SUPPORTING INFORMATION

Prenatal exposure to polybrominated flame retardants and fetal growth in the INMA Cohort (Spain)

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FLOW CHART OF THE STUDY POPULATION

Figure S1. Scheme of the study population: The INMA Cohort, 2003-2008 (Spain)

(1) Enrolled women in the cohort (≥16 years, singleton pregnancy, enrolment at 10-13 weeks of gestation, non-assisted conception, delivery scheduled at the reference hospital, and no communication impairment); (2) Women with at least two valid ultrasounds; (3) Women who gave birth to a live infant; (4) Women enrolled in this study; (5) Maternal serum with PBDE analysis; (6) Umbilical cord serum with PBDE analysis.
**DIFFERENCES BETWEEN INCLUDED AND EXCLUDED WOMEN**

Table S1. Characteristics of the study population: The INMA-Valencia Cohort, 2003-2006 (Spain)

| Variable                        | Unit or category | Excluded \((n=567)\) | Included \((n=219)\) | p*    |
|---------------------------------|------------------|----------------------|----------------------|-------|
| **Maternal characteristics**    |                  |                      |                      |       |
| Age                             | years            | 29.9±4.5             | 29.7±4.7             | 0.57  |
| Height                          | cm               | 162.2±6.2            | 161.8±6.7            | 0.47  |
| Pre-pregnancy body mass index   | Kg/m²            | 23.7±4.7             | 24.0±4.6             | 0.36  |
| GWG\(^{a}\)                     | Adequate         | 186(33)              | 85(40)               | 0.16  |
|                                | Low              | 152(27)              | 47(22)               |       |
|                                | High             | 225(40)              | 82(38)               |       |
| Country                         |                  |                      |                      |       |
| Spain                           |                 | 498(88)              | 195(89)              | 0.64  |
| Other                           |                 | 69(12)               | 24(11)               |       |
| Studies                         |                  |                      |                      |       |
| Till primary                    |                 | 189(33)              | 78(35)               | 0.62  |
| Secondary                       |                 | 247(44)              | 87(40)               |       |
| University                      |                 | 131(23)              | 54(25)               |       |
| Working in pregnancy            |                  |                      |                      |       |
| No                              |                 | 109(19)              | 26(12)               | 0.01  |
| Yes                             |                 | 458(81)              | 193(88)              |       |
| Social class\(^{b}\)            |                  |                      |                      |       |
| III (lowest)                    |                 | 291(51)              | 109(50)              | 0.45  |
| II                              |                 | 159(28)              | 56(25)               |       |
| I (highest)                     |                 | 117(21)              | 54(25)               |       |
| Zone of residence               |                  |                      |                      |       |
| Rural                           |                 | 42(7)                | 6(3)                 | 0.01  |
| Non-rural                       |                 | 525(93)              | 213(97)              |       |
| Parity                          |                  |                      |                      |       |
| None                            |                 | 311(55)              | 121(55)              | 0.92  |
| ≥1 births                       |                 | 256(45)              | 98(45)               |       |
| Consumption of tobacco at the   |                  |                      |                      |       |
| beginning of pregnancy          | No               | 326(58)              | 134(62)              | 0.34  |
|                                | Yes              | 236(42)              | 83(38)               |       |
| Passive smoking                 |                  |                      |                      |       |
| No                              |                 | 142(25)              | 58(27)               | 0.63  |
| Yes                             |                 | 414(75)              | 155(73)              |       |
| Alcohol intake                  |                  |                      |                      |       |
| No                              |                 | 457(81)              | 183(84)              | 0.46  |
| Yes                             |                 | 105(19)              | 36(16)               |       |
| **Paternal characteristics**    |                  |                      |                      |       |
| Height                          | cm               | 175.5±7.3            | 175.8±7.1            | 0.57  |
| Body mass index                 | Kg/m²            | 25.8±3.6             | 26.0±3.4             | 0.42  |
| **Child characteristics**       |                  |                      |                      |       |
| Gender                          |                  |                      |                      |       |
| Male                            |                 | 293(52)              | 123(56)              | 0.26  |
| Female                          |                 | 274(48)              | 96(44)               |       |

Values are \(n(\%)\) or mean±SD.

\(^{a}\)Gestational weight gain according to the recommendations of the Institute of Medicine.\(^{(1)}\)\(^{b}\)Class I: managerial jobs, senior technical staff, and commercial managers; class II: skilled non-manual workers; class III: manual workers. *\(X^{2}\)-test, t-Student or Mann-Whitney
FETAL GROWTH CURVES AND CALCULATION OF SD-SCORES

We built fetal growth curves in the INMA-Project to establish a relationship between the fetal characteristics and gestational age of the INMA population, taking into account those non-pathological biological factors that may affect the growth potential of each fetus. These curves were then used to estimate possible intrauterine restrictions of growth at several times within pregnancy.

