Estimating associations between childhood exposure to non-persistent endocrine disruptors, corticosteroids, and neurodevelopment: A study based on the parametric g-formula

# Abstract

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* The use of the word “effect(s)” as a proxy for “association(s)” is discouraged.
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The prevalence of several neurodevelopmental disorders has increased in the pediatric population[1](#ref-GrandjeanLandrigan:2014), and multiple environmental pollutants play a role in the increased rates of these disorders[2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3). endocrine disruptors (EDCs), chemicals that are capable of interfering with the endocrine system, have been shown to have a role in childhood neurodevelopment[**Braun:2017?**](#ref-Braun:2017). Although both pregnancy and early childhood are crucial stages of (neuro)development, most of the available literature is focused on the effects of prenatal exposure to EDCs on child neurodevelopment[2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3). Moreover, little is known about the biological mechanisms of action[2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3).

organophosphate pesticides (OP pesticides) might have a deleterious effect on neurodevelopment, although the few studies conducted on children and using a biological matrix for exposure assessment suffered from a series of limitations, including a small sample size and few organophosphate pesticide (OP pesticide) metabolites measured[2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3). Phthalates and their metabolites have been associated to several adverse effects on neurodevelopment[2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3). Similarly, these studies focused on few phthalates metabolites and were conducted in small populations. On the other hand, the effects of exposure to bisphenol A (BPA) on cognitive functions are still unclear[2](#Xd81cf38a3b251ec377f8aa13b097ea9d0c190e3).

Another major limitation of these epidemiological studies, especially when non-persistent chemicals are analyzed, is the reliance on single-spot urine samples for exposure assessment, which might not be representative of long-term exposures.

Something about corticosteroids…

In the present study, we estimated associations between 1) non-persistent EDCs and attention, 2) non-persistent EDCs and corticosteroids, and 3) corticosteroids and attention, using the parametric g-formula and average contrasts, in children of a large prospective birth cohort in Europe.

# Methods

## Study population and design

The Human Early-Life Exposome (HELIX) is an ongoing project which aims to characterize early-life exposures and their potential association with endogenous biomarkers and health outcomes[3](#ref-VrijheidSlamaRobinson:2014). It consists of six existing population-based birth cohort studies across Europe: BiB (Born in Bradford, UK)[**WrightSmallRaynor:2013?**](#ref-WrightSmallRaynor:2013), EDEN (Study of determinants of pre- and postnatal developmental, France)[4](#ref-HeudeForhanSlama:2016), INMA (Environment and Childhood, Spain)[5](#ref-GuxensBallesterEspada:2012), KANC (Kaunas Cohort, Lithuania)[6](#Xd30c40380c9e99bac70b7fa3b0ada5ae8dec3e4), MoBa (The Norwegian Mother and Child Cohort Study, Norway)[7](#ref-MagnusIrgensHaug:2006), and Rhea (Mother–Child Cohort in Crete, Greece)[8](#ref-ChatziPlanaDaraki:2009), for a total of 32,000 mother-child pairs. A HELIX subcohort of 1,200 mother-child pairs was fully characterized for the external and internal exposome, including exposure and omics biomarkers during childhood. Eligibility criteria for inclusion in the HELIX subcohort included: a) age 6-11 years, with a preference for 7-9 years; b) availability of sufficient stored pregnancy blood and urine samples; c) availability of complete address history from first to last follow-up; d) no serious health problems, which might affect the results of the clinical testing. Further information can be found in[9](#ref-MaitreBontCasas:2018).

Ethical permission was obtained from the relevant authorities in the corresponding country.

## Variables

### Confounders

For each research question, defined by a specific type of exposure and outcome, the minimal set of covariates for inclusion in the analyses was selected on the basis of a directed acyclic graph (DAG) built with DAGitty[10](#ref-TextorvanderZanderGilthorpe:2016) and ggdag[11](#ref-Barrett:2023). The sets of covariates were selected to estimate the total effect of the exposure on the outcome. Further, each minimal adjustment set was *augmented* with precision covariates, defined as the set of parents variable of the outcome that are not parents of the exposure. The adjustment sets are provided in the Supplementary Material as text files compatible with DAGitty.

