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Abstract

Background: Infant exposure to persistent organic pollutants (POPs) may contribute to obesity. However, many studies so far have been small, focused on transplacental exposure, used an inappropriate measure to assess postnatal exposure through breastfeeding if any, or did not discern between prenatal and postnatal effects.

Methods: We pooled data from 7 European birth cohorts with biomarker concentrations of polychlorinated biphenyl 153 (PCB-153) (n=2487), and *p,p*'-dichlorodiphenyldichloroethylene (*p,p*'-DDE) (n=1864), estimating prenatal and postnatal POPs exposure using a validated pharmacokinetic model. Growth was change in weight-for-age z-score between birth and 24 months. Per compound, multi-level models were fitted with either POPs total exposure from conception to 24 months, prenatal or postnatal exposure.

Results: We found a significant increase in growth associated with *p,p*'-DDE, seemingly due to prenatal exposure (per interquartile increase in exposure, adjusted β=0.12; 95% CI: 0.03, 0.22). Due to heterogeneity across cohorts, this estimate cannot be considered precise, but does indicate that an association with infant growth is present on average. In contrast, a significant decrease in growth was associated with postnatal PCB-153 exposure (β=-0.10; 95% CI: -0.19, -0.01).

Conclusion: To our knowledge, this is the largest study to date of POPs exposure and infant growth, and with state of the art exposure modelling. Prenatal *p,p*'-DDE was associated with increased infant growth, and postnatal PCB-153 with decreased growth at European exposure levels.

Introduction

Rapid weight gain during the first few months of life is a predictor for later obesity (Monteiro and Victora 2005). Perinatal exposure to chemicals may contribute to obesity by affecting endocrine and neuronal pathways (La Merrill and Birnbaum 2011). Polychlorinated biphenyls (PCBs), *p,p′*-dichlorodiphenyltrichloroethane (*p,p′*-DDT) and metabolite *p,p′*-dichlorodiphenyldichloroethylene (*p,p′*-DDE) were used in agriculture and industry until global efforts in the 1990's to eliminate them (Stockholm Convention 2001). Substantial exposure is still observed due to the persistency of these lipophilic compounds (Longnecker et al. 2003). PCB-153 has a biological half-life of ~14 years (Ritter et al. 2011) and *p,p′*-DDE ~13 years (Wolff et al. 2000).

Epidemiological studies on perinatal POPs exposure, growth and obesity have focused on transplacental exposure, with inconsistent results for PCB and a predominantly positive association for *p,p'*-DDE (reviewed in Cupul-Uicab et al., 2013). However, substantial exposure occurs postnatally through breastfeeding, research on which is limited (Grandjean et al. 2003; Rogan et al. 1987; Pan et al. 2010; Patandin et al. 1998; Jacobson et al. 1990). Most studies were limited by sample size and with no or incomplete postnatal exposure (assessed using the product of POPs concentration and breastfeeding duration). Postnatal exposure needs to be considered but is challenging as multiple factors such as child growth and maternal weight gain also influence children's internal concentrations.

In the largest study to date on POPs and growth, we pooled data from 7 European birth cohorts to investigate the association between prenatal and postnatal POPs exposure and infant growth from birth to 24 months in singleton term children, and used a recently developed pharmacokinetic model (Verner et al 2013) to improve postnatal exposure assessment.

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Methods

Description of cohorts

Previously, Govarts et al. (2012) identified 14 cohorts of women/child pairs with POPs measures from the Environmental Health Risks in European Birth Cohorts' (ENRIECO) inventory (http://www.enrieco.org/). Eleven of these cohorts had relevant weight data and were invited to participate. Four (FAROES2, FAROES3, INMA, RHEA) did not participate for reasons unrelated to this study hypothesis. Seven cohorts (N=2487) had PCB-153 and 5 cohorts (N=1864) had *p,p'*-DDE biomarkers. Concentrations were measured in cord serum/plasma in FLEHS I (Koppen et al. 2009), GRD (Huisman et al. 1995, Walkowiak et al. 2001), Michalovce (Herz-Picciotto et al. 2003) and PELAGIE (Chevrier et al. 2013), in breast milk in ELFE (Vandentorren et al. 2009), and HUMIS (Eggesbø et al. 2009) and in maternal blood during pregnancy in Duisburg (Wilhelm et al. 2008, Wittsiepe et al. 2008). Table 1 lists population characteristics, while Supplemental Material, Table S1 contains cohorts' descriptions and references. Each study was approved by national ethical committees. Mothers provided written informed consent prior to participation.

Exposure assessment

All cohorts provided lipid-adjusted and wet-weight concentrations, plus information on lipid measurement (Supplemental Material, Table S2). We replaced POP concentrations below the limit of detection/quantification (LOD/LOQ) (Table 2; Supplemental Material, Table S2) with LOD/LOQ divided by the square root of two (Hornung and Reed 1990).

We estimated individual-specific cord blood concentration (prenatal exposure) and cumulative postnatal exposure using a validated pharmacokinetic model (Verner et al. 2013). Two compartments representing maternal and child lipids are connected through placental diffusion

and excretion/intake of breast milk (Supplemental Material, Figure S1A). To generate individual-specific profiles of child POPs concentrations (e.g., Supplemental Material, Figure S1B), the pharmacokinetic model incorporated: maternal age, pre-pregnancy weight, gestational age, sex, child's weight at birth and several time points, total breastfeeding duration (exclusive/partial). We used fixed values for gestational weight gain and postpartum maternal weight (Verner et al. 2013), as this information was not collected in some cohorts and therefore could not be imputed within cohort-specific multiple imputation models, in contrast with missing data for other covariates (see below). Most studies did not distinguish exclusive from partial breastfeeding, therefore, we used total breastfeeding duration. Breast milk consumption rate was based on exclusive/partial breastfeeding data from the general population (Arcus-Arth et al. 2005). Measured POP concentrations in maternal blood, cord blood or breast milk (ng/g lipids) were used to estimate individual-specific maternal daily dose and subsequently to simulate complete time-course of child concentrations: iterative model simulations adjusting the maternal daily dose provided matching simulated and measured blood or breast milk POP concentrations at the time of collection.

