (92.6%)
Birth weight (g)	3390 (1245–5575)	3530 (2175–4950)	3614 (2015–5100)	3250 (1200–4880)	3290 (770–4785)	3600 (2130–4950)	3350 (950–5060)	3370 (1070–4760)
Gestational Age (GA) (weeks)	39 (31–42)	40 (34–42)	40 (35–44)	40 (30–42)	40 (28–42)	40 (34–42)	40 (30–43)	40 (27–42)
Determination of GA								
1st day last menstruation				964 (74.9%)		84 (100%)	1034 (100%)	
Ultrasound								394 (100%)
Combination			440 (100%)	323 (25.1%)	860 (100%)			
Missing (%)	100%	100%	0%	0%	0%	0%	0%	0%
Term								
Preterm (< 37 weeks)	38 (3.4%)	5 (2.1%)	10 (2.3%)	52 (4.0%)	29 (3.4%)	3 (3.6%)	25 (2.4%)	10 (2.5%)
Term (37–42 weeks)	1067 (96.6%)	237 (97.9%)	406 (92.3%)	1217 (94.6%)	822 (95.6%)	81 (96.4%)	1007 (97.4%)	384 (97.5%)
Over term (> 42 weeks)	0 (0%)	0 (0%)	24 (5.5%)	18 (1.4%)	9 (1.1%)	0 (0%)	2 (0.2%)	0 (0%)
Child gender								
Boy	577 (52.2%)	126 (52.1%)	227 (51.6%)	676 (52.5%)	427 (49.7%)	50 (64.1%)	526 (50.9%)	200 (50.8%)
Girl	528 (47.8%)	116 (47.9%)	213 (48.4%)	611 (47.5%)	433 (50.4%)	28 (35.9%)	508 (49.1%)	194 (49.2%)
Missing (%)	0%	0%	0%	0%	0%	7.1%	0%	0%
Maternal age at delivery (years)	29.6 (18.1–44.0)	30.2 (18.2–42.4)	29 (16–42)	31.1 (16.7–44.5)	31.8 (17.8–43.8)	31.3 (23.1–40.4)	25.5 (17.9–44.9)	30.4 (20.1–44.9)
Missing (%)	0.5%	0%	0%	1.2%	0.1%	6.0%	0.8%	0%
Maternal age at delivery								
< 25 years	157 (14.3%)	27 (11.2%)	73 (16.6%)	107 (8.4%)	35 (4.1%)	5 (6.3%)	477 (46.5%)	33 (8.4%)
25 < 30 years	425 (38.7%)	89 (36.8%)	176 (40.0%)	398 (31.3%)	234 (27.2%)	22 (27.9%)	339 (33.0%)	150 (38.1%)
30 < 35 years	404 (36.8%)	93 (38.4%)	127 (28.9%)	529 (41.6%)	392 (45.6%)	35 (44.3%)	164 (16.0%)	150 (38.1%)
≥35 years	113 (10.3%)	33 (13.6%)	64 (14.6%)	238 (18.7%)	198 (23.1%)	17 (21.5%)	46 (4.5%)	61 (15.5%)
Missing (%)	0.5%	0%	0%	1.2%	0.1%	6.0%	0.8%	0%
Maternal pre-pregnancy BMI (kg/m^2)	22.4 (14.0–44.6)	22.3 (16.0–47.4)	23.1 (16.6–43.8)	22.5 (15.8–49.6)	22.4 (14.9–53.8)	22.5 (17.7–36.5)	21.2 (14.5–40.7)	21.4 (16.5–37.6)
Missing (%)	3.0%	0.8%	1.8%	1.2%	0%	2.4%	4.4%	1.0%
Maternal pre-pregnancy BMI								
< 18.5 kg/m^2	60 (5.6%)	15 (6.3%)	14 (3.2%)	53 (4.2%)	43 (5.0%)	2 (2.4%)	126 (12.8%)	29 (7.4%)
18.5 < 25 kg/m^2	737 (68.8%)	169 (70.4%)	275 (63.7%)	911 (71.7%)	598 (69.5%)	63 (76.8%)	680 (68.8%)	303 (77.7%)
25 < 30 kg/m^2	201 (18.8%)	36 (15.0%)	99 (22.9%)	224 (17.6%)	158 (18.4%)	10 (12.2%)	128 (13.0%)	43 (11.0%)
≥30 kg/m^2	74 (6.9%)	20 (8.3%)	44 (10.2%)	83 (6.5%)	61 (7.1%)	7 (8.5%)	54 (5.5%)	15 (3.9%)
Missing (%)	3.0%	0.8%	1.8%	1.2%	0%	2.4%	4.4%	1.0%
Maternal gestational weight gain (kg)	13 (0–35)	/	14 (−3–31)	13.2 (−5.7–37.1)	13.5 (−7.4–30.4)	13 (−6–23)	14 (1–35)	13 (3–31)
Missing (%)	50.2%	100%	2.5%	36.8%	6.6%	9.5%	27.1%	38.3%
Maternal height (cm)	167 (149–184)	168 (148–183)	168 (149–199)	162 (135–185)	163 (145–180)	171 (158–187)	165 (133–186)	164 (146–190)
Missing (%)	2.0%	0.8%	0.7%	1.2%	0%	1.2%	0%	0%
Maternal height								
< 163 cm	281 (26.0%)	50 (20.8%)	84 (19.2%)	656 (51.6%)	389 (45.2%)	6 (7.2%)	362 (35.0%)	154 (39.4%)
163–169 cm	406 (37.5%)	90 (37.5%)	172 (39.4%)	422 (33.2%)	312 (36.3%)	17 (20.5%)	407 (39.4%)	152 (38.9%)
≥169 cm	396 (36.6%)	100 (41.7%)	181 (41.4%)	193 (15.2%)	159 (18.5%)	60 (72.3%)	265 (25.6%)	85 (21.7%)
Missing (%)	2.0%	0.8%	0.7%	1.2%	0%	1.2%	0%	0.8%
Parity								
0	670 (60.6%)	98 (40.5%)	184 (41.8%)	667 (51.8%)	481 (56.1%)	31 (38.3%)	438 (42.5%)	172 (43.7%)
1	297 (26.9%)	80 (33.1%)	172 (39.1%)	489 (38.0%)	323 (37.7%)	31 (38.3%)	338 (32.8%)	142 (36.0%)
≥2	138 (12.5%)	64 (26.5%)	84 (19.1%)	131 (10.2%)	54 (6.3%)	19 (23.5%)	255 (24.7%)	80 (20.3%)
Missing (%)	0%	0%	0%	0%	0.2%	3.6%	0.3%	0%
Maternal education								
Secondary education or less	847 (78.6%)	91 (38.6%)	156 (35.5%)	932 (73.5%)	541 (63.1%)	27 (33.3%)	952 (92.3%)	142 (36.0%)
Higher education	230 (21.4%)	145 (61.4%)	283 (64.5%)	336 (26.5%)	316 (36.9%)	54 (66.7%)	79 (7.7%)	252 (64.0%)
Missing (%)	2.5%	2.5%	0.2%	1.5%	0.3%	3.6%	0.3%	0%
Maternal smoking during pregnancy								
Yes	179 (16.2%)	29 (12.2%)	51 (11.6%)	383 (30.1%)	234 (27.8%)	3 (3.7%)	158 (15.3%)	56 (14.4%)
No	923 (83.8%)	208 (87.8%)	389 (88.4%)	891 (69.9%)	607 (72.2%)	78 (96.3%)	876 (84.7%)	333 (85.6%)
Missing (%)	0.3%	2.1%	0%	1.0%	2.2%	3.6%	0%	1.3%