Fetal growth curves

We obtained these fetal growth curves from linear mixed models that were built for each cohort and each parameter. We used the extended definition of the linear mixed models to allow for heteroscedasticity and autocorrelation of within-subject errors.

The full model is written as:

\[ Y_{ij}^{(A)} = X_{ij} \beta + Z_{ij} b_i + \epsilon_{ij} \]

where:

- \( Y_{ij}^{(A)} \) is a transformation of the response variable suggested in Gurrin et al.\(^2\) and Royston and Altman.\(^3\)
- \( \beta \) is the vector of fixed coefficients to be estimated, and \( X_{ij} \) is the corresponding design matrix. This matrix includes constitutional covariates and a polynomial for the relationship with gestational age.
- \( Z_{ij} \) represents the individual deviations from the mean of the fetal parameter for the population, considered to be possible at intercept and gestational age at measurement, and \( b_i \) is the corresponding vector of random effects, which is estimated for each fetus. We assumed that the \( b_i \) distribution across the fetal population is bivariate normal, and independent among the subjects.
- \( \epsilon_{ij} \) represents the deviation in size at each time \( j \) on the \( i^{th} \) fetus from the mean size. \( \epsilon_i \) are assumed to be bivariate normal and are called within-subject errors.

In our models, we used dummy variables identifying mothers who had ultrasound examinations spaced too closely in time to model the variance structure for within-subject errors. We also used an autocorrelation structure for within-subject errors. The most commonly selected function was the exponential variogram representing an
exponential decay in the correlation between observations with the difference in time between them.

**Conditional and unconditional centiles**

Once the corresponding linear mixed model was adjusted, we used the prediction of aligned estimates as observations at weeks 12, 20 and 34. And they were used to obtain unconditional SD-scores in the usual way by employing the modeled mean and variance of the transformed response, \( Z = Y^{(2)} \), at time \( j \):

\[
z_{ij} = \frac{Z_{ij} - E[Z_{ij}]}{\text{Var}[Z_{ij}]}\
\]

The linear mixed model assumes that the series of measurements within a given fetus have a multivariate normal distribution, and therefore marginal and conditional distributions of each pair of measurements \( Z_2 \) at time \( T_2 \) and \( Z_1 \) at time \( T_1 \) are univariate normal. Using the conditional distribution of \( Z_2 \) given \( Z_1 \), we obtained conditional SD-scores as follows:

\[
Z_{2|1} = \frac{Z_2 - \mu_{2|1}}{\sigma_{2|1}}
\]

where \( \mu_{2|1} = E[Z_2 \mid Z_1] = \mu_2 + \frac{\sigma^2_{21}}{\sigma^2_1} (Z_1 - \mu_1) \), \( \sigma^2_{2|1} = \text{Var}[Z_2 \mid Z_1] = \sigma^2_2 - \frac{\sigma^2_{12}}{\sigma^2_1} \) are the mean and variance of conditional distribution, respectively. The conditional SD-score is the standardization of the transformed response at time \( T_2 \) according to its conditional mean and variance at time \( T_1 \) given the observed value at time \( T_1 \). This means that the status of the \( i^{th} \) fetus at time \( T_1 \) is taken into consideration to update the mean and variance that should be used as a reference in \( T_2 \). Detailed information on fetal growth curves and SD-scores have previously been published.\(^{(4, 5)}\)
CALCULATION OF SD-SCORES FOR NEONATAL PARAMETERS

As for fetal growth during pregnancy, our aim was to consider physiological
determinants of fetal growth as explanatory variables which would allow us to obtain an
individualized rather than a population-based standard for size at birth.

We fitted models for birth weight (BW), head circumference (HC) at delivery, and birth
length (BL) adjusted for potential biological determinants of fetal growth (gestational
age in days, cohort, maternal and paternal height, maternal and paternal weight or body
mass index [BMI], maternal age, parity, maternal country of origin, and sex of
newborn).

Following a similar procedure to that outlined for ultrasounds, we adjusted a linear
mixed model.\(^{(6)}\) But in this case the data for each parameter were analyzed jointly,
thereby allowing for random effects by cohort on intercept and covariate effects.

