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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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52 **Running title**

53 Endocrine Disrupting Chemicals and SGA

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 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.

Key words: Endocrine Disrupting Chemicals (EDCs); Small for Gestational Age (SGA); Pooled analysis.

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), dichlorodipenyldichloroethylene (*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 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 $\geq 50\%$ 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.

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):

Cord serum level (ng/L) = 0.20 x maternal serum level (ng/L)

Cord serum level (ng/L) = 1.20 x 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):

Cord serum level (ng/L) = 0.265 x maternal serum level (ng/L)

Cord serum level (ng/L) = 2.18 x 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:

For PFOS: Cord serum level (ng/L) = 32 x breast milk level (ng/L)

For PFOA: Cord serum level (ng/L) = 13 x 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

215 After harmonizing and pooling the data, we assessed correlations between exposures using
216 Spearman's correlation coefficient. For the outcome SGA, we fitted a multiple logistic
217 regression model to estimate the association with each EDC independently, adjusting for
218 confounders, using a generalized estimating equation (GEE) that accounts for correlation
219 from between-cohort variation. A p -value < 0.05 was taken as significance level for the EDC
220 estimate. Potential confounders and known determinants of birth weight were included in the
221 models based on literature (Bailey and Byrom 2007; Goldenberg et al. 1997; McCowan and
222 Horgan 2009). These included sex of the newborn (male/female), maternal pre-pregnancy
223 body mass index (BMI; <18.5 kg/m², $18.5 < 25$ kg/m², $25 < 30$ kg/m², and ≥ 30 kg/m²), maternal
224 height (<163 cm, $163 < 169$ cm, ≥ 169 cm), smoking status during pregnancy (non-smoking,
225 smoking as derived from questionnaire information), maternal education (maximum
226 secondary school, higher education), maternal age at delivery (<25 years, $25 < 30$ years, $30 < 35$
227 years, ≥ 35 years) and parity (0, 1 and ≥ 2). Missing values were not imputed. We additionally
228 evaluated sex and smoking status as potential effect modifiers of EDC exposures as indicated
229 by several previous studies (Casas et al. 2015; Eggesbo et al. 2009; Hertz-Picciotto et al.
230 2005; Lamb et al. 2006; Sonneborn et al. 2008; Vafeiadi et al. 2014). Effect modification was
231 analyzed in models including main effects and cross-product terms. A p -value < 0.05 was the
232 significance level suggesting an interaction. Moreover, we tested for heterogeneity in the
233 exposure-effect association between the cohorts by fitting a model with the interaction term
234 between cohort and exposure. Not all cohorts or only a subset of some cohorts had
235 information on maternal gestational weight gain (GWG) (Table 1). We performed a
236 sensitivity analysis to explore the effect of GWG on the EDC-SGA associations, except for
237 the perfluorinated compounds, which do not accumulate in fat tissue. As information on
238 ethnicity is missing for some of the cohorts (FLEHS I & II, LINC and PELAGIE), but
239 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 greater than 5 (Kleinbaum et al. 2013) and condition index greater than 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 grams (3405 grams for boys and 3300 grams 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 7.0-13.6%, 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 measured in cord serum was much higher compared to the other cohorts with cord serum measures (LOQ ranged between 1.4-79 ng/L) (Supplemental Material, Table S2), so this sub-cohort was also excluded from the HCB analyses.