We abstracted the simulated cord blood concentration at delivery as the common prenatal exposure estimate across cohorts (vs. measures taken in different biological matrices sampled at different times). We calculated postnatal cumulative exposure 0-24 months as area under the curve (AUC) (Supplemental Material, Figure S1B). We added prenatal (multiplied by gestational age) to postnatal to get total exposure from conception to 24 months. The 3 exposure metrics are expressed as average concentrations over their respective time periods (ng/g lipids). Model simulations were performed using acsIX (Aegis Technologies Group, Inc., Huntsville, AL, USA).

Outcome variable

Cohorts provided weight and height data with minimum 2 time points after birth to 3 years. Michalovce had data up to 4 years, Duisburg had data at 1.5 and 6.5 years. Weight and height data were measured for the study by nurses or doctors (GRD, Michalovce), or recorded during pediatric examinations in children's health cards that were obtained by study staff (FLEHS I) or parent-reported (Duisburg, ELFE, HUMIS, PELAGIE). We estimated weight at exactly 24 months using a cohort-specific, sex-specific multi-level (mixed) linear model fitted with cubic polynomials and random effects for infant. We then created cohort-specific, sex-specific weight-for-age z-scores at birth and 24 months. Intra-class correlations between predicted and observed values at 24 months (±14 days) in infants with available data ranged from 0.84 (ELFE males) to ≥0.90 (ELFE females, FLEHS I, HUMIS, PELAGIE). GRD, Michalovce and Duisburg had no children with observed data at 24 months. The difference between the child's z-score at birth and 24 months (change in weight-for-age z-score), was analysed as a continuous outcome.

Statistical analysis

We imputed missing data (outcome, exposure, covariate) by cohort, using multiple imputation by chained equations (ICE) (Rubin 1987; van Buuren 2007), and performed pharmacokinetic model simulations for each imputation set. The pharmacokinetic model used lipid-adjusted concentrations since they are more stable over time (Phillips et al. 1989). Some observations in all cohorts except ELFE and HUMIS were missing lipid-adjusted concentrations, and these were imputed in a cohort-specific model including wet-weight concentrations. We assessed correlations between exposures and covariates using Pearson's correlation coefficients. We combined exposure, outcome and covariate data from individual cohorts into a pooled dataset to analyse as a single dataset, using a multi-level (mixed) linear regression model to estimate

associations between infant growth and separately, total, prenatal and postnatal exposure. For each compound, we tested for heterogeneity by fitting a model with random intercepts and slopes by cohort. There was significant heterogeneity for all exposures (Supplemental Material, Table S3). However, in the case of *p,p'*-DDE, which was available in only 5 cohorts, we had less power to fit a complex model (i.e. confidence intervals were severely inflated, Supplemental Material, Table S4). Therefore, models were fitted with random intercepts for *p,p'*-DDE, and random intercepts and slopes for PCB-153. Models were fitted via maximum likelihood, using the STATA 12.0 "mi estimate" function to pool five imputation results. For prenatal and postnatal exposure, models were fitted first with either prenatal or postnatal concentrations in the model and then with both (prenatal and postnatal mutually adjusted). We checked for collinearity between prenatal and postnatal exposure with variance inflation factors (VIFs) greater than 5-10 suggesting a problem with collinearity (Kleinbaum et al. 2013).

We identified 9 potential confounders and intermediate covariates *a priori* using directed acyclic graphs (DAGs) (Supplemental Material, Figures S2A, B, and C for total, prenatal, and postnatal exposure DAGs, respectively): maternal pre-pregnancy body mass index (BMI, continuous), maternal age (years, continuous), education (low, medium, high), smoking during pregnancy (yes/no), Roma ethnicity (yes/no), nulliparous (yes/no), gestational age (weeks, continuous), birth weight (kg, continuous), total breastfeeding (months, continuous), maternal gestational weight change (kg). Categories for primary and secondary education varied, so we combined categories to create relative low, medium, and high per cohort. ELFE and FLEHS I had no ethnicity information (important due to a large Roma population in Michalovce), so we assumed their ethnicity was not Roma. We made additional adjustment for maternal gestational weight change in FLEHS I, HUMIS, PELAGIE and Michalovce. Similarly, we assessed the results'

sensitivity to maternal consumption of fatty fish (meals/week HUMIS, FLEHS I), total fish (g/week, PELAGIE, MICHALOVCE) by adjusting for these covariates.

We looked at the effect of removing each cohort in turn. We assessed assumptions of normality and linearity using informal diagnostic plots, and assessed the combination of high leverage and residuals in order to fit regression models with and without influential observations. Results are change in weight-for-age z-score from birth to 24 months for the interquartile range (IQR) of exposure.

Results

Table 1 summarises cohort characteristics. Duisburg infants were slowest and ELFE infants fastest growers. Total breastfeeding duration varied (2.3 to 12 months), as did infants with no breastfeeding: Duisburg, ELFE, HUMIS had none, Michalovce 0.2 %, FLEHS I 25.4 %, GRD 38.1 % and PELAGIE 40.9 %.

Table 2 shows estimated prenatal and postnatal infant blood POPs concentrations. For prenatal concentrations, PELAGIE was lowest and GRD highest for PCB-153, and HUMIS lowest and Michalovce highest for *p,p'*-DDE . PELAGIE had lowest postnatal exposures, while ELFE had highest PCB-153 and Michalovce highest *p,p'*-DDE. Measured biomarker concentrations were not substantially different to the estimated cord blood (prenatal) concentrations (Supplemental Material, Table S5).

Prenatal and postnatal exposures were highly correlated (PCB-153 r=0.71, *p,p'*-DDE r=0.88, Supplemental Material, Table S6), although this varied across the cohorts. Overall correlations between prenatal PCB-153/*p,p'*-DDE concentrations were moderate (r=0.65), varying from r=0.11 to r=0.65 across cohorts (data not shown), while correlations between total breastfeeding

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and postnatal POPs exposure were lower (PCB-153 r=0.43, *p,p'*-DDE r=0.31) (Supplemental Material, Table S6).

VIFs for prenatal and postnatal exposure in the same model varied across cohorts from low (i.e. FLEHS I, PELAGIE) to high (i.e. HUMIS, ELFE), and were below 5 for the pooled dataset (Supplemental Material, Table S7).