* For RQ1 I used creatinine values from HELIX. For RQ3 the ones from the steroids dataset. For RQ2, I included in the model both variables.

### Endocrine disrupting chemicals

Children were assessed between December 2013 and February 2016, and included neurological testing and urine collection. Urine samples of the night before and the first morning void on the day of the visit were combined to provide a more reliable exposure assessment. Non-persistent EDCs assessed in urine samples from children included phthalate metabolites, phenols, and organophosphate (OP) pesticide metabolites. A list of the environmental chemicals determined in urine samples and used for the present study is given in [Table S4](#supptbl-info-chems). Briefly, we analyzed a total of 7 phenols, 4 non-specific organophosphate pesticide metabolites, and 10 phthalate metabolites originating from 6 distinct phthalate parent compounds. The laboratory protocols for the analysis are described elsewhere[12](#ref-HaugSakhiCequier:2018).

### Corticosteroids

Urine samples of the night before the day of the visit were used to measure levels of the corticosteroids. These included glucocorticosteroids, glucocorticosteroid metabolites, glucocorticosteroid precursors, glucocorticosteroid precursor metabolites, androgens, and androgen metabolites. A list of the corticosteroids determined in urine samples and used for the present study is given in [Table S5](#supptbl-info-mets).

To assess the levels of corticosteroids and their metabolites, LC-MS/MS analysis was applied at the Applied Metabolomics Research Group, IMIM (Hospital del Mar Medical Research Institute). The laboratory protocols for the analysis are described elsewhere[13](#ref-MarcosRenauCasals:2014),[14](#ref-Gomez-GomezPozo:2020). Of the 1,004 urine samples, 980 children were matched to the HELIX subcohort.

Three additional markers, cortisol production, cortisol metabolism, cortisone production, and 11bHSD activity, were computed based on the following: cortisol production as the sum of cortisol and its metabolites (20aDHF, 20bDHF, 5bDHF, 5aTHF, 5bTHF, 6OHF, 5a20acortol, 5a20bcortol, 5b20acortol, 5b20bcortol), cortisol metabolism as the inverse of the ratio between cortisol and its metabolites, cortisone production as the sum of cortisone and its metabolites (20aDHE, 20bDHE, 5aTHE, 5bTHE, 6OHE, 5b20acortolone, b20bcortolone), and 11bHSD activity as the ratio between cortisone production and cortisol production. 11bHSD activity gives a measure of conversion of cortisone to cortisol.

### Neurodevelopment

Neurodevelopmental outcomes were assessed with standardized, non-linguistic, and culturally blind computer tests, including the Attention Network Test (ANT)[15](#ref-RuedaFanMcCandliss:2004). Further information can be found in[9](#ref-MaitreBontCasas:2018). Briefly, it is a computerized test that provides a measure of efficiency in three different functions of attention: alerting, orienting, and executive attention. The outcome of interest for the present study is the hit reaction time standard error (HRT-SE)[16](#ref-SunyerEsnaolaAlvarez-Pedrerol:2015), a measure of response speed consistency throughout the test. A high HRT-SE indicates highly variable reactions, and is considered a measure of inattentiveness.