289 Figure 1 show the adjusted association between chlorinated persistent organic pollutants
290 (PCB 153, *p,p'*-DDE and HCB) and SGA. PCB 153 showed a stronger significant increased
291 odds of SGA in girls (odds ratio (OR) of 1.09 [95% CI: 1.04, 1.14]) than in boys (1.03 [95%
292 CI: 1.03, 1.04]) (*p*-interaction = 0.025) (Figure 1). For HCB, a significant increased odds of
293 SGA was found in girls (OR of 1.04 [95% CI: 1.01, 1.07]), while a decreased odds of SGA
294 was found in boys (OR of 0.90 [95% CI: 0.85, 0.95]) (*p*-interaction = 0.0003) (Figure 1).
295 Additionally, there was an indication of effect modification by smoking for HCB as there was
296 a significant association between HCB and SGA among children from smoking mothers (OR
297 of 1.03 [95% CI: 1.01, 1.06]) compared to an inverse association among children from non-
298 smoking mothers (OR of 0.97 [95% CI: 0.93, 1.00]) (*p*-interaction = 0.02) (Supplemental
299 Material, Table S6). There was an indication of a three-way interaction HCB-sex-smoking (*p*-
300 interaction = 0.055). The association remained significant in girls from smoking mothers (OR
301 of 1.18 [95% CI: 1.11-1.25]), but not those from non-smoking mothers (OR of 0.99 [95% CI:
302 0.94-1.05]). There was an inverse association between HCB and SGA for boys, regardless of
303 maternal smoking status (Supplemental Material, Table S6). There was no effect modification
304 indicated by smoking status for either PCB 153 or *p,p'*-DDE in association with SGA. No
305 statistically significant association was found for *p,p'*-DDE with SGA (Figure 1). Sensitivity
306 analysis ran removing EDCs measured in breast milk (HUMIS and subset of LINC) and
307 maternal serum (subset of INMA) yielded similar results (data not shown). The sensitivity
308 analysis using the minimum and maximum factor for the conversion of HCB breast milk to
309 cord serum levels resulted in identical estimated odds ratios and 95% CIs compared to the
310 median conversion factor as used in the original models (Supplemental Material, Table S7).
311 Multipollutant models including PCB 153, *p,p'*-DDE and HCB slightly changed the estimated
312 odds ratios of the pollutants (Supplemental Material, Table S8), but did not alter the
313 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]) (Figure 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]) (Figure 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 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 150-1057).

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 PCB 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 (PPAR γ) 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). PPAR γ 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 Σ PCBs, 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 more than 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 1997-2012, 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

563 in the levels. The conversion of available pollutant concentrations in maternal serum or breast
564 milk to cord serum levels may introduce estimation error in the pollutant concentrations.
565 However, we also performed our analysis in a subset of the dataset with EDCs measured in
566 cord blood without applying any conversion factor as a sensitivity analysis and this did not
567 change the conclusions. For HCB the sensitivity analysis, using the minimum and maximum
568 factor for the conversion of breast milk to cord serum levels yielded identical results to those
569 from the original model using the median conversion factor. A further weakness of the study
570 is that the chemicals were included one by one in the statistical models, which does not reflect
571 what happens in the real world situation in which multiple exposures and stressors may act or
572 counteract. We cannot exclude that highly correlated exposure biomarkers act as a proxy for
573 each other. However, the pooled database of 7 birth cohorts offered a large enough sample
574 size to study PCB 153, *p,p'*-DDE and HCB in a multipollutant model. The interpretation of
575 the association between individual exposures and SGA was independent of the other
576 exposures; identical results were obtained from the single versus multipollutant models.
577 Although these exposures were significantly correlated, the problem of collinearity was
578 avoided in this large study population (N=4377). This concurs with a recent simulation study
579 that shows that for properly specified models, total effect estimates remained unbiased even
580 when the exposures are highly correlated (Schisterman et al. 2017). Furthermore, we cannot
581 exclude the possibility of unmeasured confounding, both by other exposures and by other
582 possible factors. As only measures of PCB153, HCB, *p,p'*-DDE, PFOS and PFOA were used,
583 it is possible that the effects observed may be due to other, correlated chemicals that were not
584 measured, such as other PCB congeners or perfluorinated compounds as perfluorononanoic
585 acid (PFNA) or perfluorohexane sulfonic acid (PFHxS). Another limitation is differential
586 determination of gestational age. For some of the cohorts gestational age was estimated from
587 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.