Table 3 shows the relation between total exposure from conception to 24 months and infant growth. Individual cohort analyses showed significant associations only for GRD (PCB-153), and Duisburg (*p,p'*-DDE). The pooled data showed non-significant associations between change in weight-for-age z-score and PCB-153 (β=-0.06; 95% CI: -0.15, 0.03 for an IQR increase of 152 ng/g lipid) and *p,p'*-DDE (β=0.04; 95% CI: -0.001, 0.07 for an IQR increase of 515 ng/g lipid).

Figure 1 shows the secondary analyses assessing which of prenatal and postnatal exposure is the more important contributor towards associations with total exposure. After adjustment for prenatal exposure, postnatal PCB-153 was associated with a significant decrease in change in weight for age z-score β=-0.10 (95% CI: -0.19, -0.01) for an IQR increase of 183 ng/g lipid (Figure 1A). Prenatal *p,p'*-DDE was associated with a significant increase in change in weight-for-age z-score β=0.12 (95% CI: 0.03, 0.22) for an increase of 388 ng/g lipid after adjustment for postnatal exposure (Figure 1B).

In general, leaving out one cohort did not have a substantial influence on the prenatal and postnatal pooled estimates, with point estimates for the partial sample within the CI of the overall pooled result. However, for prenatal p,p'-DDE, removing Michalovce doubled the estimate (from 0.12; 95% CI: 0.03, 0.22 to 0.23; 95% CI: –0.09, 0.54) and made it non-significant (Supplemental Material, Table S8).

Additional adjustment for fish consumption or maternal gestational weight change, did not materially affect results (data not shown). Complete case and multiple imputation analyses gave essentially the same results, as did estimates of prenatal exposure from biomarker concentrations and pharmacokinetic modelled estimations (Supplemental Material, Table S9). The normality and linearity assumptions of our models held (data not shown). There was no material difference in estimates from regression models fitted without influential observations (data not shown).

Discussion

We found that prenatal *p,p'*-DDE exposure was significantly associated with increased infant growth and postnatal PCB-153 exposure with decreased infant growth. Our estimates suggest that on average, children with an 388 ng/g higher prenatal concentration of *p,p'*-DDE would weigh 200 g more than other children at 24 months of age, while children with an 183 ng/g higher postnatal concentration of PCB-153 would weight 200 g less.

Prenatal PCB-153 concentrations were not significantly associated with infant growth. Since PCB-153 is a proxy biomarker for a number of PCB congeners of varying toxicity (Glynn et al. 2000), inconsistent results from previous studies (i.e. Gladen et al. 2000; Blanck et al. 2002; Hertz-Picciotto et al. 2005; Lamb et al. 2006; Karmaus et al. 2009; Verhulst et al. 2009; Cupul-Uicab et al. 2010; Mendez et al. 2011; Valvi et al. 2012; Cupul-Uicab et al. 2013; Warner et al. 2013; Valvi et al. 2014) could be due to heterogeneity in the underlying PCB congeners mixture. Indeed higher chlorinated PCBs have been associated with increased abdominal obesity in seniors, while the lower chlorinated PCBs showed an inverse relation (Lee et al. 2012).

The negative change in weight z-score associated with postnatal PCB-153 exposure is unlikely to be an an artifact of design (i.e. including weight in the pharmacokinetic model) as we did not

find a significant association with postnatal *p,p'*-DDE exposure. Grandjean et al. (2003) also reported attenuated growth of breastfed children exposed to major PCB congeners (138, 153 and 180) at 18 months. Concentrations in that study were higher than in ours, while total breastfeeding duration was similar. However, 4 other studies reported no significant associations (Rogan et al. 1987; Pan et al. 2010; Patandin et al. 1998; Jacobson et al. 1990). Two studies investigated PCB concentration in formula-fed and breastfed babies (Patandin et al. 1998; Jacobson et al. 1990), while 3 estimated postnatal exposure simply as the product of PCB concentration and exclusive/total breastfeeding duration (Grandjean et al. 2003; Pan et al. 2010; Rogan et al. 1987). Exposure assessment that does not account for the dilution effect from weight increases in the growing child would lead to differential misclassification, overestimating exposure in the heavier children. Therefore, this would bias results upwards, and if the association between PCB-153 and growth is negative, could explain null findings reported in previous studies. The significant decline in birth weight of 150 g (95% CI : -250, -50) per 1 µg/L increase in PCB-153 reported by Govarts et al. (2012), indicates that PCB-153 may have a similar mode of action transplacentally and postnatally.

Prenatal *p,p'*-DDE exposure was significantly associated with increased change in weight-for-age z-score, a positive trend seen in 4 of the 5 cohorts. A change in z-score of 0.12 is modest, below the 0.67 cut-point for rapid growth (Monteiro and Victora 2005). Conversely, postnatal *p,p'*-DDE exposure was not associated with infant growth, consistent with 2 previous studies (Pan et al. 2010; Rogan et al. 1987). Two limitations apply when interpreting this evidence. Firstly, we found significant heterogeneity when pooling the cohorts in the *p,p'*-DDE analysis, however, fitting a more flexible model was not possible. Therefore, our estimate of the average effect does not account for the magnitude of variation among the cohorts.. Secondly, although

VIFs were below 5, variance doubled when prenatal and postnatal were mutually adjusted, suggesting collinearity. However, although our point estimate may be uncertain, the confidence intervals incorporate uncertainty generated by any collinearity (Kleinbaum et al. 2013). The more appropriate prenatal *p,p'*-DDE estimate probably lies between the unadjusted and adjusted one.

Our *p,p'*-DDE results are plausible. The majority of previous studies also found a positive association between *p,p'*-DDE and: rapid growth and higher BMI in infancy (Verhulst et al. 2009; Mendez et al. 2011; Valvi et al. 2014) , overweight and BMI around 7 years (Valvi et al. 2012, Warner et al. 2013), weight-for-height at puberty in males (Gladen et al. 2000) and in adulthood for females (Karmaus et al. 2009). Studies with high concentrations, however, reported no significant associations (Garced et al. 2012; Cupul-Uicab et al. 2010; Cupul-Uicab et al. 2013; Gladen et al.2004). This could be chance findings or suggest a mode of action that operates at lower-doses, in line with the non-monotonic relationship seen between endocrine-disrupting chemicals (EDCs) and hormones (Vandenberg et al. 2012). No studies to date reported a negative effect of DDE on growth/BMI (Cupul-Uicab et al. 2013, Table S7).