(*continued on next page*)

Table 1 (*continued*)

Characteristics	FLEHS I (Belgium, 2002–2004)	FLEHS II (Belgium, 2008–2009)	HUMIS (Norway, 2002–2006)	INMA cord (Spain, 1997–2008)	INMA mat (Spain, 2004–2008)	LINC (The Netherlands, 2011–2012)	PCB cohort (Slovakia, 2002–2004)	PELAGIE (France, 2002–2006)
Ethnicity								
Caucasian			415 (94.3%)	1223 (96.1%)	834 (97.0%)		799 (78.9%)	
Inuit			3 (0.7%)					
Roma			1 (0.2%)				214 (21.1%)	
Other			4 (0.9%)	49 (3.9%)	26 (3.0%)			
Missing (%)	100%	100%	3.9%	1.2%	0%	100%	2.0%	100%
Sample type[b]								
Cord blood	1105 (100%)	242 (100%)		1287 (100%)		66 (78.6%)	1026 (99.2%)	394 (100%)
Maternal blood					860 (100%)			
Breast milk			440 (100%)			61 (72.6%)	210 (20.3%)	
Caesarean section								
Yes	53 (4.8%)	11 (4.6%)	60 (13.6%)	151 (12.8%)	101 (14.4%)	3 (3.6%)		50 (12.9%)
No	1052 (95.2%)	230 (95.4%)	380 (86.4%)	1032 (87.2%)	599 (85.6%)	81 (96.4%)		337 (87.1%)
Missing (%)	0%	0.4%	0%	8.1%	18.6%	0%	100%	1.8%

Continuous measures described by median (min-max); categorical measures described by frequencies (%). Abbreviations: SGA, Small for Gestational Age; BMI, body mass index.

[a] Number of live-born singleton births with exposure levels and information on at least one outcome.

[b] Some mothers of the PCB and LINC cohort had more than one biological sample (cord blood and breast milk), however to assess exposure, only one sample type was used depending on the compound.

The non-dioxin-like organochlorine compounds PCB 153, *p,p'*-DDE and HCB were measured in cord plasma or serum for FLEHS I & II, the PCB cohort and PELAGIE, in breast milk for HUMIS, in cord plasma or breast milk for the LINC cohort, and in cord or maternal serum for the INMA cohort. For the recalculation of PCB 153 and *p,p'*-DDE to cord serum levels, we used conversion factors obtained from a previous study (Govarts et al., 2012):

$$\text{Cord serum level (ng/L)} = 0.20 \times \text{maternal serum level (ng/L)}$$

$$\text{Cord serum level (ng/L)} = 1.20 \times \text{breast milk level (ng/g fat)}$$

For HCB, we obtained conversion factors from available data in the literature (Palkovicova Murinova et al., 2017; Patayova et al., 2013):

$$\text{Cord serum level (ng/L)} = 0.265 \times \text{maternal serum level (ng/L)}$$

$$\text{Cord serum level (ng/L)} = 2.18 \times \text{breast milk level (ng/g fat)}$$

Due to variability between the published milk/maternal serum HCB concentration ratios (Palkovicova Murinova et al., 2017), a sensitivity analysis was performed using the minimum and maximum ratios of 0.848 and 1.87, respectively, which resulted in a conversion factor of 1.42 and 3.13, respectively, for the conversion of breast milk levels to cord serum levels.

The perfluorinated compounds PFOS and PFOA were measured in breast milk samples for HUMIS and the PCB cohort, in cord plasma for FLEHS II and in cord plasma or breast milk for the LINC cohort. Based on the recently published partitioning coefficients for breast milk:-plasma of 0.014 and 0.058 and fetal:maternal plasma concentrations of 0.45 and 0.78 for PFOS and PFOA respectively in Verner et al. (Verner et al., 2016), the following conversion factors were obtained:

$$\text{For PFOS:Cord serum level (ng/L)} = 32 \times \text{breast milk level (ng/L)}$$

$$\text{For PFOA:Cord serum level (ng/L)} = 13 \times \text{breast milk level (ng/L)}$$

2.3. Outcome variable

The outcome of interest was SGA, calculated as birth weight below the 10th percentile of birth weight for each week of pregnancy defined by available country- and sex-specific reference weight curves (FLEHS I and II: The Flemish Centre for the Study of Perinatal Epidemiology 2001–2010; HUMIS: (Skjaerven et al., 2000); INMA: (Carrascosa et al., 2008); LINC: (Visser et al., 2009); PCB cohort: (Kucera et al., 1998); PELAGIE: (Audipog Sentinel Network, 2008)). An overview of the country- and sex-specific reference percentiles used for each cohort is given in the Supplemental Material, Table S3 and Table S4. Birth weight was extracted from medical records collected in the birth cohorts and information on gestational age was estimated from the questionnaires based on date of the last menstrual period and/or by ultrasound. For HUMIS and some of the INMA cohorts, the data obtained from the last menstrual period were replaced by ultrasound determination if the discrepancy between the two methods exceeded 7–14 days (Table 1).