REFERENCES

- Agency for Toxic Substances and Disease Registry (ATSDR). 2002. Toxicological profile for ddt, dde, and ddd. Atlanta, GA:U.S. Department of Health and Human Services, Public Health Service.
- Albrecht ED, Pepe GJ. 2010. Estrogen regulation of placental angiogenesis and fetal ovarian development during primate pregnancy. *The International journal of developmental biology* 54:397-408.
- Allison P. 2008. Convergence failures in logistic regression. SAS Global Forum 2008 paper 360:1-11.
- Alvarez L, Hernandez S, Martinez-de-Mena R, Kolliker-Frers R, Obregon MJ, Kleiman de Pisarev DL. 2005. The role of type i and type ii 5' deiodinases on hexachlorobenzene-induced alteration of the hormonal thyroid status. *Toxicology* 207:349-362.
- Audipog Sentinel Network. 2008. Neonatal morphometrics curves. Available: <http://www.audipog.net/>.
- Bach CC, Bech BH, Brix N, Nohr EA, Bonde JP, Henriksen TB. 2015. Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: A systematic review. *Crit Rev Toxicol* 45:53-67.
- Bailey BA, Byrom AR. 2007. Factors predicting birth weight in a low-risk sample: The role of modifiable pregnancy health behaviors. *Matern Child Health J* 11:173-179.
- Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. 1989. Weight in infancy and death from ischaemic heart disease. *Lancet* 2:577-580.
- Barker DJ. 1998. In utero programming of chronic disease. *Clin Sci (Lond)* 95:115-128.
- Basterrechea M, Lertxundi A, Iniguez C, Mendez M, Murcia M, Mozo I, et al. 2014. Prenatal exposure to hexachlorobenzene (hcb) and reproductive effects in a multicentre birth cohort in Spain. *Sci Total Environ* 466-467:770-776.
- Belsley DA. 1991. Conditioning diagnostics: Collinearity and weak data in regression. New York:Wiley.
- Berkowitz GS, Lapinski RH, Wolff MS. 1996. The role of dde and polychlorinated biphenyl levels in preterm birth. *Arch Environ Contam Toxicol* 30:139-141.
- Butt K, Lim K. 2014. Determination of gestational age by ultrasound. *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC* 36:171-181.
- Carrascosa LA, Ferrandez LA, Yeste FD, Garcia-Dihinx VJ, Romo MA, Copil CA, et al. 2008. [spanish cross-sectional growth study 2008. Part i: Weight and height values in newborns of 26-42 weeks of gestational age]. *An Pediatr (Barc)* 68:544-551.

644 Casas M, Nieuwenhuijsen M, Martinez D, Ballester F, Basagana X, Basterrechea M, et al.
645 2015. Prenatal exposure to pcb-153, p,p'-dde and birth outcomes in 9000 mother-child pairs:
646 Exposure-response relationship and effect modifiers. *Environ Int* 74:23-31.

647 Cheek AO, Kow K, Chen J, McLachlan JA. 1999. Potential mechanisms of thyroid disruption
648 in humans: Interaction of organochlorine compounds with thyroid receptor, transthyretin, and
649 thyroid-binding globulin. *Environ Health Perspect* 107:273-278.

650 de Cock M, van de Bor M. 2014. Obesogenic effects of endocrine disruptors, what do we
651 know from animal and human studies? *Environ Int* 70:15-24.

652 Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al.
653 2009. Endocrine-disrupting chemicals: An endocrine society scientific statement. *Endocr Rev*
654 30:293-342.

655 Eggesbo M, Stigum H, Longnecker MP, Polder A, Aldrin M, Basso O, et al. 2009. Levels of
656 hexachlorobenzene (hcb) in breast milk in relation to birth weight in a norwegian cohort.
657 *Environ Res* 109:559-566.

658 EURO-PERISTAT. 2013. European perinatal health report. Health and care of pregnant
659 women and babies in europe in 2010.

660 Ferreira CP, De-Oliveira AC, Paumgartten FJ. 2011. Serum concentrations of ddt and dde
661 among malaria control workers in the amazon region. *J Occup Health* 53:115-122.

662 Gladen BC, Shkiryak-Nyzhnyk ZA, Chyslovska N, Zadorozhnaja TD, Little RE. 2003.
663 Persistent organochlorine compounds and birth weight. *Ann Epidemiol* 13:151-157.