Our approach has strengths and limitations. We pooled data from 7 European birth cohorts, examining associations between POPs and infant growth across larger samples of individuals with heterogeneous and distinct prenatal/postnatal exposure profiles. Compared with single cohort studies, the pooled design controls better for unmeasured confounding (including from other compounds), since the underlying confounder-structure varies across cohorts. Furthermore it reduces or eliminates reporting bias by showing results for all eligible European cohorts.

We attempted to isolate prenatal from postnatal exposure, however, as discussed, the p,p'-DDE results suggest some collinearity. To ascertain a closer estimate of prenatal exposure, we would ideally restrict our analyses to babies who were not breastfed. Too few cohorts had non-breastfed babies (3 for PCB-153, 2 for p,p'-DDE), precluding meaningful sensitivity analyses.

Our postnatal exposure modelling was more appropriate than the simple models used in previous studies, which only incorporated breastfeeding. The pharmacokinetic model generated exposure profiles based on cord, maternal blood or breast milk levels and known determinants of children's blood concentration. This model was validated in Michalovce and an Inuit cohort with repeated POPs measurements: estimated concentrations from the pharmacokinetic model explained from 40 % to 83 % of p,p'-DDE and 51 % to 81 % of PCB-153 measured in children's blood at 6 and 16 months (Verner et al. 2013). Estimations based on maternal blood were better than cord blood estimations, which were better than breast milk estimations. Repeated samples for model validation (e.g., cord/child blood concentrations) were unavailable in other cohorts in this study. It may be that the model predictability is lower in these cohorts, and model accuracy is lower in cohorts with estimations made from cord blood/breast milk. Despite these limitations, pharmacokinetic modeling presents a major improvement on metrics that do not account for important parameters (i.e. change in child weight, breast milk consumption or lipid content). We did not have POPs dietary exposure information, however, breastfeeding is the main determinant of infant blood concentrations (Ayotte et al. 2003). Few cohorts distinguished exclusive from partial breastfeeding, therefore, we used total duration and descriptions of breast milk consumption in the general population. Furthermore, information on gestational weight gain and weight changes after pregnancy, influential in sensitivity analyses (Verner et al. 2013), were not available in most cohorts. These factors may have decreased model precision, and could lead to

small differential misclassification, overestimating heavier children's blood concentrations and resulting in a positive bias (in this case towards the null).

We added together the prenatal and postnatal exposure AUCs to assess total exposure from conception to 2 years, which has not been investigated in previous studies. Our prenatal AUC was calculated as the cord blood exposure estimate multiplied by gestational age. Although prenatal concentrations would be influenced by maternal weight gain over pregnancy, which would vary the volume of distribution, this information was not available in some of the cohorts. Our prenatal AUC is not expected to be more biased than using cord-blood concentration as a proxy for prenatal exposure. Furthermore, adjustment for maternal gestational weight gain in cohorts where this was available did not affect our results (data not shown).

We used lipid-adjusted POP concentrations in our pharmacokinetic model, assuming an equilibrium across body lipids. Differential transport, or protection of the placenta or mammary gland due to molecular size, could require a conversion factor. However, considerable uncertainty is associated with conversion factors due to the variability from factors other than differing measurement matrices (i.e. maternal body weight), which are not taken into account. Study-specific conversion factors are also difficult to apply to other studies with differing distributions of underlying co-factors. We therefore decided against applying conversion factors.

In addition, we were not able to test for exposure to combinations of these POPs and other EDCs, and may have missed important mixture effects.

We modelled weight at 24 months using a mixed-model for growth with cubic polynomials, standardising the children's weights using cohort-specific data. Infant growth between 0-24 months has previously been identified as a risk factor for obesity at a later age (Monteiro and

Victora 2005). We did not test growth from birth to 6 months or 12 months as only 4 cohorts had appropriate measurements, and possibly missed a critical window for growth trajectory (Botton et al. 2008).

We did not have information fatty fish intake in all cohorts, however, restricting analysis to the 4 cohorts where this was available found no material difference (data not shown).

Breastfeeding duration unadjusted for other covariates is associated with reduced growth in our study. Breastfeeding is an important contributor to postnatal POP exposure and relates to nutritional intake and other socio-economic factors. However, additional adjustment for breastfeeding duration in the postnatal PCB-153 model had limited impact on the estimates (i.e. β=-0.12; 95% CI -0.21, -0.03 vs. β=-0.10; 95% CI -0.19, -0.01). Breastfeeding reduced the estimated increase in infant growth from prenatal *p,p'*-DDE by 14% (i.e. β=0.14; 95% CI: 0.06, 0.22 vs. β=0.12; 95% CI: 0.03, 0.22), possibly reflecting increased PCB-153 breastfeeding exposure.

Michalovce is a large cohort accounting for 38 % (PCB-153) and 50 % (*p,p'*-DDE) of our total population. Although Michalovce drives the precision of the associations, these relations held after removing these children from the analyses. The postnatal PCB-153 and prenatal *p,p'*-DDE estimates became non-significant, as expected with a large sample size reduction, and the later doubled in size.

Conclusion

In a large and heterogenous European population, we found an increase in infant growth associated with prenatal *p'p*-DDE and a decrease associated with postnatal PCB-153 exposure.

To understand the importance of POPs breastfeeding exposure on health, future investigations

should assess both prenatal and postnatal exposure.

References

Arcus-Arth A, Krowech G, Zeise L. 2005. Breast milk and lipid intake distributions for assessing cumulative exposure and risk. J Expo Anal Environ Epidemiol 15:357–365; doi:10.1038/sj.jea.7500412.

Ayotte P, Muckle G, Jacobson JL, Jacobson SW, Dewailly E, Inuit Cohort Study. 2003. Assessment of pre- and postnatal exposure to polychlorinated biphenyls: Lessons from the Inuit Cohort Study. Environ Health Perspect 111:1253-1258.

Blanck HM, Marcus M, Rubin C, Tolbert PE, Hertzberg VS, Henderson AK, et al. 2002. Growth in girls exposed in utero and postnatally to polybrominated biphenyls and polychlorinated biphenyls. Epidemiology 13:205–210.