As in fetal growth curves, we also transformed the response variable using the power
transformation suggested by Box and Cox. For the relationship with gestational age, we
considered 2\(^{nd}\) and 3\(^{rd}\) entire order polynomials and fractional order polynomials of
degree 2.\(^{(3)}\) Potential determinants of growth and their interactions with gestational age
were tested to be included in the model (conditional LR test; p<0.05). The basic model
was extended to allow for the heteroscedasticity explained by the covariates, in two
ways: equal or different effects by cohort.

Finally, we tested for random effects by cohort on intercept and slope (covariates) in the
model using the LR test (p<0.05). We also tested the normality and independence of
residuals to assess the goodness of fit. We dropped extreme outliers (>4 SD), and
conducted tests for the presence of influential data. As in fetal curves, after adjusting for
covariates and modeling the variance structure, random effects were not necessary,
although the categorical variable “cohort” was always incorporated. A summary of
terms in the models for BW, BL and HC has previously been published.\(^{(4)}\)

SD-scores were calculated using this model in the standard procedure as described in
the section on “Conditional and unconditional centiles”.

\(^{(3)}\) Box, D.L., and Cox, D.R. (1964). An analysis of transformation. Journal of
the Royal Statistical Society, Series B, 26(2), 211-243.

\(^{(4)}\) Schifflers, E.M., et al. (2017). "Conditional and unconditional centiles for
birth weight, length and head circumference in a modern population of
European newborns." American Journal of Human Biology, 29(5), e22889.
ULTRASOUND MEASURES AND NEONATAL PARAMETERS

Table S2. Details on ultrasound measures and neonatal parameters: The INMA Cohort, 2003-2008 (Spain)

| Characteristics                  | Asturias (n=478) | Valencia (n=786) | Overall (n=1264) |
|----------------------------------|------------------|------------------|------------------|
| **US (n):**                      |                  |                  |                  |
| Week 12                          | 461              | 775              | 1236             |
| Week 20                          | 491              | 806              | 1297             |
| Week 34                          | 609              | 849              | 1458             |
| Availability of CRL (%)          | 98.7             | 98.9             | 98.8             |
| CRL-based GA<sup>a</sup> (%)     | 11.3             | 12.3             | 11.9             |
| **GA at US (weeks):**            |                  |                  |                  |
| Week 12                          | 12.7±1.1         | 12.5±0.7         | 12.5±0.9         |
| Week 20                          | 20.7±0.8         | 20.4±1.0         | 20.5±0.9         |
| Week 34                          | 33.9±1.8         | 32.6±1.9         | 33.2±2.0         |
| **US per mother (%):**           |                  |                  |                  |
| 2                                | 9.8              | 7.6              | 8.5              |
| 3                                | 61.5             | 77.2             | 71.3             |
| ≥4                               | 28.7             | 15.1             | 20.3             |
| **AC (mm):**                     |                  |                  |                  |
| Week 12                          | 92.3±27.3        | 62.0±10.7        | 63.4±13.6        |
| Week 20                          | 159.8±10.2       | 155.1±13.8       | 156.9±12.8       |
| Week 34                          | 295.3±21.6       | 288.4±23.7       | 291.3±23.1       |
| **EFW (grams):**                 |                  |                  |                  |
| Week 12                          | 138.2±47.2       | 62.6±19.8        | 65.8±26.3        |
| Week 20                          | 398.4±80.4       | 364.3±99.3       | 377.3±94.0       |
| Week 34                          | 2307.7±407.7     | 2052.9±464.4     | 2160.2±458.9     |
| **BPD (mm):**                    |                  |                  |                  |
| Week 12                          | 22.0±4.5         | 22.4±3.3         | 21.0±3.9         |
| Week 20                          | 49.5±3.1         | 47.6±3.8         | 48.3±3.7         |
| Week 34                          | 85.2±4.5         | 81.4±4.9         | 83.0±5.1         |
| **FL (mm):**                     |                  |                  |                  |
| Week 12                          | 13.4±5.8         | 7.4±2.7          | 7.9±3.5          |
| Week 20                          | 34.2±2.4         | 32.4±3.2         | 33.1±3.1         |
| Week 34                          | 65.1±4.2         | 61.2±4.2         | 62.8±4.6         |
| GA at birth (weeks)              | 39.4±1.8         | 39.5±1.9         | 39.5±1.9         |
| Birth weight (grams)             | 3267.2±474.8     | 3226.9±527.3     | 3241.9±508.6     |
| Birth length (cm)                | 49.7±2.1         | 50.1±2.5         | 49.9±2.4         |
| HC at delivery (cm)              | 34.3±1.4         | 34.0±1.7         | 34.1±1.6         |

AC: abdominal circumference; BPD: biparietal diameter; CRL: crown-rump length; EFW: estimated fetal weight; FL: femur length; GA: gestational age; HC: head circumference; US: ultrasound examination.