664 Goldenberg RL, Cliver SP, Neggers Y, Copper RL, DuBard MD, Davis RO, et al. 1997. The
665 relationship between maternal characteristics and fetal and neonatal anthropometric
666 measurements in women delivering at term: A summary. *Acta Obstet Gynecol Scand Suppl*
667 165:8-13.

668 Govarts E, Nieuwenhuijsen M, Schoeters G, Ballester F, Bloemen K, de Boer M, et al. 2012.
669 Birth weight and prenatal exposure to polychlorinated biphenyls (pcbs) and
670 dichlorodiphenyldichloroethylene (dde): A meta-analysis within 12 european birth cohorts.
671 *Environ Health Perspect* 120:162-170.

672 Hagmar L, Wallin E, Vessby B, Jonsson BA, Bergman A, Rylander L. 2006. Intra-individual
673 variations and time trends 1991-2001 in human serum levels of pcb, dde and
674 hexachlorobenzene. *Chemosphere* 64.

675 Harris A, Seckl J. 2011. Glucocorticoids, prenatal stress and the programming of disease.
676 *Horm Behav* 59:279-289.

677 Hertz-Picciotto I, Charles MJ, James RA, Keller JA, Willman E, Teplin S. 2005. In utero
678 polychlorinated biphenyl exposures in relation to fetal and early childhood growth.
679 *Epidemiology* 16:648-656.

680 Hofman PL, Regan F, Harris M, Robinson E, Jackson W, Cutfield WS. 2004. The metabolic
681 consequences of prematurity. *Growth Horm IGF Res* 14 Suppl A:S136-S139.

682 Hornung RW, Reed LD. 1990. Estimation of average concentration in the presence of
683 nondetectable values. *Appl Occup Environ Hyg* 5:46-51.

684 Janesick A, Blumberg B. 2011. Endocrine disrupting chemicals and the developmental
685 programming of adipogenesis and obesity. *Birth Defects Res C Embryo Today* 93:34-50.

686 Janesick A, Blumberg B. 2012. Obesogens, stem cells and the developmental programming of
687 obesity. *Int J Androl* 35:437-448.

688 Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, et al. 2014. The navigation guide
689 - evidence-based medicine meets environmental health: Systematic review of human evidence
690 for pfoa effects on fetal growth. *Environ Health Perspect* 122:1028-1039.

691 Kelce WR, Stone CR, Laws SC, Gray LE, Kemppainen JA, Wilson EM. 1995. Persistent ddt
692 metabolite p,p'-dde is a potent androgen receptor antagonist. *Nature* 375:581-585.

693 Khanjani N, Sim M. 2006. Maternal contamination with dichlorodiphenyltrichloroethane and
694 reproductive outcomes in an australian population. *Environ Res* 101.

695 Kleinbaum DG, Kupper LL, Nizam A, Rosener ES. 2013. Applied regression analysis and
696 other multivariable methods. 5th ed. Boston:Cengage Learning.

697 Korrick SA, Altshul LM, Tolbert PE, Burse VW, Needham LL, Monson RR. 2000.
698 Measurement of pcbs, dde, and hexachlorobenzene in cord blood from infants born in towns
699 adjacent to a pcb-contaminated waste site. *J Expo Anal Environ Epidemiol* 10:743-754.

700 Kucera J, Kubelik J, Melichar J, Ztembera Z, Velebil P, Kucerova I. 1998. Nove tabulky
701 normalni porodni hmotnosti novorozencu v ceske republice (new tables of normal birth
702 weights in czech republic). *Neonatologicke listy* 4:3.

703 Lamb MR, Taylor S, Liu X, Wolff MS, Borrell L, Matte TD, et al. 2006. Prenatal exposure to
704 polychlorinated biphenyls and postnatal growth: A structural analysis. *Environ Health*
705 *Perspect* 114:779-785.

706 Lauritzen HB, Larose TL, Oien T, Sandanger TM, Odland JO, van de Bor M, et al. 2017.
707 Maternal serum levels of perfluoroalkyl substances and organochlorines and indices of fetal
708 growth: A scandinavian case-cohort study. *Pediatr Res* 81:33-42.