2.4. Statistical analysis

After harmonizing and pooling the data, we assessed correlations between exposures using Spearman's correlation coefficient. For the outcome SGA, we fitted a multiple logistic regression model to estimate the association with each EDC independently, adjusting for confounders, using a generalized estimating equation (GEE) that accounts for correlation from between-cohort variation. A p-value < 0.05 was taken as significance level for the EDC estimate. Potential confounders and known determinants of birth weight were included in the models based on literature (Bailey and Byrom, 2007; Goldenberg et al., 1997; McCowan and Horgan, 2009). These included sex of the newborn (male/female), maternal pre-pregnancy body mass index (BMI; $< 18.5\,kg/m^2$, $18.5 < 25\,kg/m^2$, $25 < 30\,kg/m^2$, and $\geq 30\,kg/m^2$), maternal height (< 163 cm, $163 < 169$ cm, ≥ 169 cm), smoking status during pregnancy (non-smoking, smoking as derived from questionnaire information), maternal education (maximum secondary school, higher education), maternal age at delivery (< 25 years, $25 < 30$ years, $30 < 35$ years, ≥ 35 years) and parity (0, 1 and ≥ 2). Missing values were not imputed. We additionally evaluated sex and smoking status as potential effect modifiers of EDC exposures as indicated by several previous studies (Casas et al., 2015; Eggesbo et al., 2009; Hertz-Picciotto et al., 2005; Lamb et al., 2006; Sonneborn et al., 2008; Vafeiadi et al., 2014). Effect modification was analyzed in models including main effects and cross-product terms. A p-value < 0.05 was the significance level suggesting an interaction. Moreover, we tested for heterogeneity in the exposure-effect association between the cohorts by fitting a model with the interaction term between cohort and exposure. Not all cohorts or only a subset of some cohorts had information on maternal gestational weight gain (GWG) (Table 1). We performed a sensitivity analysis to explore the effect of GWG on the EDC-SGA associations, except for the perfluorinated compounds, which do not accumulate in fat tissue. As information on ethnicity is missing for some

Table 2
Concentration of the PCB 153, *p,p'*-DDE and HCB (ng/L) exposure biomarkers in cord serum, actual or obtained by conversion, of the 8 study populations.

	PCB 153 (ng/L)					*p,p'*-DDE (ng/L)					HCB (ng/L)				
Study population	n	Mean ± SD	Median	P25-P75	n < LOD/ n < LOQ (%)	n	Mean ± SD	Median	P25-P75	n < LOD/ n < LOQ (%)	n	Mean ± SD	Median	P25-P75	n < LOD/ n < LOQ (%)
FLEHS I[a]	1048	73.1 ± 56.3	60.0	30.0–105.0	206 (19.7%)	1094	315.4 ± 347.4	220.0	130.0–376.0	19 (1.7%)	1027	48.4 ± 35.6	40.0	20.0–61.0	249 (24.3%)
FLEHS II[a]	242	62.9 ± 35.8	53.0	38.0–78.0	7 (2.9%)	242	207.6 ± 212.1	153.5	93.0–238.0	0 (0%)	242	Not calculated[d]			121 (50%)
HUMIS[b]	440	43.5 ± 20.8	39.0	30.6–52.0	0 (0%)	440	74.4 ± 108.4	49.7	34.1–79.7	0 (0%)	440	26.2 ± 9.7	24.4	20.2–29.3	0 (0%)
INMA cord[a]	1216	157.1 ± 112.5	136.0	91.4–194.2	111 (9.1%)	1217	959.3 ± 1761	486.6	266.7–1007	20 (1.6%)	886	300.1 ± 373.8	177.0	93.7–340.2	156 (17.6%)
INMA mat[c]	859	52.7 ± 34.6	46.4	30.8–66.1	56 (6.5%)	857	212.1 ± 325.6	131.1	82.3–205.6	5 (0.6%)	860	76.7 ± 62.5	59.8	34.0–98.0	80 (9.3%)
LINC[e]	79	36.0 ± 20.1	30.0	< LOQ-42.0	30 (38.0%)	79	101.6 ± 94.6	79.0	42.0–114.1	13 (16.5%)	79	Not calculated[d]			53 (67.1%)
PCB cohort[a]	1026	394.1 ± 459.7	271.8	169.3–449.9	2 (0.2%)	1025	1309 ± 1194	1015	554.7–1678	8 (0.8%)	1017	274.1 ± 363.0	178.4	102.8–313.6	39 (3.8%)
PELAGIE[a]	394	126.7 ± 77.4	110.0	75.0–160.0	0 (0%)	393	254.4 ± 336.3	180.0	100.0–300.0	74 (18.8%)	394	37.3 ± 22.6	32.5	< LOQ-51.0	99 (25.1%)
Combined	5304	151.7 ± 246.7	88.0	45.0–170.0	412 (7.8%)	5347	603.6 ± 1114	258.0	117.0–646.3	139 (2.6%)	4624	148.5 ± 265.2	63.8	30.0–156.6	623 (13.5%)

Abbreviations: PCB, polychlorinated biphenyl; *p,p'*-DDE, dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; SD, standard deviation; P, percentile; LOD, limit of detection; LOQ, limit of quantification.

[a] Observed cord serum concentrations.

[b] Estimated cord serum concentrations based on measured concentrations in breast milk.

[c] Estimated cord serum concentrations based on measured concentrations in maternal serum.

[d] For exposure biomarkers with ≥50% of the measures < LOD or LOQ, the mean (SD) and median were not calculated. This cohort was excluded in the analysis of that exposure biomarker.

[e] Combination of observed and estimated cord serum concentrations based on measured concentrations in breast milk.

of the cohorts (FLEHS I & II, LINC and PELAGIE), but probably a high percentage is Caucasian, a sensitivity analysis was performed excluding the Roma participants as they constituted about 21% of the PCB cohort (Table 1). Furthermore, we reran the final analysis restricting to studies where EDCs have been measured in cord blood for the non-dioxin-like organochlorine compounds without applying conversion factors. Moreover, multipollutant models were studied for the pooled database including PCB 153, *p,p'*-DDE and HCB as these pollutants were measured in all 7 birth cohorts. We did not attempt to include also the perfluorinated compounds in the multipollutant model due to small sample size with all exposures and covariates available ($N = 344$). We checked for collinearity with variance inflation factors > 5 (Kleinbaum et al., 2013) and condition index > 30 (Belsley, 1991) suggesting a problem of collinearity.

For each pollutant model, the assumption that the exposure is linearly related to the log-odds of the binary outcome SGA was not rejected (*p*-value > 0.05) by restricted cubic splines, therefore the exposure concentrations were introduced into the model as a continuous variable. To quantify the exposure-response association, the estimates are presented as odds per interquartile range (IQR) increase of cord serum contaminant concentration.

All statistical analyses were performed in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) was used to construct the figures.

3. Results

Table 1 summarizes the characteristics of all 8 study populations. The median birth weight and gestational age were 3350 g (3405 g for boys and 3300 g for girls) and 40 weeks, respectively. INMA babies were the lightest and HUMIS and LINC babies the heaviest. The percentage of mothers who indicated they smoked during pregnancy varied across the cohorts (4% for LINC to 30% for INMA). In the PCB cohort, 46.5% of the mothers were < 25 years at delivery, while in the other cohorts this proportion was between 4.1 and 16.6%. Overall, most women delivered their first child (38–61%). The proportion of overweight/obese women was higher in HUMIS (33%) compared to the other cohorts. There were 570 (10.5%) SGA-babies. The proportion of SGA across the cohorts varied between 7.0 and 13.6%, except in the LINC cohort (4 SGA-babies, 4.8%). Information on GWG was available for between 0 (FLEHS II)-97.5% (HUMIS) of the participants in the different cohorts (Table 1).