## Statistical methods

### Data pre-processing

Concentrations of the corticosteroids were classified as quantifiable, below the limit of quantification (LOQ), possible interference or out of range, and not detected. For each metabolite, we computed the fraction of values below the LOQ and not detected, both within each cohort and overall. We proceeded to impute these values using half the value of the corresponding lower limit of quantification (LLOQ), for those metabolites that had less than 30% of missings within each cohort and 20% of missings overall. Information about the LLOQ for the corticosteroids is provided in [Table S6](#supptbl-lloq-mets). The remaining missing values were imputed using kNN from the VIM R package[17](#ref-KowarikTempl:2016), for those metabolites that had less than 40% of remaining missings within each cohort and 30% of remaining missings overall. We used 5 nearest neighbors. We natural log-transformed them to improve model fit, assessed with posterior predictive checks. To do so, replicated data were simulated with the fitted models and compared to the observed data. We used the check\_predictions function from the performance R package using the default arguments[18](#ref-LudeckeBen-ShacharPatil:2021). Values of cortisol production and cortisone production were expressed in nanograms per millilitre, whereas values of cortisol metabolism and 11bHSD activity were unitless.

Concentrations of the non-persistent EDCs were classified as quantifiable, below the limit of detection (LOD), possible interference or out of range, and not analysed. Concentrations below the LOD were singly imputed using a quantile regression approach for the imputation of left-censored missing data, as implemented in the impute.QRILC function from the imputeLCMD R package[19](#ref-lazar2015imputelcmd). Information about the lower limits of detection can be found in[12](#ref-HaugSakhiCequier:2018). Chemicals with more than 70% of observations below the LOD were not considered in the present study. Remaining missing values were imputed similarly using kNN. Values of the chemicals were expressed in grams per litre.

Missing values in the clinical outcome were imputed similarly using kNN. Similarly, we natural log-transformed them to improve model fit, assessed with posterior predictive checks. Values of the clinical outcome were expressed in milliseconds (ms).

Missing values in the covariates were imputed similarly using kNN. Categorical covariates were imputed using the maxCat function, which chooses the level with the most occurrences. Creatinine values were expressed in grams per litre.

### Estimation of balancing weights

Stabilized balancing weights were estimated using the energy method available in the WeightIt R package[20](#ref-Greifer:2023). This methods estimates weights by minimizing an energy statistic related to covariate balance[21](#ref-HulingGreiferChen:2023), thus avoiding the need to specify a parametric model. Weights below the 0.1 and above the 0.9 quantiles were trimmed. Trimming might lead to decreased covariate balance and potentially change the estimand, but can also decrease the variability of the weights. Covariate balance was assessed using functionalities provided by the cobalt R package[22](#ref-Greifer:2023a). Specifically, we used *Love* plots to visualize covariate balance before and after adjusting.

### G-computation

We estimated average contrasts with the parametric g-formula, a method of standardization. The parametric g-formula involves the following steps: 1) fit a outcome model including both covariates and balancing weights; 2) create two new datasets identical to the original one but with the exposure shifted according to a user-specified intervention set by a deterministic function of the observed exposure levels; 3) use the outcome model to compute adjusted predictions in the two counterfactual datasets; 4) compute the difference between the means of the adjusted predictions in the counterfactual datasets. The causal parameter of interest was thus specified as the difference in the expected counterfactual outcomes under the shifted exposure levels . In order for this parameter to be identified, the usual causal identifiability conditions (no unmeasured confounding, positivity, and consistency) are required. Since these conditions are likely not satisfied, we focused on the estimation of a statistical estimand that is as close as possible to the causal parameter of interest.

We fit the outcome model using the glm function and a Gaussian family with identity link from base R. The exposure variable was modeled using natural cubic splines with 3 degrees of freedom, to more flexibly capture the average dose-response function (ADRF). When the outcome was a ratio, as was the case for cortisol metabolism and 11bHSD activity, we included the logarithm of its denominator, cortisol and cortisol production, respectively, as a control variable[23](#ref-BartlettPartnoy:2020).

To estimate the average contrasts, we used the avg\_comparisons function from the marginaleffects R package[24](#ref-Arel-Bundock:2023). The two counterfactual datasets were obtained by setting the exposures levels to 90th percentile () and the 10th percentile (), for each cohort separately. The average contrasts were computed using the estimated balancing weights above. Robust standard errors were computed with the sandwich R package, using cohort as variable indicating clustering of observations[25](#ref-Zeileis:2004),[26](#ref-ZeileisKollGraham:2020). For each outcome, we report the results as differences between average contrasts.