709 Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. 2013. National and
710 regional estimates of term and preterm babies born small for gestational age in 138 low-
711 income and middle-income countries in 2010. *The Lancet Global health* 1:e26-36.

712 Leon G, Murcia M, Rebagliato M, Alvarez-Pedrerol M, Castilla AM, Basterrechea M, et al.
713 2015. Maternal thyroid dysfunction during gestation, preterm delivery, and birthweight. The
714 infancia y medio ambiente cohort, spain. *Paediatric and perinatal epidemiology* 29:113-122.

715 Longnecker MP, Klebanoff MA, Brock JW, Guo X. 2005. Maternal levels of polychlorinated
716 biphenyls in relation to preterm and small-for-gestational-age birth. *Epidemiology* 16:641-
717 647.

718 Lundgren EM, Tuvemo T. 2008. Effects of being born small for gestational age on long-term
719 intellectual performance. *Best Pract Res Clin Endocrinol Metab* 22:477-488.

720 Malisch R, Kotz A. 2014. Dioxins and pcbs in feed and food--review from european
721 perspective. *Sci Total Environ* 491-492:2-10.

722 Manzano-Salgado CB, Casas M, Lopez-Espinosa MJ, Ballester F, Iniguez C, Martinez D, et
723 al. 2017. Prenatal exposure to perfluoroalkyl substances and birth outcomes in a spanish birth
724 cohort. *Environ Int* 108:278-284.

725 McCowan L, Horgan RP. 2009. Risk factors for small for gestational age infants. *Best Pract*
726 *Res Clin Obstet Gynaecol* 23:779-793.

727 Newbold RR, Padilla-Banks E, Jefferson WN. 2009. Environmental estrogens and obesity.
728 *Mol Cell Endocrinol* 304:84-89.

729 Newbold RR. 2011. Developmental exposure to endocrine-disrupting chemicals programs for
730 reproductive tract alterations and obesity later in life. *Am J Clin Nutr* 94:1939S-1942S.

731 OECD. 2012. Infant health: Low birth weight. In: *Health at a glance: Europe 2012*.
732 Paris:OECD Publishing.

733 Oelberg DG. 2006. Consultation with the specialist: Prenatal growth: The sum of maternal,
734 placental, and fetal contributions. *Pediatr Rev* 27:224-229.

735 Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, et al. 2007.
736 Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and
737 perfluorooctanoate in retired fluorochemical production workers. *Environ Health Perspect*
738 115:1298-1305.

739 Palkovicova Murinova L, Wimmerova S, Lancz K, Patayova H, Kostiakova V, Richterova D,
740 et al. 2017. Partitioning of hexachlorobenzene between human milk and blood lipid. *Environ*
741 *Pollut* 229:994-999.

742 Patayova H, Wimmerova S, Lancz K, Palkovicova L, Drobna B, Fabisikova A, et al. 2013.
743 Anthropometric, socioeconomic, and maternal health determinants of placental transfer of
744 organochlorine compounds. *Environ Sci Pollut Res Int* 20:8557-8566.

745 Ritter R, Scheringer M, MacLeod M, Moeckel C, Jones KC, Hungerbuhler K. 2011. Intrinsic
746 human elimination half-lives of polychlorinated biphenyls derived from the temporal
747 evolution of cross-sectional biomonitoring data from the united kingdom. *Environ Health*
748 *Perspect* 119:225-231.

749 Schisterman EF, Perkins NJ, Mumford SL, Ahrens KA, Mitchell EM. 2017. Collinearity and
750 causal diagrams: A lesson on the importance of model specification. *Epidemiology* 28:47-53.

751 Schoeters G, Govarts E, Bruckers L, Den Hond E, Nelen V, De Henauw S, et al. 2017. Three
752 cycles of human biomonitoring in flanders - time trends observed in the flemish environment
753 and health study. *Int J Hyg Environ Health* 220:36-45.

754 Scollon EJ, Carr JA, Cobb GP. 2004. The effect of flight, fasting and p,p'-ddt on thyroid
755 hormones and corticosterone in gambel's white-crowned sparrow, *zonotrichia leucophrys*
756 *gambelli*. *Comparative biochemistry and physiology Toxicology & pharmacology : CBP*
757 137:179-189.