Percentage (%) or sample size (n) is presented for categorical variables. Mean±SD is presented for continuous variables. <sup>a</sup>Percentage of GA based on CRL measurements.
DETAILS ON THE MULTIPLE IMPUTATION MODELING

**Imputation method:** We used fully conditional specification or multivariate imputation by chained equations. \(^{(7, 8)}\)

**Software and statistical packages:** We used R.3.1.1, \(^{(9)}\) mice package. \(^{(8)}\) We defined an additional function for bootstrap multiple imputation of censored variables. \(^{(10)}\)

**Number of imputed datasets and iterations:** In order to diminish simulation error, we imputed 50 datasets with 20 cycles each one.

**Variables included in the imputation procedure:** We included outcome and exposure variables, covariates and potential confounders. We also included other variables possibly related with variables which have a moderate number of missing or censored values (Table S3).

**Heterogeneity in the imputation modeling:** We did not include statistical interactions in the imputation models; yet we did conduct multiple imputation analyses stratified by cohort (Asturias and Valencia). \(^{(11)}\)

**Criteria of inclusion:** Variables were included in the models for multiple imputation based on their prediction ability (correlation) and their relation to the non-response. We excluded variables with too many missing values within the subgroup of incomplete cases (proportion of usable cases). \(^{(8)}\) We used outcome variables to impute exposure variables and vice versa in order to avoid bias. \(^{(8, 12)}\)

**Diagnostics:** We assessed convergence by plotting parameters (mean and SD in each imputed dataset) against iteration number. We checked imputations of missing and censored values graphically, and compared them with observed data. We also show results from multiple imputation analysis *versus* complete case analysis (Figure 2 and Figures S2-S5).
Table S3. Number (%) of imputed values and regression model for each variable:
The INMA Cohort, 2003-2008 (Spain)

n: 686 cases with ultrasound measurements and PBDEs in maternal and/or cord serum

| Outcome variablesa | Imputed | Missing | Censored | Method                  |
|--------------------|---------|---------|----------|-------------------------|
|                    | n (%)   | n (%)   | n (%)    |                         |
| EFW: growth at weeks 12-20 | 7 (1.0) | 7* (1.0) | 0 (0.0) | Linear regression       |
| EFW: growth at weeks 20-34 | 8 (1.2) | 8* (1.2) | 0 (0.0) | Linear regression       |
| BW: size at birth     | 11 (1.6)| 11* (1.6)| 0 (0.0) | Linear regression       |
| AC: growth at weeks 12-20 | 6 (0.9) | 6* (0.9) | 0 (0.0) | Linear regression       |
| AC: growth at weeks 20-34 | 6 (0.9) | 6* (0.9) | 0 (0.0) | Linear regression       |
| BPD: growth at weeks 12-20 | 1 (0.1) | 1* (0.1) | 0 (0.0) | Linear regression       |
| BPD: growth at weeks 20-34 | 1 (0.1) | 1* (0.1) | 0 (0.0) | Linear regression       |
| HC: size at birth      | 21 (3.1)| 21* (3.1)| 0 (0.0) | Linear regression       |
| FL: growth at weeks 12-20 | 4 (0.6) | 4* (0.6) | 0 (0.0) | Linear regression       |
| FL: growth at weeks 20-34 | 4 (0.6) | 4* (0.6) | 0 (0.0) | Linear regression       |
| BL: size at birth      | 19 (2.8)| 19* (2.8)| 0 (0.0) | Linear regression       |

| Exposure variables   | Imputed | Missing | Censored | Method                  |
|----------------------|---------|---------|----------|-------------------------|
| log(maternal BDE-47) | 416 (60.6)| 16* (2.3)| 400 (58.3)| Censored linear regression |
| log(maternal BDE-99) | 298 (43.4)| 16* (2.3)| 282 (41.1)| Censored linear regression |
| log(maternal BDE-153) | 83 (12.1)| 17* (2.5)| 66 (9.6)  | Censored linear regression |
| log(maternal BDE-154) | 143 (20.8)| 16* (2.3)| 127 (18.5)| Censored linear regression |
| log(maternal BDE-209) | 366 (53.4)| 16* (2.3)| 350 (51.0)| Censored linear regression |
| log(maternal ΣPBDEs)  | 595 (86.7)| 17* (2.5)| 578 (84.2)| Passive imputation       |
| log(cord BDE-47)     | 371 (54.1)| 152* (22.2)| 219 (31.9)| Censored linear regression |
| log(cord BDE-99)     | 410 (59.8)| 152* (22.2)| 258 (37.6)| Censored linear regression |
| log(cord BDE-153)    | 417 (60.8)| 152* (22.2)| 265 (38.6)| Censored linear regression |
| log(cord BDE-154)    | 551 (80.3)| 152* (22.2)| 399 (58.1)| Censored linear regression |
| log(cord BDE-209)    | 539 (78.6)| 152* (22.2)| 387 (56.4)| Censored linear regression |
| log(cord ΣPBDEs)     | 643 (93.7)| 152* (22.2)| 491 (71.6)| Passive imputation       |