Overall correlations between biomarkers for prenatal organochlorine compounds were moderate to high ($r = 0.63$ and $r = 0.64$ for respectively PCB 153 and *p,p'*-DDE with HCB; $r = 0.73$ for PCB 153 with *p,p'*-DDE), whereas the correlations between the two perfluorinated compounds were lower ($r = 0.47$) (Supplemental Material, Table S5). Correlations between other exposure biomarkers were small (r ranging from 0.12 to 0.35), except for PFOA with *p,p'*-DDE ($r = 0.59$) (Supplemental Material, Table S5).

3.1. Non-dioxin-like organochlorine compounds

The median (range of cohort medians) cord serum concentrations for PCB 153, *p,p'*-DDE and HCB in the pooled cohort populations were 88.0 ng/L (30.0 for LINC to 271.8 ng/L for PCB cohort), 258.0 ng/L (49.7 for HUMIS to 1015.3 ng/L for PCB cohort) and 63.8 ng/L (24.4 for HUMIS to 178.4 ng/L for PCB cohort), respectively (Table 2). In FLEHS II and LINC, the detection frequency for HCB was only 50% and 33% respectively (Table 2) and these cohorts were excluded from the HCB analyses. For the INMA Menorca cohort the LOQ of 484.1 ng/L for HCB

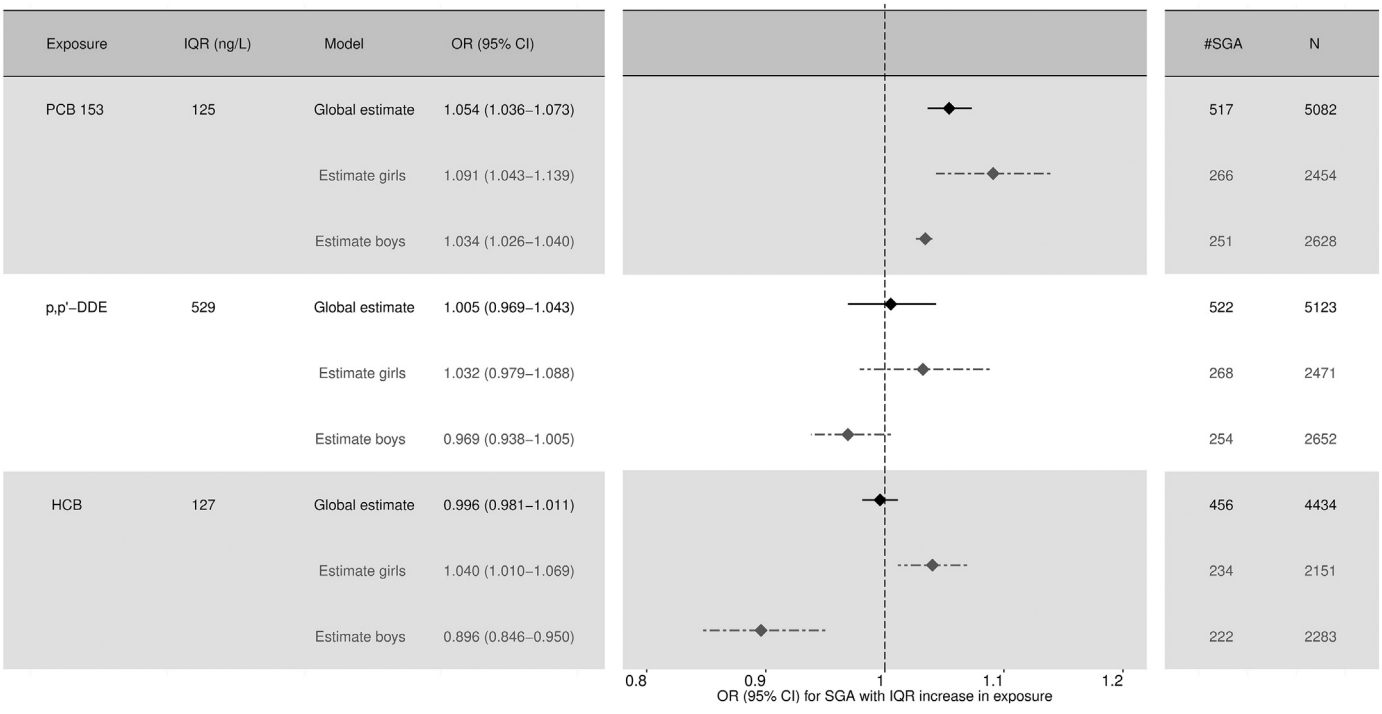

Fig. 1. Adjusted odds ratio (OR) (95% CI) for IQR increase of cord serum PCB 153, *p,p'*-DDE and HCB with SGA.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; IQR: interquartile range; PCB: polychlorinated biphenyl; *p,p'*-DDE, dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; SGA: Small for Gestational Age.
Global estimate: Estimate for IQR increase in exposure in model adjusted for maternal education, maternal age at delivery, maternal height, maternal pre-pregnancy BMI, smoking during pregnancy, parity and child's sex;
Estimate girls/boys: Estimate for IQR increase in exposure for girls/boys in model with interaction term for child's sex adjusted for maternal education, maternal age at delivery, maternal height, maternal pre-pregnancy BMI, smoking during pregnancy and parity;
p-interaction sex-PCB 153 = 0.025; *p*-interaction sex-*p,p'*-DDE = 0.006 and *p*-interaction sex-HCB = 0.0003.

measured in cord serum was much higher compared to the other cohorts with cord serum measures (LOQ ranged between 1.4 and 79 ng/L) (Supplemental Material, Table S2), so this sub-cohort was also excluded from the HCB analyses.