758 Skjaerven R, Gjessing HK, Bakketeig LS. 2000. Birthweight by gestational age in Norway.
759 *Acta obstetrica et gynecologica Scandinavica* 79:440-449.

760 Sonneborn D, Park HY, Petrik J, Kocan A, Palkovicova L, Trnovec T, et al. 2008. Prenatal
761 polychlorinated biphenyl exposures in eastern Slovakia modify effects of social factors on
762 birthweight. *Paediatr Perinat Epidemiol* 22:202-213.

763 Stefanidou M, Maravelias C, Spiliopoulou C. 2009. Human exposure to endocrine disruptors
764 and breast milk. *Endocrine, metabolic & immune disorders drug targets* 9:269-276.

765 Tang-Peronard JL, Andersen HR, Jensen TK, Heitmann BL. 2011. Endocrine-disrupting
766 chemicals and obesity development in humans: A review. *Obes Rev* 12:622-636.

767 To-Figueras J, Barrot C, Sala M, Otero R, Silva M, Ozalla MD, et al. 2000. Excretion of
768 hexachlorobenzene and metabolites in feces in a highly exposed human population. *Environ*
769 *Health Perspect* 108:595-598.

770 US-EPA. 2016. Health effects support document for perfluorooctanoic acid (pfoa).
771 https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_hesd_final-plain.pdf.

772 Vafeiadi M, Vrijheid M, Fthenou E, Chalkiadaki G, Rantakokko P, Kiviranta H, et al. 2014.
773 Persistent organic pollutants exposure during pregnancy, maternal gestational weight gain,
774 and birth outcomes in the mother-child cohort in Crete, Greece (Rhea study). *Environ Int*
775 64:116-123.

776 van Raaij JA, Frijters CM, van den Berg KJ. 1993a. Hexachlorobenzene-induced
777 hypothyroidism. Involvement of different mechanisms by parent compound and metabolite.
778 *Biochemical pharmacology* 46:1385-1391.

779 van Raaij JA, Kaptein E, Visser TJ, van den Berg KJ. 1993b. Increased glucuronidation of
780 thyroid hormone in hexachlorobenzene-treated rats. *Biochemical pharmacology* 45:627-631.

781 Verner MA, McDougall R, Glynn A, Andersen ME, Clewell HJ, III, Longnecker MP. 2013.
782 Is the relationship between prenatal exposure to PCB-153 and decreased birth weight
783 attributable to pharmacokinetics? *Environ Health Perspect* 121:1219-1224.

784 Verner MA, Loccisano AE, Morken NH, Yoon M, Wu H, McDougall R, et al. 2015.
785 Associations of perfluoroalkyl substances (PFAS) with lower birth weight: An evaluation of
786 potential confounding by glomerular filtration rate using a physiologically based
787 pharmacokinetic model (PBPK). *Environ Health Perspect* 123:1317-1324.

788 Verner MA, Ngueta G, Jensen ET, Fromme H, Volkel W, Nygaard UC, et al. 2016. A simple
789 pharmacokinetic model of prenatal and postnatal exposure to perfluoroalkyl substances
790 (PFAS). *Environ Sci Technol* 50:978-986.

791 Vesterinen HM, Johnson PI, Atchley DS, Sutton P, Lam J, Zlatnik MG, et al. 2015. Fetal
792 growth and maternal glomerular filtration rate: A systematic review. *The journal of maternal-*
793 *fetal & neonatal medicine : the official journal of the European Association of Perinatal*
794 *Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of*
795 *Perinatal Obstet* 28:2176-2181.

796 Visser GH, Eilers PH, Elferink-Stinkens PM, Merkus HM, Wit JM. 2009. New dutch
797 reference curves for birthweight by gestational age. *Early Hum Dev* 85:737-744.

798 Vizcaino E, Grimalt JO, Glomstad B, Fernandez-Somoano A, Tardon A. 2014. Gestational
799 weight gain and exposure of newborns to persistent organic pollutants. *Environ Health*
800 *Perspect* 122:873-879.