| Covariates           | Imputed | Missing | Censored | Method                  |
|----------------------|---------|---------|----------|-------------------------|
| Maternal height      | 0 (0.0) | 0 (0.0) | 0 (0.0)  | -                       |
| Paternal height      | 11 (1.6)| 11 (1.6)| 0 (0.0)  | Linear regression       |
| log(maternal BMI)    | 0 (0.0) | 0 (0.0) | 0 (0.0)  | -                       |
| log(paternal BMI)    | 23 (3.4)| 23 (3.4)| 0 (0.0)  | Linear regression       |
| Maternal age         | 0 (0.0) | 0 (0.0) | 0 (0.0)  | -                       |
| Zone of residence    | 0 (0.0) | 0 (0.0) | 0 (0.0)  | -                       |
| Country of birth     | 0 (0.0) | 0 (0.0) | 0 (0.0)  | -                       |
| Education            | 0 (0.0) | 0 (0.0) | 0 (0.0)  | -                       |
| Employment during pregnancy | 0 (0.0) | 0 (0.0) | 0 (0.0)  | -                       |
| Socio-economic status| 1 (0.1) | 1 (0.1) | 0 (0.0)  | Ordered logistic regression |
| Parity               | 0 (0.0) | 0 (0.0) | 0 (0.0)  | -                       |
| Previous lactation   | 1 (0.1) | 1 (0.1) | 0 (0.0)  | Ordered logistic regression |
| Consumption of tobacco| 29 (4.2)| 29 (4.2)| 0 (0.0)  | Logistic regression     |
| Passive smoking      | 33 (4.8)| 33 (4.8)| 0 (0.0)  | Logistic regression     |
| Season of last menstrual period | 0 (0.0)| 0 (0.0)| 0 (0.0)  | -                       |
| Sex of fetus         | 0 (0.0) | 0 (0.0) | 0 (0.0)  | -                       |
| Consumption of eggs, oils and fats, seafood, meat products, and total energy intake in pregnancy | 0 (0.0)| 0 (0.0)| 0 (0.0)  | -                       |
| Alcohol intake       | 3 (0.4) | 3 (0.4) | 0 (0.0)  | Logistic regression     |
| log2(maternal serum lipids) | 200 (29.2)| 200 (29.2)| 0 (0.0)| Linear regression     |
| log2(cord serum lipids) | 197 (28.7)| 197 (28.7)| 0 (0.0)| Linear regression     |
| Carpets at home      | 29 (4.2)| 29 (4.2)| 0 (0.0)  | Logistic regression     |
| Curtains at home     | 29 (4.2)| 29 (4.2)| 0 (0.0)  | Logistic regression     |
| Type of mattress     | 51 (7.4)| 51 (7.4)| 0 (0.0)  | Multinomial logistic regression |
| Frequency of housekeeping | 29 (4.2)| 29 (4.2)| 0 (0.0)  | Ordered logistic regression |
| Vacuum cleaner use   | 29 (4.2)| 29 (4.2)| 0 (0.0)  | Logistic regression     |
| Resident density at home | 29 (4.2)| 29 (4.2)| 0 (0.0)  | Predictive mean matching |
| Hours per week of TV use | 1 (0.1)| 1 (0.1)| 0 (0.0)  | Linear regression     |