Fig. 1 show the adjusted association between chlorinated persistent organic pollutants (PCB 153, *p,p′*-DDE and HCB) and SGA. PCB 153 showed a stronger significant increased odds of SGA in girls (odds ratio (OR) of 1.09 [95% CI: 1.04, 1.14]) than in boys (1.03 [95% CI: 1.03, 1.04]) (*p*-interaction = 0.025) (Fig. 1). For HCB, a significant increased odds of SGA was found in girls (OR of 1.04 [95% CI: 1.01, 1.07]), while a decreased odds of SGA was found in boys (OR of 0.90 [95% CI: 0.85, 0.95]) (*p*-interaction = 0.0003) (Fig. 1). Additionally, there was an indication of effect modification by smoking for HCB as there was a significant association between HCB and SGA among children from smoking mothers (OR of 1.03 [95% CI: 1.01, 1.06]) compared to an inverse association among children from non-smoking mothers (OR of 0.97 [95% CI: 0.93, 1.00]) (*p*-interaction = 0.02) (Supplemental Material, Table S6). There was an indication of a three-way interaction HCB-sex-smoking (*p*-interaction = 0.055). The association remained significant in girls from smoking mothers (OR of 1.18 [95% CI: 1.11–1.25]), but not those from non-smoking mothers (OR of 0.99 [95% CI: 0.94–1.05]). There was an inverse association between HCB and SGA for boys, regardless of maternal smoking status (Supplemental Material, Table S6). There was no effect modification indicated by smoking status for either PCB 153 or *p,p′*-DDE in association with SGA. No statistically significant association was found for *p,p′*-DDE with SGA (Fig. 1). Sensitivity analysis ran removing EDCs measured in breast milk (HUMIS and subset of LINC) and maternal serum (subset of INMA) yielded similar results (data not shown). The sensitivity analysis using the minimum and maximum factor for the conversion of HCB breast milk to cord serum levels resulted in identical estimated odds ratios and 95% CIs compared to the median conversion factor as used in the original models (Supplemental Material, Table S7).

Multipollutant models including PCB 153, *p,p′*-DDE and HCB slightly changed the estimated odds ratios of the pollutants (Supplemental Material, Table S8), but did not alter the interpretation of the results. Only the increased odds of SGA in girls declined for HCB when adjusting for PCB 153 and *p,p′*-DDE. Although these exposures were significantly correlated, their variance inflation factors were around 1.3 and the largest condition index was equal to 18.8, indicating that the problem of collinearity was avoided in this large study population (N = 4377).

3.2. Perfluorinated compounds

For the perfluorinated compounds, the pooled median cord serum concentration was 1984 ng/L (960 for PCB cohort to 2700 ng/L for FLEHS II) for PFOS and 550 ng/L (312 for HUMIS to 1500 ng/L for FLEHS II) for PFOA (Table 3). The adjusted pooled analysis of perfluorinated compounds showed PFOA exposure associated with a higher odds of having an SGA-baby (OR of 1.64 [95% CI: 0.97, 2.76]) (Fig. 2). The association between PFOA and SGA was stronger for mothers who smoked during pregnancy with an OR of 2.18 (95% CI: 1.02, 4.64) versus 1.51 (95% CI: 0.87, 2.63) in non-smoking mothers, although not statistically significant (*p*-interaction = 0.33). Significant effect modification by maternal smoking during pregnancy was observed for the association between PFOS and SGA (*p*-interaction = 0.0004): newborns of non-smoking mothers had a significant decreased odds of SGA (OR of 0.66 [95% CI: 0.61, 0.72]) associated with PFOS exposure, while those of smoking mothers had an increased odds of SGA (OR of 1.63 [95% CI: 1.02, 2.59]) (Fig. 2). There was no effect modification indicated by child's sex for either PFOS or PFOA.

There was some evidence (*p*-interaction < 0.05), of effect modification by cohort, but the direction of the estimates was not heterogeneous (data not shown). In general, additional adjustment for GWG had no influence on the associations between EDCs and SGA, although the estimates slightly reduced for PCB 153 (Supplemental Material, Table S9). The estimated odds ratios changed slightly, but the interpretation of the results remained when fitting the final models again excluding the Roma participants (Supplemental Material, Table S10).

4. Discussion

We examined the association between prenatal exposure to different EDCs and SGA in seven European birth cohorts (eight study populations). This is the first epidemiological study to pool different birth cohorts for assessing the association between different EDCs and the clinical outcome SGA. Exposure to PCB 153 was associated with a significantly increased risk of SGA, with a stronger association in girls. For HCB, we found significant increased odds of SGA for girls, while the odds of SGA was significantly decreased in boys. The association of HCB with SGA in girls was, however, only observed in newborns of smoking mothers. We also observed PFOA concentrations associated with increased odds of having an SGA-baby. Furthermore, the association was even stronger in newborns of mothers who smoked during pregnancy. Also PFOS was associated with increased odds of SGA in newborns of mothers who smoked during pregnancy, while an inverse association was observed in newborns of non-smoking mothers. No significant associations were found for *p,p′*-DDE. In addition, we found that maternal gestational weight gain only had a small to no influence on these associations.

4.1. Adverse outcome SGA

This is the largest study to date on the associations between some EDCs and the adverse birth outcome SGA. SGA represents a fetus that is relatively small according to its gestational age. This is important since intra-uterine growth restriction is a risk factor for neonatal

Table 3
Concentration of the perfluorinated compounds (ng/L) in cord serum, actual or obtained by conversion, of the OBELIX birth cohorts.

	PFOS (ng/L)					PFOA (ng/L)				
Cohort	N	Mean ± SD	Median	P25-P75	n < LOD/LOQ (%)	n	Mean ± SD	Median	P25-P75	n < LOD/LOQ (%)
FLEHS II[a]	208	2950 ± 1542	2700	1700–3800	0 (0%)	210	1651 ± 676	1500	1100–2100	0 (0%)
HUMIS[b]	196	2899 ± 1343	2624	1968–3520	0 (0%)	196	381 ± 293	312	228–442	13 (6.6%)
LINC[c]	80	1624 ± 696	1600	1000–2058	0 (0%)	80	881 ± 470	805	560–1122	0 (0%)
PCB cohort[b]	204	1217 ± 985	960	576–1440	22 (10.8%)	207	433 ± 294	403	221–533	35 (16.9%)
Combined	688	2267 ± 1484	1984	1200–3008	22 (3.2%)	693	839 ± 723	550	299–1200	48 (6.9%)

Abbreviations: PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; SD, standard deviation; P, percentile; LOD, limit of detection; LOQ, limit of quantification.

[a] Observed cord serum concentrations.

[b] Estimated cord serum concentrations based on measured concentrations in breast milk.

[c] Combination of observed and estimated cord serum concentrations based on measured concentrations in breast milk.