801 Vrijkotte TG, Hruvey EJ, Twickler MB. 2017. Early maternal thyroid function during
802 gestation is associated with fetal growth, particularly in male newborns. *J Clin Endocrinol*
803 *Metab* 102:1059-1066.

804 White SS, Fenton SE, Hines EP. 2011. Endocrine disrupting properties of perfluorooctanoic
805 acid. *J Steroid Biochem Mol Biol* 127:16-26.

806 WHO/UNEP. 2013. State of the science of endocrine disrupting chemicals - 2012.
807 Geneva:<http://www.who.int/ceh/publications/endocrine/en/>.

808 Wolff MS, Engel S, Berkowitz G, Teitelbaum S, Siskind J, Barr DB, et al. 2007. Prenatal
809 pesticide and pcb exposures and birth outcomes. *Pediatr Res* 61:243-250.

810 Xu XJ, Su JG, Bizzarri AR, Cannistraro S, Liu M, Zeng Y, et al. 2013. Detection of persistent
811 organic pollutants binding modes with androgen receptor ligand binding domain by docking
812 and molecular dynamics. *BMC Struct Biol* 13:16.

813 Xu Y, Wang Q, Cook TJ, Knipp GT. 2007. Effect of placental fatty acid metabolism and
814 regulation by peroxisome proliferator activated receptor on pregnancy and fetal outcomes.
815 *Journal of pharmaceutical sciences* 96:2582-2606.

816 Yamamoto J, Yamane T, Oishi Y, Kobayashi-Hattori K. 2015. Perfluorooctanoic acid binds
817 to peroxisome proliferator-activated receptor gamma and promotes adipocyte differentiation
818 in 3t3-l1 adipocytes. *Biosci Biotechnol Biochem* 79:636-639.

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820

822 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				964 (74.9%)		84 (100%)	1034 (100%)	
1 st day last menstruation								394 (100%)
Ultrasound								
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)

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)
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 18.5<25 kg/m ² 25<30 kg/m ² ≥30 kg/m ² Missing (%)	60 (5.6%) 737 (68.8%) 201 (18.8%) 74 (6.9%) 3.0%	15 (6.3%) 169 (70.4%) 36 (15.0%) 20 (8.3%) 0.8%	14 (3.2%) 275 (63.7%) 99 (22.9%) 44 (10.2%) 1.8%	53 (4.2%) 911 (71.7%) 224 (17.6%) 83 (6.5%) 1.2%	43 (5.0%) 598 (69.5%) 158 (18.4%) 61 (7.1%) 0%	2 (2.4%) 63 (76.8%) 10 (12.2%) 7 (8.5%) 2.4%	126 (12.8%) 680 (68.8%) 128 (13.0%) 54 (5.5%) 4.4%	29 (7.4%) 303 (77.7%) 43 (11.0%) 15 (3.9%) 1.0%
Maternal gestational weight gain (kg) Missing (%)	13 (0-35) 50.2%	/ 100%	14 (-3-31) 2.5%	13.2 (-5.7-37.1) 36.8%	13.5 (-7.4-30.4) 6.6%	13 (-6-23) 9.5%	14 (1-35) 27.1%	13 (3-31) 38.3%
Maternal height (cm) Missing (%)	167 (149-184) 2.0%	168 (148-183) 0.8%	168 (149-199) 0.7%	162 (135-185) 1.2%	163 (145-180) 0%	171 (158-187) 1.2%	165 (133-186) 0%	164 (146-190) 0%
Maternal height <163 cm 163-169 cm ≥169 cm Missing (%)	281 (26.0%) 406 (37.5%) 396 (36.6%) 2.0%	50 (20.8%) 90 (37.5%) 100 (41.7%) 0.8%	84 (19.2%) 172 (39.4%) 181 (41.4%) 0.7%	656 (51.6%) 422 (33.2%) 193 (15.2%) 1.2%	389 (45.2%) 312 (36.3%) 159 (18.5%) 0%	6 (7.2%) 17 (20.5%) 60 (72.3%) 1.2%	362 (35.0%) 407 (39.4%) 265 (25.6%) 0%	154 (39.4%) 152 (38.9%) 85 (21.7%) 0.8%
Parity 0 1 ≥2 Missing (%)	670 (60.6%) 297 (26.9%) 138 (12.5%) 0%	98 (40.5%) 80 (33.1%) 64 (26.5%) 0%	184 (41.8%) 172 (39.1%) 84 (19.1%) 0%	667 (51.8%) 489 (38.0%) 131 (10.2%) 0%	481 (56.1%) 323 (37.7%) 54 (6.3%) 0.2%	31 (38.3%) 31 (38.3%) 19 (23.5%) 3.6%	438 (42.5%) 338 (32.8%) 255 (24.7%) 0.3%	172 (43.7%) 142 (36.0%) 80 (20.3%) 0%
Maternal education Secondary education or less Higher education Missing (%)	847 (78.6%) 230 (21.4%) 2.5%	91 (38.6%) 145 (61.4%) 2.5%	156 (35.5%) 283 (64.5%) 0.2%	932 (73.5%) 336 (26.5%) 1.5%	541 (63.1%) 316 (36.9%) 0.3%	27 (33.3%) 54 (66.7%) 3.6%	952 (92.3%) 79 (7.7%) 0.3%	142 (36.0%) 252 (64.0%) 0%
Maternal smoking during pregnancy Yes No Missing (%)	179 (16.2%) 923 (83.8%) 0.3%	29 (12.2%) 208 (87.8%) 2.1%	51 (11.6%) 389 (88.4%) 0%	383 (30.1%) 891 (69.9%) 1.0%	234 (27.8%) 607 (72.2%) 2.2%	3 (3.7%) 78 (96.3%) 3.6%	158 (15.3%) 876 (84.7%) 0%	56 (14.4%) 333 (85.6%) 1.3%
Ethnicity Caucasian Inuit			415 (94.3%) 3 (0.7%)	1223 (96.1%)	834 (97.0%)		799 (78.9%)	