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### Other variables (not used in main analysis)

| Variable Description | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Analysis Method |
|----------------------|-----------|-----------|-----------|-----------|-----------------|
| Gestational weight gain | 17 (2.5) | 17 (2.5) | 0 (0.0) | Ordered logistic regression |
| \( \log_2(\text{maternal HCB}) \) | 25 (3.6) | 18 (2.6) | 7 (1.0) | Censored linear regression |
| \( \log_2(\text{maternal PCB 138}) \) | 25 (3.6) | 18 (2.6) | 7 (0.0) | Censored linear regression |
| \( \log_2(\text{maternal PCB 153}) \) | 21 (3.1) | 18 (2.6) | 3 (0.4) | Censored linear regression |
| \( \log_2(\text{maternal PCB 180}) \) | 27 (3.9) | 18 (2.6) | 9 (1.3) | Censored linear regression |
| \( \log_2(\text{maternal } \Sigma \text{PCBs}) \) | 30 (4.4) | 18 (2.6) | 12 (1.7) | Censored linear regression |
| \( \log_2(\text{cord HCB}) \) | 179 (26.1) | 151 (22.0) | 28 (4.1) | Passive imputation |
| \( \log_2(\text{cord PCB 138}) \) | 185 (27.0) | 151 (22.0) | 34 (5.0) | Censored linear regression |
| \( \log_2(\text{cord PCB 153}) \) | 174 (25.4) | 151 (22.0) | 27 (3.9) | Censored linear regression |
| \( \log_2(\text{cord PCB 180}) \) | 178 (25.9) | 151 (22.0) | 27 (3.9) | Censored linear regression |
| \( \log_2(\text{cord } \Sigma \text{PCBs}) \) | 196 (28.6) | 151 (22.0) | 45 (6.6) | Passive imputation |
| Intake of proteins, fat, carbohydrates, and caffeine during pregnancy | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |
| Maternal urinary cotinine (\( >50 \text{ ng/mL} \)) | 76 (11.1) | 76 (11.1) | 0 (0.0) | Logistic regression |
| Season of maternal blood | 13 (1.9) | 13 (1.9) | 0 (0.0) | Multinomial logistic regression |
| Season of cord blood | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |

AC: abdominal circumference; BL: birth length; BW: birth weight; BPD: biparietal diameter; EFW: estimated fetal weight; FL: femur length; GWG: gestational weight gain; HC: head circumference; HCB: hexachlorobenzene; \( \Sigma \text{PCBs} \): sum of PCB 138, 153 and 180; PBDE: polybrominated diphenyl ether.

\(^a\)In order to define a single imputed dataset (n=686), missing values in the outcomes and exposure variables (measured in maternal and cord serum) were multiple-imputed. Subsequently, these values were deleted before analysis and recombination.

\(^b\)Gestational weight gain according to the Institute of Medicine recommendations (IOM). (1)
### VARIABLES OF ADJUSTMENT IN MODELS

Table S4. Covariates of adjustment in multivariate regression models of PBDEs and fetal growth: The INMA Cohort, 2003-2008 (Spain)

|          | AC | EFW | BW | BPD | HC | FL | BL |
|----------|----|-----|----|-----|----|----|----|
|          | 12-20 wks | 20-34 wks | 12-20 wks | 20-34 wks | At birth | 12-20 wks | 20-34 wks | At birth | 12-20 wks | 20-34 wks | At birth |
| Maternal PBDE | | | | | | | | | | | |
| BDE-47   | 1  | 2, 3 | 1  | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3, 4 | 8  | 2, 4 | 2  |
| BDE-99   | 1  | 2, 3 | 1  | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 2, 4 | 2  |
| BDE-153  | 1  | 2, 3 | 1  | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 2, 4 | 2  |
| BDE-154  | 1  | 2, 3 | 1  | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 2, 4 | 2  |
| BDE-209  | 1, 9, 10 | 2, 3 | 1  | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 2, 4 | 2  |
| ΣPBDEs   | 1  | 2, 3 | 1  | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 2, 4 | 2  |
| Cord PBDE | | | | | | | | | | | |
| BDE-47   | 1  | 2, 3, 11 | 1 | 2, 3, 11, 13 | 4 | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 2, 4 | 2  |
| BDE-99   | 1  | 2, 3 | 1  | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 14 | 2, 4 | 2  |
| BDE-153  | 1  | 2, 3 | 1  | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 2, 4 | 2  |
| BDE-154  | 1  | 2, 3 | 1  | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 2, 4 | 2  |
| BDE-209  | 1  | 2, 3 | 1, 12 | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 2, 4 | 2  |
| ΣPBDEs   | 1  | 2, 3 | 1  | 2, 3 | 4  | 1, 5, 6 | 2, 4, 7 | 2, 3 | 8  | 14 | 2, 4 | 2  |

AC: abdominal circumference; BL: birth length; BW: birth weight; BPD: biparietal diameter; EFW: estimated fetal weight; FL: femur length; HC: head circumference; PBDE: polybrominated diphenyl ether.