Botton J, Heude B, Maccario J, Ducimetière P, Charles MA, FLVS Study Group. 2008. Postnatal weight and height growth velocities at different ages between birth and 5 y and body composition in adolescent boys and girls. Am J Clin Nutr 87:1760–1768.

Chevrier C, Warembourg C, Gaudreau E, Monfort C, Blanc A Le, Guldner L, et al. 2013. Organochlorine pesticides, polychlorinated biphenyls, seafood consumption, and time-to-pregnancy. Epidemiol 24:251–260.

Cupul-Uicab LA, Hernández-Avila M, Terrazas-Medina EA, Pennell ML, Longnecker MP. 2010. Prenatal exposure to the major DDT metabolite 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) and growth in boys from Mexico. Environ Res 110:595–603; doi:10.1016/j.envres.2010.06.001.

Cupul-Uicab LA, Klebanoff MA, Brock JW, Longnecker MP. 2013. Prenatal exposure to persistent organochlorines and childhood obesity in the U.S. Collaborative Perinatal Project. Environ Health Perspect 121:1103–1109; doi:dx.doi.org/10.1289/ehp.1205901.

Eggesbø M, Stigum H, Longnecker M, Polder A, Aldrin M, Basso O, et al. 2009. Levels of hexachlorobenzene (HCB) in breast milk in relation to birth weight in a Norwegian cohort. Environ Res 109:559–566.

Garced S, Torres-Sánchez L, Cebrián ME, Claudio L, López-Carrillo L. 2012. Prenatal dichlorodiphenyldichloroethylene (DDE) exposure and child growth during the first year of life. Environ Res 113:58-62; doi: 10.1016/j.envres.2011.12.002.

Gladen BC, Ragan NB, Rogan WJ. 2000. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. J Pediatr 136:490–496; doi: 10.1016/S0022-3476(00)90012-X.

Gladen BC, Klebanoff MA, Hediger ML, Katz SH, Barr DB, Davis MD et al. 2004. Prenatal DDT exposure in relation to anthropometric and pubertal measures in adolescent males. Environ Health Perspect 112:1761–1767; doi: 10.1289/ehp.7287.

Glynn AW, Wolk A, Aune M, Atuma S, Zettermark S, Maehle-Schmid M, et al. 2000. Serum concentrations of organochlorines in men: a search for markers of exposure. Sci Total Env. 263:197–208; doi: 10.1016/S0048-9697(00)00703-8.

Govarts E, Nieuwenhuijsen M, Schoeters G, Ballester F, Bloemen K, Boer M de, et al. 2012. Prenatal exposure to polychlorinated biphenyls (PCB) and dichlorodiphenyldichloroethylene (DDE) and birth weight: A meta-analysis within 12 European Birth Cohorts. Environ Health Perspect 120:162–170; doi: 10.1289/ehp.1103767.

Grandjean P, Budtz-Jørgensen E, Steuerwald U, Heinzow B, Needham LL, Jørgensen PJ, et al. 2003. Attenuated growth of breast-fed children exposed to increased concentrations of methylmercury and polychlorinated biphenyls. FASEB J 17:699–701; doi:10.1096/fj.02-0661fje.

Hertz-Picciotto I, Trnovec T, Kocan A, Charles M, Ciznar P, Langer P, et al. 2003. PCBs and early childhood development in Slovakia: study design and background. Fresenius Environ Bull 12:208–214.

Hertz-Picciotto I, Charles MJ, James RA, Keller JA, Willman E, Teplin S. 2005. In utero polychlorinated biphenyl exposures in relation to fetal and early childhood growth. Epidemiology 16:648–656; doi: 10.1097/01.ede.0000173043.85834.f3.

Hornung RW, Reed LD. 1990. Estimation of average concentration in the presence of nondetectable values. Appl Occup Environ Hyg 5:46–51; doi: 10.1080/1047322X.1990.10389587.

Huisman M, Koopman-Esseboom C, Fidler V, Hadders-Algra M, Paauw C van der, Tuinstra L, et al. 1995. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. Early Hum Dev 41:111–127.

Jacobson JL, Jacobson SW, Humphrey HE. 1990. Effects of exposure to PCBs and related compounds on growth and activity in children. Neurotoxicol Teratol 12:319–326; doi:10.1016/0892-0362(90)90050-M.

Karmaus W, Osuch JR, Eneli I, Mudd LM, Zhang J, Mikucki D, et al. 2009. Maternal levels of dichlorodiphenyl-dichloroethylene (DDE) may increase weight and body mass index in adult female offspring. Occup Environ Med 66:143–149; doi:10.1136/oem.2008.041921.

Kleinbaum DG, Kupper LL, Nizam A, Rosenerg ES. 2013. Applied Regression and Other Multivariable Methods. 5th ed. Boston:Cengage Learning.

Koppen G, Den H, Nelen V, Mieroop E Van De, Bruckers L, Bilau M, et al. 2009. Organochlorine and heavy metals in newborns: results from the Flemish Environment and Health Survey (FLEHS 2002–2006). Environ Int 35:1015–1022.

Lamb MR, Taylor S, Liu X, Wolff MS, Borrell L, Matte TD, et al. 2006. Prenatal exposure to polychlorinated biphenyls and postnatal growth: a structural analysis. Environ Health Perspect 114:779–785; doi: 10.1289/ehp.8488.

La Merrill M, Birnbaum LS. 2011. Childhood obesity and environmental chemicals. Mt Sinai J Med 78:22–48; doi:10.1002/msj.20229.

Lee DH, Lind L, Jacobs DR Jr, Salihovic S, van Bavel B, Lind PM. 2012. Associations of persistent organic pollutants with abdominal obesity in the elderly: The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Environ Int 40:170-178; doi: 10.1016/j.envint.2011.07.010.

Longnecker MP, Korrick SA, Moysich KB. 2003. Human health effects of polychlorinated biphenyls, in Dioxins and Health, 2nd ed (Schecter A, Gasiewicz TA, eds), Hoboken: John Wiley & Sons, Inc., 679–728.

Mendez MA, Garcia-Esteban R, Guxens M, Vrijheid M, Kogevinas M, Goñi F, et al. 2011. Prenatal organochlorine compound exposure, rapid weight gain, and overweight in infancy. Environ Health Perspect 119:272–278; doi:10.1289/ehp.1002169.