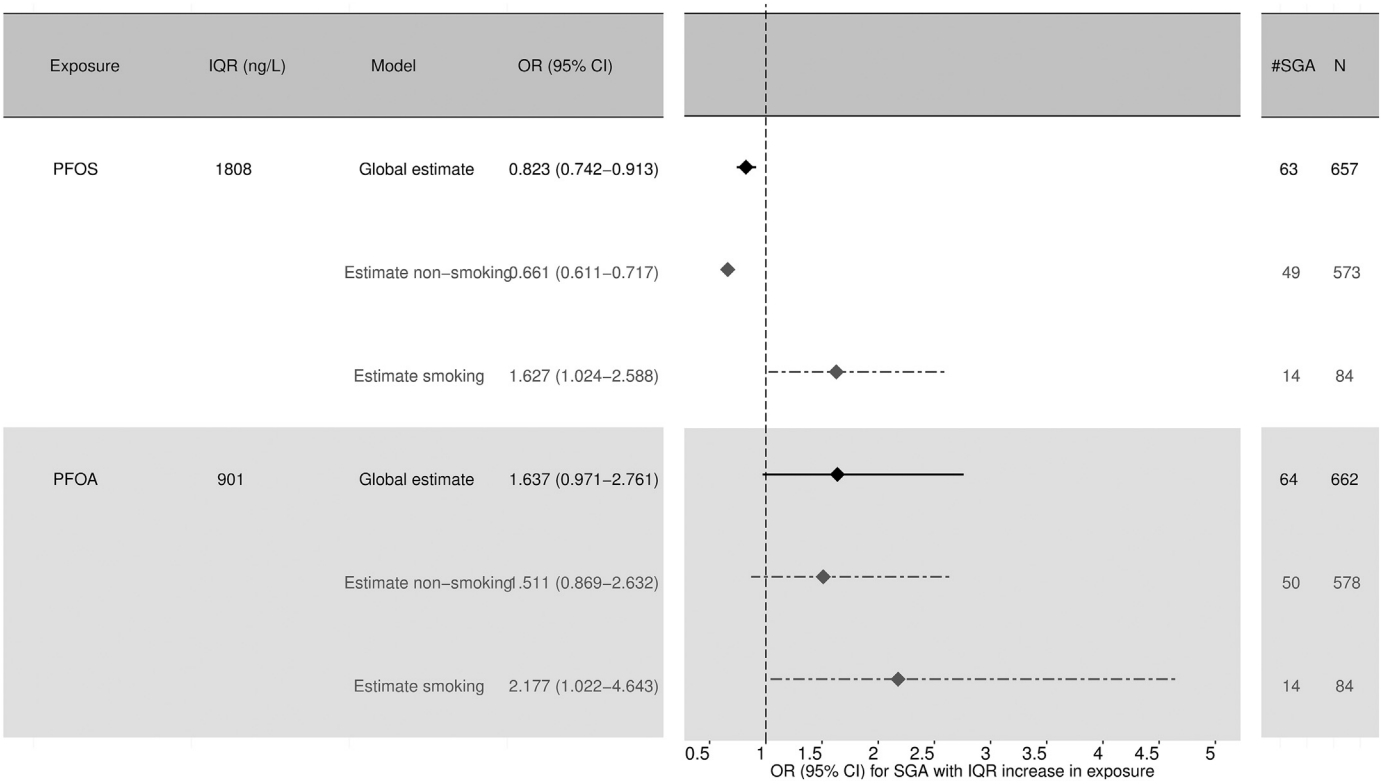

Fig. 2. Adjusted odds ratio (OR) (95% CI) for IQR increase of cord serum PFOS and PFOA with SGA.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; IQR: interquartile range; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; SGA: Small for Gestational Age.
Global estimate: Estimate for IQR increase in exposure in model adjusted for maternal education, maternal age at delivery, maternal height, maternal pre-pregnancy BMI, smoking during pregnancy, parity and child's sex;
Estimate non-smoking/smoking: Estimate for IQR increase in exposure for non-smoking/smoking in model with interaction term for smoking during pregnancy adjusted for maternal education, maternal age at delivery, maternal height, maternal pre-pregnancy BMI, parity and child's sex;
p-interaction smoking-PFOS = 0.0004; *p*-interaction smoking-PFOA = 0.33.

complications, neurobehavioral disorders, insulin resistance, central adiposity, as well as metabolic conditions and cardiovascular disorders in adulthood (Barker et al., 1989; Hofman et al., 2004; Lundgren and Tuvemo, 2008; Oelberg, 2006). As SGA is by definition an outcome that occurs in about 10% of the population, it is difficult to explore exposure-response analysis in separate, rather small cohorts. As the associations have to be adjusted for several important confounders, the chance of observing (quasi-) complete separation in the data points is high, i.e. when the outcome variable separates a combination of predictor variables completely (to a certain degree). For binary outcomes with a rather low prevalence such as the one studied here, pooling different databases results in more power to explore associations. Quasi-complete separation of data points was observed in some of the cohort separate analyses of the current study, namely PELAGIE for all organochlorine analyses, HUMIS and the PCB cohort for the perfluorinated compounds, therefore the obtained estimates were not reliable (Allison, 2008). However, this was not a problem for the pooled analyses.

As SGA was calculated based on country-specific birth weight for gestational age reference curves, the classification is country-dependent. The birth weights from the obtained reference percentiles are variable across countries. This was expected as there is a north-south gradient for birth weight in Europe, i.e. the Nordic countries having higher birth weights and countries from Southern Europe having lower birth weights (OECD, 2012). This gradient is both reflected in the obtained country-specific reference percentiles as in our cohort data, i.e. the HUMIS cohort (Norway) having the highest median birth weight and in general higher reference birth weights and the INMA (Spain) and PCB cohort (Slovakia) having the lowest median birth weight and reference birth weights. The variation in birth weight across countries is as such taken into account.

4.2. Non-dioxin-like organochlorine compounds

In the current pooled analysis, significantly higher odds of SGA were observed with increasing PCB 153 concentrations, and no significant associations were found for *p,p'*-DDE. The positive association of PCBs with SGA was also observed by Lauritzen et al. and Longnecker et al. (Lauritzen et al., 2017; Longnecker et al., 2005). Recently, a significant inverse association between environmental exposure to PCB 153 and birth weight was found in a pooled analysis of 9000 mother-child pairs, enrolled in 11 European birth cohorts (Casas et al., 2015), but none found for *p,p'*-DDE. All our cohorts, except the LINC cohort were included in those analyses. Casas et al. (Casas et al., 2015) also showed a stronger effect of PCB 153 in girls whose mothers smoked during pregnancy. In our study a stronger association was also seen in girls, but no effect modification by smoking was indicated. This stronger effect of PCB 153 in girls was previously found in a study by Lamb et al. (Lamb et al., 2006), but other studies have also reported a stronger effect in boys (Hertz-Picciotto et al., 2005; Lauritzen et al., 2017; Sonneborn et al., 2008). These studies were, however, too small to explore effect modification by sex (n between 150 and 1057).

Our findings that HCB was significantly associated with increased odds of being SGA for girls and decreased odds for boys are somewhat consistent with results found in a recent Greek study (Vafeiadi et al., 2014). In that study, HCB measured in maternal serum during pregnancy had a significant inverse association with birth weight in girls, while there was no statistically significant association found in boys.