All models were adjusted for cohort. In addition, models were adjusted for: 1: Working in pregnancy; 2: Smoking at week 12; 3: Education; 4: Season of last menstrual period; 5: Residence; 6: Maternal age; 7: Social class; 8: Passive smoking; 9: Sex of the fetus; 10: Frequency of housekeeping; 11: Resident density at home; 12: Type of mattress; 13: Alcohol intake; 14: Intake of fish and shellfish and total calories.
SENSITIVITY ANALYSIS

Figures S2-S6. Sensitivity analyses of the association between prenatal concentrations of BDE-47, BDE-99, BDE-153, BDE-154, and BDE-209, and fetal growth measurements or newborn size: The INMA Cohort, 2003-2008 (Spain). % change in fetal (shaded white) or newborn (shaded gray) measurements associated with a 2-fold increase in PBDE concentrations.

AC: abdominal circumference; BL: birth length; BW: birth weight; BPD: biparietal diameter; EFW: estimated fetal weight; HC: head circumference; HCB: hexachlorobenzene; FL: femur length; PBDE: polybrominated diphenyl ether; ΣPCBs: sum of PCB 138, 153 and 180.

Main analysis: results from multiple imputation (i.e., analysis imputing missing information in covariates and imputing a value between 0 and LOD for undetected values of PBDEs); Complete case: excluded cases with missing values in covariates and fixed imputation of values <LOD in PBDEs with ½ LOD; Gestational weight gain: main analysis adjusted for this variable; Lipids: Main analysis adjusted for lipid levels; ΣPCBs + lipids or HCB + lipids: Main analysis adjusted for either ΣPCBs and lipids or HCB and lipids. Maternal PBDE analyses were adjusted for maternal levels of either ΣPCBs or HCB and maternal lipids and cord PBDE analyses for these two contaminants and lipids measured in cord serum.
Figure S2. Association between prenatal BDE-47 concentrations and fetal growth measurements or newborn size: The INMA Cohort, 2003-2008 (Spain)

| Outcome | Interval      | % Change in maternal serum | % Change in cord serum |
|---------|---------------|----------------------------|------------------------|
| AC      | 12-20 wks     | ![Graph](chart1.png)       | ![Graph](chart2.png)   |
| AC      | 20-34 wks     | ![Graph](chart3.png)       | ![Graph](chart4.png)   |
| EFW     | 12-20 wks     | ![Graph](chart5.png)       | ![Graph](chart6.png)   |
| EFW     | 20-34 wks     | ![Graph](chart7.png)       | ![Graph](chart8.png)   |
| BW      | Birth         | ![Graph](chart9.png)       | ![Graph](chart10.png)  |
| BPD     | 12-20 wks     | ![Graph](chart11.png)      | ![Graph](chart12.png)  |
| BPD     | 20-34 wks     | ![Graph](chart13.png)      | ![Graph](chart14.png)  |
| HC      | Birth         | ![Graph](chart15.png)      | ![Graph](chart16.png)  |
| FL      | 12-20 wks     | ![Graph](chart17.png)      | ![Graph](chart18.png)  |
| FL      | 20-34 wks     | ![Graph](chart19.png)      | ![Graph](chart20.png)  |
| BL      | Birth         | ![Graph](chart21.png)      | ![Graph](chart22.png)  |

- Main analysis
- Complete case
- Gestational weight gain
- Lipids
- ∑PCBs + lipids
- ∑PBDE + lipids
Figure S3. Association between prenatal BDE-99 concentrations and fetal growth measurements or newborn size: The INMA Cohort, 2003-2008 (Spain)

| Outcome | Interval   | % Change in maternal serum | % Change in cord serum |
|---------|------------|----------------------------|------------------------|
| AC      | 12-20 wks  | ![Graph](image1)            | ![Graph](image2)       |
| AC      | 20-34 wks  | ![Graph](image3)            | ![Graph](image4)       |
| EFW     | 12-20 wks  | ![Graph](image5)            | ![Graph](image6)       |
| EFW     | 20-34 wks  | ![Graph](image7)            | ![Graph](image8)       |
| BW      | Birth      | ![Graph](image9)            | ![Graph](image10)      |
| BPD     | 12-20 wks  | ![Graph](image11)          | ![Graph](image12)      |
| BPD     | 20-34 wks  | ![Graph](image13)          | ![Graph](image14)      |
| HC      | Birth      | ![Graph](image15)          | ![Graph](image16)      |
| FL      | 12-20 wks  | ![Graph](image17)          | ![Graph](image18)      |
| FL      | 20-34 wks  | ![Graph](image19)          | ![Graph](image20)      |
| BL      | Birth      | ![Graph](image21)          | ![Graph](image22)      |