Monteiro POA, Victora CG. 2005. Rapid growth in infancy and childhood and obesity in later life: a systematic review. Obes Rev 6:143–154; doi: 10.1111/j.1467-789X.2005.00183.x.

Pan IJ, Daniels JL, Herring AH, Rogan WJ, Siega-Riz AM, Goldman BD, et al. 2010. Lactational exposure to polychlorinated biphenyls, dichlorodiphenyltrichloroethane, and dichlorodiphenyldichloroethylene and infant growth: an analysis of the Pregnancy, Infection, and Nutrition Babies Study. Paediatr Perinat Epidemiol 24:262–271; doi:10.1111/j.1365-3016.2010.01114.x.

Patandin S, Koopman-Esseboom C, de Ridder MA, Weisglas-Kuperus N, Sauer PJ. 1998. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch Children. Pediatr Res 44:538–545; doi: 10.1203/00006450-199810000-00012.

Phillips DL, Pirkle JL, Burse VW, Bernert JT, Henderson LO, Needham LL. 1989. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch Environ Contam Toxicol 18:495–500; doi: 10.1007/BF01055015.

Ritter R, Scheringer M, MacLeod M, Moeckel C, Jones K, Hungerbühler K. 2011. Intrinsic human elimination half-lives of polychlorinated biphenyls derived from the temporal evolution of cross-sectional biomonitoring data from the United Kingdom. Environ Health Perspect 119:225–231; doi:10.1289/ehp.1002211.

Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, Thullen J, et al. 1987. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects on growth, morbidity, and duration of lactation. Am J Public Health 77:1294–1297.

Rubin D. 1987. Multiple Imputation for Nonresponse in Surveys. New York:Wiley.

Stockholm Convention. 2001. Stockholm Convention on Persistent Organic Pollutants. Geneva:United Nations Environment Program.

Valvi D, Mendez MA, Martinez D, Grimalt J, Torrent M, Sunyer J, et al. 2012. Prenatal concentrations of polychlorinated biphenyls, DDE, and DDT and overweight in children: a prospective birth cohort study. Environ Health Perspect 120:451–457; doi:10.1289/ehp.1103862.

Valvi D, Mendez MA, Garcia-Esteban R, Ballester F, Ibarluzea J, Goñi F, et al. 2014. Prenatal exposure to persistent organic pollutants and rapid weight gain and oveweight in infancy. Obesity (Silver Spring) 22:488–496; doi:10.1002/oby.20603.

Van Buuren S. 2007. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 16:219–242; doi:10.1177/0962280206074463.

Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr, Lee DH, et al. 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev. 33:378-455; doi: 10.1210/er.2011-1050.

Vandentorren S, Bois C, Pirus C, Sarter H, Salines G, Leridon H. 2009. Rationales, design and recruitment for the Elfe longitudinal study. BMC Pediatr 9:58.

Verhulst SL, Nelen V, Hond ED, Koppen G, Beunckens C, Vael C, et al. 2009. Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. Environ Health Perspect 117:122–126; doi:10.1289/ehp.0800003.

Verner MA, Sonneborn D, Lancz K, Muckle G, Ayotte P, Dewailly É, et al. 2013. Toxicokinetic modeling of persistent organic pollutant levels in blood from birth to 45 months of age in longitudinal birth cohort studies. Environ Health Perspect 121:131–137; doi:10.1289/ehp.1205552.

Walkowiak J, Wiener J, Fastabend A, Heinzow B, Kramer U, Schmidt E, et al. 2001. Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. Lancet 358:1602–1607.

Warner M, Aguilar Schall R, Harley KG, Bradman A, Barr D, Eskenazi B. 2013. In utero DDT and DDE exposure and obesity status of 7-year-old Mexican-American children in the CHAMACOS cohort. Environ Health Perspect 121:631-636; doi: 10.1289/ehp.1205656.

Wilhelm M, Wittsiepe J, Lemm F, Ranft U, Kramer U, Furst P, et al. 2008. The Duisburg birth cohort study: influence of the prenatal exposure to PCDD/Fs and dioxin-like PCBs on thyroid hormone status in newborns and neurodevelopment of infants until the age of 24 months. Mutat Res 659:83–92.

Wittsiepe J, Schrey P, Lemm F, Eberwein G, Wilhelm M. 2008. Polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), and organochlorine pesticides in human blood of pregnant women from Germany. J Toxicol Environ Health A 71:703–709.

Wolff MS, Zeleniuch-Jacquotte A, Dubin N, Toniolo P. 2000. Risk of breast cancer and organochlorine exposure. Cancer Epidemiol Biomarkers Prev 9:271–277.

Table 1. Characteristics of the cohorts [median (range) or N (%)].