Moreover, that study observed stronger associations between HCB and birth weight among babies of smokers or ex-smokers compared to non-smokers, which was also observed in our study. Similar results were observed by Eggesbø et al. (Eggesbo et al., 2009), where the inverse association between HCB and birth weight was present only among smokers. We observed a three-way interaction sex-smoking-HCB. To our knowledge, such a finding has not been previously reported. Vafeiadi et al. (Vafeiadi et al., 2014) also conducted a multipollutant model including the sum of 6 PCB congeners, *p,p′*-DDE and HCB and showed that the association with birth weight was mainly driven by HCB. However, no collinearity diagnostics were mentioned and the analysis was conducted in a sample size of 522 newborns. In our pooled multipollutant model including PCB 153, *p,p′*-DDE and HCB, the interpretation of the results of the single pollutant models was not affected, and both PCB 153 and HCB appeared to drive the association with SGA. The association of HCB with SGA in girls was, however, less strong when mutually adjusting for PBC 153 and *p,p′*-DDE.

4.3. Perfluorinated compounds

The association between increasing PFOA concentrations and the increased odds of having an SGA-baby are consistent with the conclusion of a recent systematic review of Bach et al. (Bach et al., 2015). In 14 studies with PFOA/PFOS measurements in maternal blood during pregnancy or in umbilical cord blood, in utero PFOA exposure was associated with decreased birth weight, even though the magnitude of the association differed and many results were not statistically significant. In a meta-analysis of 9 out of 18 studies on PFOA exposure in relation to fetal growth a significant decrease in birth weight (−18.9 g (95% CI: -29.8, −7.9)) was found for a 1 ng/mL increase in serum or plasma PFOA (Johnson et al., 2014). In a recent Scandinavian study, prenatal exposure to PFOA was associated with higher odds for SGA (Lauritzen et al., 2017). For PFOS exposure the association with birth weight was observed in some studies, while others found no significant association (Bach et al., 2015; Lauritzen et al., 2017; Manzano-Salgado et al., 2017). In our study, PFOS was associated with SGA in newborns of smoking mothers, while an inverse association was observed in those of non-smoking mothers. For both PFOS and PFOA we found indication of effect modification by smoking, but this was not considered in any previous studies.

In the recent report of US-EPA (US-EPA, 2016) on the health effects of PFOA was concluded, that the association observed between PFOA plasma/serum concentration and birth weight is possibly explained by the influence of the glomerular filtration rate (GFR) (Verner et al., 2015; Vesterinen et al., 2015). Women who give birth to babies with low birth weight have lower GFR. A lower GFR in turn decreases the removal of PFOA from the blood. Therefore, it is possible that women who give birth to babies with a lower birth weight have higher serum PFOA concentrations because of a lower GFR. However, as we did not see the same effect for PFOS in our study, it seems that the observed association between PFOA and SGA could not solely be attributed to confounding. In a recent Spanish study (Manzano-Salgado et al., 2017) maternal GFR measured early during pregnancy did not confound the estimated associations between perfluorinated compounds and birth outcomes.

4.4. Mechanisms

Identifying the mechanisms whereby EDCs influence weight homeostasis and energy balance remains an important area of research. It is clear from our results that not all endocrine disrupting compounds exert similar effects. Indeed, there are a variety of direct mechanisms such as binding to nuclear receptors or indirect mechanisms by which these chemicals may interfere with weight homeostasis and energy balance. Various PCB congeners bind to the estrogen receptor, acting as agonists or antagonists and change normal fetal programming (Newbold et al., 2009). PCB metabolites are high-affinity ligands for the thyroid hormone transport protein transthyretin (Cheek et al., 1999). *p,p′*-DDE binds to the androgen receptor (Kelce et al., 1995; Xu et al., 2013), while PFOA promotes adipocyte differentiation as a peroxisome proliferator-activated receptor gamma (PPARγ) ligand (White et al., 2011; Yamamoto et al., 2015). Several studies in rats demonstrated the thyroid-disrupting effect of the pesticides DDT (Scollon et al., 2004) and HCB (Alvarez et al., 2005; van Raaij et al., 1993a; van Raaij et al., 1993b), as they decreased serum levels of thyroid hormones. High maternal free thyroxine levels during the first half of pregnancy were related to lower birth weight and increased risk of SGA newborns, suggesting that maternal thyroid function may affect fetal growth, even within the normal range. Sexual dimorphism appears to be present in the relationship between maternal thyroid metabolism and fetal intrauterine growth, with stronger associations in male infants (Leon et al., 2015; Vrijkotte et al., 2017). PPARγ is the main regulator of placental metabolism, controlling the amounts of maternal nutrients that go across to the fetus and hence will influence fetal growth (Xu et al., 2007). Estrogens are known to play an important role for placental angiogenesis, which is crucial for transport of nutrients to the fetus (Albrecht and Pepe, 2010). It has been shown that obesogenic EDCs can alter the epigenome of multipotent stromal cells, which is preprogrammed toward an adipogenic fate (Janesick and Blumberg, 2011, 2012). Other proposed endocrine disrupting mechanisms are changes in glucocorticoids and steroid hormones that may affect neuronal cells and release of brain-produced substances that bind to nuclear receptors and may affect energy regulation (Harris and Seckl, 2011). The exact target tissue is unknown and probably involves multiple target sites, e.g. adipocytes, brain, liver, stomach, pancreas, and the effects may be age, dose and sex dependent. Our results suggested that sex and smoking during pregnancy were potential effect modifiers on SGA, although mechanisms underlying these potential interactions remain unclear. For HCB, even opposite effects were found in girls (significant increased risk of SGA) versus boys (significant decreased risk of SGA). It is difficult to hypothesize the mechanism through which this effect modification is caused. Since HCB is a known EDC it might also disrupt sex hormone pathways, and as such a finding specific to girls or boys would not be unexpected. The biological mechanism underlying the possible modifying effect of sex and smoking remains to be established.

4.5. Confounders and risk factors

Maternal gestational weight gain (GWG) will dilute the EDC concentrations in maternal blood and is also overall positively associated with birth weight of the child, and may therefore be a confounder of the associations between EDCs and birth weight (Verner et al., 2013). Associations between GWG and cord serum concentrations of ΣPCBs, 4,4′-DDE and HCB have been reported (Vizcaino et al., 2014). We evaluated whether GWG confounded the associations of the EDCs with SGA in the subset of the pooled data having information on GWG (Table 1). Maternal GWG influenced the association between EDCs and SGA to a limited extent in this study. The estimated odds ratios did not change substantially after additional adjustment for GWG for *p,p′*-DDE and HCB. For PCB 153, the odds ratios slightly reduced but remained significant when correcting for GWG, indicating a degree of partial confounding.