Legend:
- Main analysis
- Complete case
- Gestational weight gain
- Lipids
- Σ PCBs + lipids
- PCBs + lipids

% change with respect to the mean

S14
Figure S4. Association between prenatal BDE-153 concentrations and fetal growth measurements or newborn size: The INMA Cohort, 2003-2008 (Spain)

| Outcome | Interval | % Change in maternal serum | % Change in cord serum |
|---------|----------|----------------------------|------------------------|
| AC      | 12-20 wks| ![Graph](image1)           | ![Graph](image2)       |
| AC      | 20-34 wks| ![Graph](image3)           | ![Graph](image4)       |
| EFW     | 12-20 wks| ![Graph](image5)           | ![Graph](image6)       |
| EFW     | 20-34 wks| ![Graph](image7)           | ![Graph](image8)       |
| BW      | Birth    | ![Graph](image9)           | ![Graph](image10)      |
| BPD     | 12-20 wks| ![Graph](image11)          | ![Graph](image12)      |
| BPD     | 20-34 wks| ![Graph](image13)          | ![Graph](image14)      |
| HIC     | Birth    | ![Graph](image15)          | ![Graph](image16)      |
| FL      | 12-20 wks| ![Graph](image17)          | ![Graph](image18)      |
| FL      | 20-34 wks| ![Graph](image19)          | ![Graph](image20)      |
| BL      | Birth    | ![Graph](image21)          | ![Graph](image22)      |

Legend:
- Main analysis
- Complete case
- Gestational weight gain
- Lipids
- ΣPCBs + lipids
- RCB + lipids

% change with respect to the mean
Figure S5. Association between prenatal BDE-154 concentrations and fetal growth measurements or newborn size: The INMA Cohort, 2003-2008 (Spain)

| Outcome | Interval | % Change in maternal serum | % Change in cord serum |
|---------|----------|-----------------------------|------------------------|
| AC      | 12-20 wks| ![Graph](image1)            | ![Graph](image2)       |
| AC      | 20-34 wks| ![Graph](image3)            | ![Graph](image4)       |
| EFW     | 12-20 wks| ![Graph](image5)            | ![Graph](image6)       |
| EFW     | 20-34 wks| ![Graph](image7)            | ![Graph](image8)       |
| BW      | Birth    | ![Graph](image9)            | ![Graph](image10)      |
| BPD     | 12-20 wks| ![Graph](image11)          | ![Graph](image12)      |
| BPD     | 20-34 wks| ![Graph](image13)          | ![Graph](image14)      |
| HIC     | Birth    | ![Graph](image15)          | ![Graph](image16)      |
| FL      | 12-20 wks| ![Graph](image17)          | ![Graph](image18)      |
| FL      | 20-34 wks| ![Graph](image19)          | ![Graph](image20)      |
| BL      | Birth    | ![Graph](image21)          | ![Graph](image22)      |

- **Main analysis**
- **Complete case**
- **Gestational weight gain**
- **Lipids**
- **Σ PCBs + lipids**
- **PCB + lipids**

% change with respect to the mean

-8 -6 -4 -2 0 2 4

-8 -6 -4 -2 0 2 4
Figure S6. Association between prenatal BDE-209 concentrations and fetal growth measurements or newborn size: The INMA Cohort, 2003-2008 (Spain)

| Outcome | Interval   | % Change in maternal serum | % Change in cord serum |
|---------|------------|----------------------------|-----------------------|
| AC      | 12-20 wks  | ![Graph](image1)            | ![Graph](image2)      |
| AC      | 20-34 wks  | ![Graph](image3)            | ![Graph](image4)      |
| EFW     | 12-20 wks  | ![Graph](image5)            | ![Graph](image6)      |
| EFW     | 20-34 wks  | ![Graph](image7)            | ![Graph](image8)      |
| BW      | Birth      | ![Graph](image9)            | ![Graph](image10)     |
| BPD     | 12-20 wks  | ![Graph](image11)           | ![Graph](image12)     |
| BPD     | 20-34 wks  | ![Graph](image13)           | ![Graph](image14)     |
| HC      | Birth      | ![Graph](image15)           | ![Graph](image16)     |
| FL      | 12-20 wks  | ![Graph](image17)           | ![Graph](image18)     |
| FL      | 20-34 wks  | ![Graph](image19)           | ![Graph](image20)     |
| BL      | Birth      | ![Graph](image21)           | ![Graph](image22)     |

Legend:
- Main analysis
- Complete case
- Gestational weight gain
- Lipids
- ∑ PCBs + lipids
- PCBs + lipids

% change with respect to the mean
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