Characteristic		Duisburg (Germany, 2000-2002) (n=222)	ELFE (France, 2007) (n=35)	FLEHS I (Belgium, 2002-2004) (n=134)	GRD (Germany, Netherlands, 1990-1995) (n=588)	HUMIS (Norway, 2002-2006) (n=399)	Michalovce (Slovakia, 2002-2004) (n=938)	PELAGIE (France, 2002-2006) (n=171)
Change in weight-for-age z-score 0-24 months		-0.13 (-2.74–4.83)	0.06 (-2.38–2.21)	0.04 (-2.59–3.40)	-0.03 (-3.87–3.46)	-0.03 (-3.91–3.83)	-0.01 (-5.01–3.72)	0.03 (-2.85–3.63)
	Missing (%)	0	0	0	0	1	3	0
Weight 24m (kg)		13.56 (10.35–17.50)	12.00 (9.93–13.47)	12.53 (10.01–15.87)	13.21 (9.89–18.54)	12.19 (8.36–18.49)	13.66 (10.08–20.26)	12.39 (8.86–16.78)
	Missing (%)					1	2	
Height 24m (cm)		87.4 (76.6–95.8)	87.6 (82.9–104.7)	88.0 (77.7–94.4)	88.6 (80.5–98.1)	86.3 (71.2–108.3)	86.2 (74.9–96.3)	87.5 (78.8—96.3)
	Missing (%)	0	0	0	0	1	2	0
Birth weight (g)		3.460 (1.960–4.925)	3.340 (2.800–4.110)	3.383 (2.600–4.530)	3.500 (2.140–5.000)	3.680 (2.030–5.100)	3.370 (2.060–5.060)	3.370 (2.320–4.760)
	Missing (%)	0	0	0	0	0	3	0
Birth length (cm)		52 (42–61)	49 (47–52)	50.7 (48.2–53.1)	52.5 (44–60)	51 (42–55)	50 (40–57)	50 (43–55)
	Missing (%)	0	0	0	0	10	22	0
Gestational age (weeks)		40 (37–42)	40 (38–41)	40 (37–41)	40 (37–43)	40 (37–44)	40 (37–43)	40 (37–42)
	Missing (%)	1	0	0	0	5	10	0
Sex								
	Male	108 (48.7)	18 (51.4)	72 (53.7)	322 (54.8)	203 (51.1)	477 (51.0)	92 (53.8)
	Female	114 (51.4)	17 (48.6)	62 (46.3)	266 (45.2)	195 (49.0)	459 (49.0)	79 (46.2)
	Missing (%)	0	0	0	0	1	2	0
Maternal age (years)		31.9 (19.3–42.6)	32.9 (24.3–41.3)	31.1 (20.3–41.1)	29 (18–40)	29 (16–42)	25.7 (17.9–45)	31.1 (20.1–45)
	Missing (%)	0	0	0	0	0	11	0
Maternal pre-pregnancy BMI		23.0 (14.9–51.4)	21.5 (18.1–27.7)	22.4 (16.9–37.4)	22.1 (15.0–48.3)	23.3 (16.6–43.8)	21.2 (14.5–40.7)	21.9 (17.3–37.6)
	Missing (%)	0	1	1	1	6	44	0
Maternal pre-pregnancy weight (kg)		65 (42–140)	58 (47–78)	62 (45–112)	64 (44–133)	66 (43–120)	58 (38–115)	58 (46–105)
	Missing (%)	0	0	1	1	4	44	0
Maternal gestational weight gain (kg)		NA	NA	15.0 (1.0–30.0)	NA	14.0 (-3.0–31.0)	14.0 (1.0–35.0)	13.0 (5.0–31.0)
	Missing (%)	222	35	60	588	8	250	0

Characteristic		Duisburg (Germany, 2000-2002) (n=222)	ELFE (France, 2007) (n=35)	FLEHS I (Belgium, 2002-2004) (n=134)	GRD (Germany, Netherlands, 1990-1995) (n=588)	HUMIS (Norway, 2002-2006) (n=399)	Michalovce (Slovakia, 2002-2004) (n=938)	PELAGIE (France, 2002-2006) (n=171)
Maternal height (cm)		168 (151–183)	163 (148–173)	168 (150–183)	170 (150–193)	168 (149–199)	165 (133–186)	165 (150–190)
	Missing (%)	0	1	1	0	3	0	0
Parity								
	0	0 (0.0)	12 (34.3)	84 (62.7)	294 (50.0)	154 (38.6)	391 (41.7)	68 (39.8)
	≥1	222 (100.0)	23 (65.7)	50 (37.3)	294 (50.0)	245 (61.4)	547 (58.3)	103 (60.2)
	Missing (%)	0	0	0	0	0	1	0
Education								
	Low	50 (22.5)	1 (2.9)	5 (3.7)	73 (12.4)	53 (13.4)	177 (19.0)	29 (17.0)
	Medium	83 (37.4)	8 (22.9)	96 (73.3)	184 (31.4)	253 (64.1)	687 (73.7)	26 (15.2)
	High	89 (40.1)	26 (74.3)	30 (22.9)	330 (56.2)	89 (22.5)	68 (7.3)	116 (67.84)
	Missing (%)	0	0	3	1	4	6	0
Maternal smoking during pregnancy[a]								
	No	169 (76.1)	33(100.0)	120 (90.2)	438 (74.5)	357 (89.5)	805 (85.8)	137 (80.6)
	Yes	53 (23.9)	0	13 (9.8)	150 (25.5)	42 (10.5)	133 (14.2)	33 (19.4)
	Missing (%)	0	2	1	0	0	0	1
Ethnicity								
	Caucasian	211 (95.1)	NA	NA	588 (100.0)	374 (98.2)	738 (80.7)	171 (100.0)
	Inuit	0	NA	NA	0	2 (0.5)	0	0
	Roma	0	NA	NA	0	1 (0.3)	177 (19.3)	0
	Other	11 (5.0)	NA	NA	0	4 (1.1)	0	0
	Missing (%)	0	35	134	0	17	23	0
Sample type								
	Blood mother	216	0	0	0	0	0	0
	Cord blood	0	0	130	267	0	880	168
	Breastmilk	0	35	0	321	399	0	0
	Missing (%)	6	0	4	0	0	58	3
Sample collection time (days from birth)		-51 (-107–42)	51 (36–70)	0 (0–0)	CB: 0 (0–0) BM: 14 (14–14)	32 (2–158)	0 (0–0)	0 (0–0)
	Missing (%)	6	0	4	0	18	58	3
Total breastfeeding (months)		6.9 (0.2–18)	5.0 (1.6–23)	3 (0–48)	2.3 (0–6)	12 (1–31.2)	5 (0–48)	3.1 (0–24.8)
	Missing (%)	38	2	42	5	0	5	8

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Characteristic	Duisburg (Germany, 2000-2002) (n=222)	ELFE (France, 2007) (n=35)	FLEHS I (Belgium, 2002-2004) (n=134)	GRD (Germany, Netherlands, 1990-1995) (n=588)	HUMIS (Norway, 2002-2006) (n=399)	Michalovce (Slovakia, 2002-2004) (n=938)	PELAGIE (France, 2002-2006) (n=171)
No months breastfeeding	0 (0)	0 (0)	34 (25.4)	224 (38.1)	0 (0)	2 (0.2)	70 (40.9)
Missing (%)	38	2	42	5	0	5	8
Exclusive breastfeeding (months)	4.8 (0–9.9)	NA	0 (0–1)	NA	5 (0–10)	3 (0–12)	NA
Missing (%)	39	35	76	588	0	3	171

Continuous measures described by median (min-max); categorical measures described by frequencies (%).NA Not available BM breastmilk; CB cord blood; ELFE

Etude Longitudinale Française depuis l'Enfance (French longitudinal study of children); FLEHS I Flemish Environment and Health Survey I; GRD Groningen–

Rotterdam–Düsseldorf; HUMIS Human Milk Study; PELAGIE Endocrine disruptors: longitudinal study on pathologies of pregnancy, infertility and childhood.