We further estimated the ADRF using the avg\_predictions function from the marginaleffects R package, examining 50 exposure values from the 10th to the 90th percentiles of the exposure. As done for the average contrasts, we included the estimated balancing weights and used cohort as a clustering variable when computing robust standard errors.

### Effect-modification analysis

We tested for possible effect-modification by sex. To do so, balancing weights were estimated separately for each level of the sex variable, and an interaction term between the exposure and sex was included in the outcome model. Similarly, the average contrasts were aggregated separately for each level of sex. We further tested for significance of the difference between the average contrasts of males and females.

# Results

## Participants

In total, 1,297 children were included in the dataset. Of these, 976 had information also about the corticosteroids. The sample consisted of 55% girls. The median HRT-SE was 300 ms (interquartile range (IQR), 231-368), with lower median values for EDEN, MOBA, and SAB, corresponding to the cohorts with older children. At the time of visit, the median age of the children was 8.06 years. The children were mostly Caucasian (90%) or Pakistani (6.2%). [Table 1](#tbl-pop-desc) provides descriptive statistics for the outcome and covariates, by cohort and overall. Codebooks for the used covariates, by research question, are provided in [Table S1](#supptbl-codebook-1), [Table S2](#supptbl-codebook-2), and [Table S3](#supptbl-codebook-3).

## Descriptive data

Levels of unprocessed non-persistent EDCs and corticosteroids, by cohort and overall, are presented in [Table 2](#tbl-edc-desc) and [Table 3](#tbl-met-desc), respectively.

## Main results

* All results on which study conclusions or inferences are based, including null findings and results of secondary or sensitivity analyses, must be reported. Use of sub-headings that describe the nature of the results (but no declarative statements).
  + Provide a clear and concise description of all findings without extrapolating beyond the study results.
  + Do not limit results to those *statistically significant* or that support the study hypotheses. Avoid using statistical significance testing as the sole or primary criterion for interpreting the obtained results. If significance testing or *p*-values are used, report numeric *p*-values, rounded to 1-2 digits, for all results. Use an uppercase italic letter “P”, and the values should not be bolded. Indicate whether are 1- or 2-sided.
* Give unadjusted and confounder-adjusted estimates and their precision (e.g., confidence interval). Make clear which confounders were adjusted for and why they were included. Include the number of observations for each analysis after accounting for missing data. Include numeric data within figures (e.g., forest plots), or provide tables with corresponding numeric data for all figures.
  + [marginaleffects tables](https://vincentarelbundock.github.io/marginaleffects/articles/tables.html).
* Report category boundaries when continuous variables were categorized.

## Other analyses

* Report other analyses done (e.g., analyses of subgroups and interactions, and sensitivity analyses).

# Discussion

## Key results

* Summarise key results with reference to study objectives.
* Provide a review of the relevant literature to put the study findings into context.
  + It should be complete and balanced, including inconsistent results.
  + It should include, for each source, sufficient details: study design, sample size, population, specific exposures and outcomes.

### What does the literature say?

* EDCs and neurodevelopment (ANT).
* EDCs and corticosteroids.
* Corticosteroids and neurodevelopment (ANT).

## Limitations

* Discuss limitations of the study, taking into account sources of potential bias or imprecision.
* Discuss both direction and magnitude of any potential bias.

Some limitations:

* Cross-sectional study.
* Chemicals measured in night and morning samples, whereas metabolites (the outcome) were measured only in night samples.
* Cortisol measured at night, when should be lowest.
* Change of estimand when trimming weights.
* Model misspecification.
* Mixtures effect.
* Residual confounding.
* Some confounders were not used since large percentage of missing values.
* Multiple comparisons.

## Interpretation

* End with a summary of the key findings and their implications for the study hypotheses, future research, and policy.
* Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.