In a previous paper exploring the association between PCBs and birth weight in the PCB cohort, effect modification was observed by Roma ethnicity where maternal PCB concentrations were associated with lower birth weight in Roma boys (Sonneborn et al., 2008). Information on ethnicity is however not known for four of the seven birth cohorts, but the percentage of Caucasian participants within these cohorts is likely very high, and for HUMIS and INMA respectively 94% and 96% of the participants were Caucasian. In the PCB cohort about 21% of the population was Roma and in the HUMIS cohort there was

also one Roma participant. As such we decided to do a sensitivity analysis excluding the Roma population from the final models. The interpretation of the EDC-SGA associations was not influenced in this sensitivity analysis.

There are many established risk factors for babies who are SGA (McCowan and Horgan, 2009). The confirmed maternal risk factors identified in the models for SGA in this study include small maternal height, low maternal pre-pregnancy BMI, smoking during pregnancy and nulliparity. All the models were adjusted for these identified risk factors and additionally for maternal education, maternal age at delivery and child's sex. Some potential risk factors such as cocaine use, vitamin status, mother/father born SGA were not available in the questionnaires or there were not enough cases present in the cohorts (e.g. pre-eclampsia, hypertension). In the pooled model, mothers smoking during pregnancy had about 2.5 times higher odds of having an SGA-baby than non-smoking mothers, adjusting for the other factors in the model. For an increase of PCB 153, HCB, PFOS and PFOA with the IQR, we obtain respectively an odds ratio of: 1.09 (girls) and 1.03 (boys) for PCB 153 (for an increase of 125 ng/L); 1.04 for HCB in girls (for an increase of 127 ng/L); 1.6 (smoking mothers during pregnancy) for PFOS (for an increase of 1808 ng/L) and of 1.5 (non-smoking mothers during pregnancy) and 2.2 (smoking mothers during pregnancy) for PFOA (for an increase of 901 ng/L). The results indicate that smoking, a well-known risk factor for SGA, is more strongly associated with SGA, than the pollutants studied. On the other hand almost all babies had measurable EDC concentrations and hence are exposed. In addition, for the perfluorinated compounds the odds of SGA in those already exposed to maternal smoking were rather substantial.

4.6. Strengths and limitations

The particular strength of this study was that by pooling the results, information was obtained on the risks of being born small for gestational age. The pooled analysis included > 5000 mother-child pairs for the analysis of the prenatal growth effects of PCB 153, HCB and *p,p'*-DDE; and nearly 700 for the perfluorinated compounds (PFOA and PFOS). As such, a large enough sample size was attained to explore effect modification by child's sex and smoking. For outcome parameters that are not highly prevalent but clinically relevant, pooling of data is very useful. However, pooling data from different cohorts could lead to effect modification by cohort due to underlying heterogeneity of the populations. The direction of the estimates was however not heterogeneous when including the interaction term with cohort in the models. By pooling data from different cohorts over Europe we obtained considerable variability in exposure levels. Nevertheless, as the birth cohorts span a fifteen year period from 1997 to 2012, the exposure to the selected EDCs could have changed over time, i.e. changes in behaviors or manufacturing practices that could have reduced exposure over time, and this might have affected the analysis. As such, a decrease over time of the non-dioxin-like organochlorine compounds (Schoeters et al., 2017) appears to attribute to the low detection frequency of HCB in the most recent cohorts FLEHS II (2008–2009) and LINC (2011 − 2012) together with the relatively high quantification limit in cord serum versus milk samples which have higher lipid content. There is a potential of exposure misclassification induced by different methods of measuring the exposures across the cohorts. The organochlorine compounds were measured by different laboratories using different methodologies, however the LODs/LOQs were very similar, typically within a range of a factor of 2, except for HCB within the INMA Menorca cohort, which was therefore excluded from the analyses. For the perfluorinated compounds, the sensitivity of the analyses in cord plasma differed between the two laboratories, but as the detection frequency for all cord plasma measures was 100% this would not have led to misclassification. The analysis of perfluorinated compounds in breast milk samples were performed in the same laboratory. Although biomarker concentrations were measured in different laboratories, these labs performed their analysis according to internal lab quality systems and participated in international ring tests to verify their analytical results and to ensure the comparability of their data. As different biological matrices (cord plasma/serum, maternal serum and breast milk) were used to assess EDC exposure, variation is introduced with respect to the period of exposure it represents. Conversion factors were used to estimate the corresponding cord serum levels. However, while the EDCs studied are persistent, mobilization of these during different periods of pregnancy could lead to variation in the levels. The conversion of available pollutant concentrations in maternal serum or breast milk to cord serum levels may introduce estimation error in the pollutant concentrations. However, we also performed our analysis in a subset of the dataset with EDCs measured in cord blood without applying any conversion factor as a sensitivity analysis and this did not change the conclusions. For HCB the sensitivity analysis, using the minimum and maximum factor for the conversion of breast milk to cord serum levels yielded identical results to those from the original model using the median conversion factor. A further weakness of the study is that the chemicals were included one by one in the statistical models, which does not reflect what happens in the real world situation in which multiple exposures and stressors may act or counteract. We cannot exclude that highly correlated exposure biomarkers act as a proxy for each other. However, the pooled database of 7 birth cohorts offered a large enough sample size to study PCB 153, *p,p'*-DDE and HCB in a multipollutant model. The interpretation of the association between individual exposures and SGA was independent of the other exposures; identical results were obtained from the single versus multipollutant models. Although these exposures were significantly correlated, the problem of collinearity was avoided in this large study population ($N = 4377$). This concurs with a recent simulation study that shows that for properly specified models, total effect estimates remained unbiased even when the exposures are highly correlated (Schisterman et al., 2017). Furthermore, we cannot exclude the possibility of unmeasured confounding, both by other exposures and by other possible factors. As only measures of PCB153, HCB, *p,p'*-DDE, PFOS and PFOA were used, it is possible that the effects observed may be due to other, correlated chemicals that were not measured, such as other PCB congeners or perfluorinated compounds as perfluorononanoic acid (PFNA) or perfluorohexane sulfonic acid (PFHxS). Another limitation is differential determination of gestational age. For some of the cohorts gestational age was estimated from the date of the last menstrual period which is less accurate than ultrasound determination (Butt and Lim, 2014). Also smoking status during pregnancy was derived from questionnaire information and could be under reported.

5. Conclusions

A pooled analysis of 7 European birth cohorts found that prenatal environmental exposures to organochlorine and perfluorinated compounds with endocrine properties, may contribute to the prevalence of SGA. Child's sex and smoking during pregnancy were identified as potential effect modifiers in these associations. The EDCs studied did not all exhibit associations in the same direction, suggesting diverse mechanisms of action and biological pathways.

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Competing financial interests

The authors declare they have no competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.03.017.

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