[a]In PELAGIE smoking status at inclusion used as proxy of smoking during pregnancy.

Table 2. Infant blood concentrations for PCB-153 and *p,p'*-DDE prenatal and postnatal exposure, estimated through pharmacokinetic modelling (ng/g lipid).

Study	N	Prenatal PCB-153 Mean ± sd	Median	<LOD n (%)	Postnatal PCB-153 Mean ± sd	Median	N	Prenatal *p,p'*-DDE Mean ± sd	Median	<LOD n (%)	Postnatal *p,p'*-DDE Mean ± sd	Median
Duisburg[a]	215	63.6 ± 45.9	56.7	0[d]	126.1 ± 98.8	108.7	215	141.4 ± 205.1	95.2	0[d]	255.3 ± 287.6	178.1
ELFE[b]	35	92.6 ± 41.9	83.3	0	301.1 ± 133.0	268.1	0	NA	NA	NA	NA	NA
FLEHS I[c]	129	54.0 ± 38.4	41.3	6 (4.5)[d]	66.5 ± 69.6	47.1	130	214.7 ± 244.5	145.6	0[d]	272.6 ± 412.9	150.6
GRD[c]	321	184.7 ± 72.9	176.7	0	280.4 ± 152.0	252.4	0	NA	NA	NA	NA	NA
HUMIS[b]	399	36.4 ± 17.1	33.1	0[d]	104.7 ± 52.2	96.8	399	63.4 ± 94.8	42.1	0[d]	177.3 ± 236.9	123.1
Michalovce[c]	880	164.4 ± 219.2	111.2	2 (0.2)	292.4 ± 425.4	175.3	880	540.5 ± 459.0	413.5	6 (0.7)	954.3 ± 1032.8	619.6
PELAGIE[c]	168	43.0 ± 31.5	32.1	0[d]	48.3 ± 55.9	26.2	168	73.5 ± 74.4	53.9	28 (16.4)[d]	75.7 ± 99.8	36.6

NA not available; LOD limit of detection.

[a]Prenatal and postnatal concentrations estimated from maternal blood concentration. [b]Prenatal and postnatal concentrations estimated from breast milk concentration. [c]Prenatal and postnatal concentrations estimated from cord blood concentrations. [d]Provided limit of quantification (LOQ) instead of LOD.

Table 3. Associations between total exposure from conception to 2 years to PCB-153 (152 ng/g) and *p,p'*-DDE (515 ng/g) and change in weight-for-age z-score.

Cohort	N	PCB-153 β (95% CI)	N	*p,p'*-DDE β (95% CI)
Duisburg	222	0.13 (-0.19, 0.46)	222	0.54 (0.22, 0.86)
ELFE	35	-0.19 (-0.74, 0.35)		NA
FLEHS I	134	0.06 (-0.50, 0.62)	134	0.05 (-0.22, 0.32)
GRD	588	-0.24 (-0.39, -0.09)		NA
HUMIS	399	-0.32 (-0.72, 0.08)	399	-0.26 (-0.56, 0.04)
Michalovce	938	0.01 (-0.02, 0.03)	938	0.02 (-0.02, 0.06)
PELAGIE	171	0.44 (-0.24, 1.12)	171	0.73 (-0.34, 1.81)
Pooled estimate (random)	2487	-0.06 (-0.15, 0.03)	1864	0.04 (-0.001, 0.07)

NA not available. Results for both pooled sample and individual cohorts are per IQR increase for the pooled sample (ng/g lipid). Models adjusted for birth weight, parity, gestational age, maternal smoking during pregnancy, maternal age at birth, maternal height and weight, Roma ethnicity and breastfeeding, and, for the pooled estimate, fitted with random intercept (*p,p'*-DDE) and random intercept and slope (PCB-153) by cohort.

Figure Legend

Figure 1. Associations between change in weight-for-age z-score and total exposure from conception to 2 years, prenatal exposure (unadjusted and adjusted for postnatal exposure) and postnatal exposure (unadjusted and adjusted for prenatal exposure) to A) PCB-153 and B) *p,p'*-DDE. Results per IQR increase (ng/g lipid). PCB-153 IQRs: total exposure 152 ng/g, prenatal exposure 120 ng/g, postnatal exposure 183 ng/g. *p,p'*-DDE IQRs: total exposure 515 ng/g, prenatal exposure 388 ng/g, postnatal exposure 571 ng/g. Models adjusted for birth weight, parity, gestational age, maternal smoking during pregnancy, maternal age at birth, maternal height and weight, Roma ethnicity and breastfeeding, and fitted with random slope (*p,p'*-DDE) and slope (PCB-153) by cohort. Prenatal unadj. Prenatal exposure adjusted for covariates except postnatal; Prenatal adj. Prenatal exposure adjusted for covariates including postnatal; Postnatal unadj. Postnatal exposure adjusted for covariates except prenatal; Postnatal adj. Postnatal exposure adjusted for covariates including prenatal.

Figure 1.

A.

Exposure	β (95% CI)		N
PCB total exposure	-0.06 (-0.15, 0.03)		2487
Prenatal unadj.	-0.001 (-0.07, 0.07)		2487
Prenatal adj.	0.05 (-0.05, 0.14)		2487
Postnatal unadj.	-0.06 (-0.15, 0.02)		2487
Postnatal adj.	-0.10 (-0.19, -0.01)		2487

Change in z-score

B.

Exposure	β (95% CI)		N
DDE total exposure	0.04 (-0.001, 0.07)		1864
Prenatal unadj.	0.07 (0.02, 0.12)		1864
Prenatal adj.	0.12 (0.03, 0.22)		1864
Postnatal unadj.	0.03 (-0.01, 0.06)		1864
Postnatal adj.	-0.04 (-0.11, 0.02)		1864

Change in z-score

● Total exposure from conception to 24 months
▲ Prenatal exposure
■ Postnatal exposure