## Generalisability

* Discuss the generalisability (external validity) of the study results.

# Funding

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# Descriptive data

## Study populations

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| Table 1: Characteristics of the children included in the analyses, by cohort and overall   | **Characteristic** | **Overall**, N = 1,297*1* | **BIB**, N = 204*1* | **EDEN**, N = 198*1* | **KANC**, N = 203*1* | **MOBA**, N = 272*1* | **RHEA**, N = 199*1* | **SAB**, N = 221*1* | | --- | --- | --- | --- | --- | --- | --- | --- | | hs\_hitrtse | 300 (231, 368) | 355 (292, 398) | 238 (185, 307) | 368 (324, 407) | 249 (193, 301) | 341 (281, 399) | 256 (197, 314) | | Unknown | 18 | 3 | 11 | 0 | 0 | 1 | 3 | | Age of the child at clinical assessment (years) | 8.06 (6.50, 8.93) | 6.61 (6.45, 6.80) | 10.86 (10.41, 11.23) | 6.40 (6.13, 6.85) | 8.46 (8.17, 8.76) | 6.47 (6.36, 6.62) | 8.82 (8.43, 9.25) | | Child breastfeeding | 1,093 (85%) | 147 (72%) | 128 (65%) | 187 (93%) | 260 (96%) | 176 (88%) | 195 (89%) | | Unknown | 6 | 1 | 1 | 1 | 2 | 0 | 1 | | Height of the child (m) | 1.28 (1.21, 1.36) | 1.19 (1.17, 1.23) | 1.44 (1.39, 1.49) | 1.21 (1.18, 1.26) | 1.34 (1.30, 1.38) | 1.20 (1.17, 1.24) | 1.34 (1.30, 1.37) | | Weight of the child (kg) | 27 (23, 33) | 22 (20, 25) | 36 (32, 41) | 24 (21, 27) | 29 (26, 32) | 23 (21, 27) | 31 (27, 37) | | Head circumference of the child (cm) | 51.75 (50.56, 52.90) | 51.40 (50.34, 52.32) | 50.50 (49.50, 52.00) | 52.00 (51.00, 53.00) | 52.45 (51.55, 53.56) | 51.18 (50.19, 52.01) | 52.30 (51.30, 53.25) | | Unknown | 3 | 0 | 0 | 0 | 0 | 3 | 0 | | Visits a fast food restaurant/take away (times / week) | 0.13 (0.13, 0.50) | 0.50 (0.13, 1.00) | 0.13 (0.13, 0.50) | 0.13 (0.00, 0.13) | 0.13 (0.13, 0.50) | 0.50 (0.13, 0.50) | 0.13 (0.13, 0.50) | | Unknown | 7 | 0 | 0 | 2 | 0 | 0 | 5 | | Eats organic food (times / week) | 0.50 (0.00, 3.00) | 0.00 (0.00, 0.50) | 0.50 (0.13, 3.00) | 1.00 (0.13, 3.00) | 1.00 (0.50, 3.00) | 0.00 (0.00, 1.00) | 0.00 (0.00, 0.50) | | Unknown | 7 | 0 | 0 | 2 | 0 | 0 | 5 | | Food group: fish and seafood (times / week) | 2.00 (1.13, 3.53) | 2.00 (1.00, 3.13) | 2.13 (1.39, 3.00) | 1.00 (0.39, 1.63) | 2.63 (1.63, 5.00) | 1.50 (1.00, 2.00) | 3.50 (2.13, 5.00) | | Unknown | 5 | 1 | 0 | 2 | 0 | 0 | 2 | | Food group: fruits (times / week) | 9 (6, 18) | 16 (10, 21) | 7 (3, 14) | 7 (4, 10) | 14 (9, 21) | 9 (6, 14) | 