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)
Roma Other Missing (%)	100%	100%	1 (0.2%) 4 (0.9%) 3.9%	49 (3.9%) 1.2%	26 (3.0%) 0%	100%	214 (21.1%) 2.0%	100%
Sample type ^b Cord blood Maternal blood Breast milk	1105 (100%)	242 (100%)	440 (100%)	1287 (100%)	860 (100%)	66 (78.6%) 61 (72.6%)	1026 (99.2%) 210 (20.3%)	394 (100%)
Caesarean section Yes No Missing (%)	53 (4.8%) 1052 (95.2%) 0%	11 (4.6%) 230 (95.4%) 0.4%	60 (13.6%) 380 (86.4%) 0%	151 (12.8%) 1032 (87.2%) 8.1%	101 (14.4%) 599 (85.6%) 18.6%	3 (3.6%) 81 (96.4%) 0%	100%	50 (12.9%) 337 (87.1%) 1.8%

823 Continuous measures described by median (min-max); categorical measures described by frequencies (%).

824 Abbreviations: SGA, Small for Gestational Age; BMI, body mass index.

825 ^aNumber of live-born singleton births with exposure levels and information on at least one outcome.

826 ^bSome 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
827 type was used depending on the compound.

828

829 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
830 8 study populations

	PCB 153 (ng/L)					<i>p,p'</i> -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 ^{ab}	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%)

831 Abbreviations: PCB, polychlorinated biphenyl; *p,p'*-DDE, dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; SD, standard deviation; P, percentile;

832 LOD, limit of detection; LOQ, limit of quantification

833 ^aObserved cord serum concentrations

834 ^bEstimated cord serum concentrations based on measured concentrations in breast milk

835 ^cEstimated cord serum concentrations based on measured concentrations in maternal serum

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

838

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

Cohort	PFOS (ng/L)					PFOA (ng/L)				
	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 ^{ab}	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%)

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

842 ^aObserved cord serum concentrations

843 ^bEstimated cord serum concentrations based on measured concentrations in breast milk

FIGURE LEGENDS

Figure 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.

Figure 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.