8 (4, 13) | | Unknown | 7 | 2 | 0 | 2 | 1 | 0 | 2 | | Food group: vegetables (times / week) | 7 (4, 10) | 6 (4, 10) | 8 (4, 11) | 6 (4, 9) | 9 (6, 14) | 7 (4, 10) | 6 (3, 9) | | Unknown | 6 | 1 | 0 | 2 | 1 | 0 | 2 | | Which of the following best describes your consumption of tobacco? |  |  |  |  |  |  |  | | Non-smoker and has never smoked | 681 (53%) | 148 (73%) | 87 (44%) | 104 (52%) | 138 (51%) | 101 (51%) | 103 (47%) | | Non-smoker but previously smoked although not daily | 163 (13%) | 12 (5.9%) | 19 (9.6%) | 32 (16%) | 63 (23%) | 14 (7.0%) | 23 (10%) | | Non-smoker but previously smoked daily | 186 (14%) | 11 (5.4%) | 37 (19%) | 21 (10%) | 53 (19%) | 22 (11%) | 42 (19%) | | Smoker but not daily | 64 (4.9%) | 6 (2.9%) | 10 (5.1%) | 20 (10.0%) | 12 (4.4%) | 9 (4.5%) | 7 (3.2%) | | Daily smoker | 200 (15%) | 27 (13%) | 45 (23%) | 24 (12%) | 6 (2.2%) | 53 (27%) | 45 (20%) | | Unknown | 3 | 0 | 0 | 2 | 0 | 0 | 1 | | hs\_creatinine\_cg | 1.02 (0.79, 1.24) | 1.02 (0.79, 1.24) | 1.22 (1.00, 1.50) | 0.90 (0.68, 1.13) | 0.90 (0.72, 1.13) | 0.90 (0.70, 1.13) | 1.02 (0.79, 1.26) | | Mood of the child in the last few days before assessment |  |  |  |  |  |  |  | | Usual | 1,232 (95%) | 198 (97%) | 176 (89%) | 187 (92%) | 262 (96%) | 195 (98%) | 214 (97%) | | Not usual | 64 (4.9%) | 6 (2.9%) | 21 (11%) | 16 (7.9%) | 10 (3.7%) | 4 (2.0%) | 7 (3.2%) | | Unknown | 1 | 0 | 1 | 0 | 0 | 0 | 0 | | Child rested the night before assessment |  |  |  |  |  |  |  | | Yes | 1,209 (93%) | 192 (94%) | 170 (86%) | 200 (99%) | 259 (95%) | 182 (91%) | 206 (93%) | | Not as well as usual | 87 (6.7%) | 12 (5.9%) | 27 (14%) | 3 (1.5%) | 13 (4.8%) | 17 (8.5%) | 15 (6.8%) | | Unknown | 1 | 0 | 1 | 0 | 0 | 0 | 0 | | Which is the ethnicity of the child? |  |  |  |  |  |  |  | | African | 7 (0.5%) | 7 (3.4%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | | Asian | 21 (1.6%) | 13 (6.4%) | 1 (0.5%) | 0 (0%) | 7 (2.6%) | 0 (0%) | 0 (0%) | | Caucasian | 1,157 (90%) | 87 (43%) | 196 (99%) | 200 (100%) | 254 (96%) | 199 (100%) | 221 (100%) | | Native American | 2 (0.2%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (0.8%) | 0 (0%) | 0 (0%) | | Other | 19 (1.5%) | 17 (8.3%) | 0 (0%) | 0 (0%) | 2 (0.8%) | 0 (0%) | 0 (0%) | | Pakistani | 80 (6.2%) | 80 (39%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | | White non European | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | | Unknown | 11 | 0 | 1 | 3 | 7 | 0 | 0 | | Family affluence scale continuous |  |  |  |  |  |  |  | | 0 | 6 (0.5%) | 2 (1.0%) | 0 (0%) | 1 (0.5%) | 0 (0%) | 2 (1.0%) | 1 (0.5%) | | 1 | 12 (0.9%) | 4 (2.0%) | 0 (0%) | 4 (2.0%) | 1 (0.4%) | 1 (0.5%) | 2 (0.9%) | | 2 | 28 (2.2%) | 16 (7.8%) | 0 (0%) | 4 (2.0%) | 0 (0%) | 7 (3.5%) | 1 (0.5%) | | 3 | 92 (7.1%) | 34 (17%) | 2 (1.0%) | 22 (11%) | 3 (1.1%) | 20 (10%) | 11 (5.0%) | | 4 | 174 (13%) | 40 (20%) | 13 (6.6%) | 38 (19%) | 16 (5.9%) | 45 (23%) | 22 (10%) | | 5 | 325 (25%) | 48 (24%) | 29 (15%) | 69 (34%) | 57 (21%) | 57 (29%) | 65 (30%) | | 6 | 410 (32%) | 34 (17%) | 64 (32%) | 50 (25%) | 142 (52%) | 45 (23%) | 75 (34%) | | 7 | 248 (19%) | 26 (13%) | 90 (45%) | 14 (6.9%) | 53 (19%) | 22 (11%) | 43 (20%) | | Unknown | 2 | 0 | 0 | 1 | 0 | 0 | 1 | | How well would you say your family is managing financially these days? |  |  |  |  |  |  |  | | Living comfortably | 412 (32%) | 59 (29%) | 49 (25%) | 48 (24%) | 202 (74%) | 25 (13%) | 29 (13%) | | Doing alright | 414 (32%) | 73 (36%) | 94 (47%) | 61 (31%) | 64 (24%) | 58 (29%) | 64 (29%) | | Getting by | 331 (26%) | 59 (29%) | 36 (18%) | 70 (35%) | 4 (1.5%) | 80 (40%) | 82 (37%) | | Finding it quite difficult | 86 (6.7%) | 8 (3.9%) | 9 (4.5%) | 12 (6.0%) | 1 (0.4%) | 27 (14%) | 29 (13%) | | Finding it very difficult | 40 (3.1%) | 5 (2.5%) | 10 (5.1%) | 2 (1.0%) | 0 (0%) | 8 (4.0%) | 15 (6.8%) | | Does not wish to answer | 8 (0.6%) | 0 (0%) | 0 (0%) | 7 (3.5%) | 1 (0.4%) | 0 (0%) | 0 (0%) | | Unknown | 6 | 0 | 0 | 3 | 0 | 1 | 2 | | Marital status |  |  |  |  |  |  |  | | Living with the father | 39 (3.0%) | 0 (0%) | 2 (1.0%) | 31 (16%) | 3 (1.1%) | 3 (1.5%) | 0 (0%) | | Living alone | 1,212 (95%) | 178 (87%) | 193 (98%) | 168 (84%) | 260 (98%) | 194 (98%) | 219 (99%) | | Other situation | 31 (2.4%) | 26 (13%) | 2 (1.0%) | 0 (0%) | 1 (0.4%) | 0 (0%) | 2 (0.9%) | | Unknown | 15 | 0 | 1 | 4 | 8 | 2 | 0 | | Maternal active smoking during pregnancy | 190 (15%) | 25 (14%) | 47 (24%) | 12 (6.0%) | 9 (3.4%) | 42 (21%) | 55 (25%) | | Unknown | 40 | 22 | 0 | 4 | 11 | 1 | 2 | | Maternal passive smoking during pregnancy | 514 (40%) | 55 (28%) | 43 (22%) | 97 (49%) | 14 (5.3%) | 179 (90%) | 126 (58%) | | Unknown | 21 | 4 | 1 | 4 | 8 | 1 | 3 | | Any previous child neuropsychological diagnosis? | 95 (7.3%) | 3 (1.5%) | 58 (29%) | 1 (0.5%) | 1 (0.4%) | 8 (4.0%) | 24 (11%) | | Date of test (season) |  |  |  |  |  |  |  | | autumn | 300 (23%) | 49 (24%) | 1 (0.5%) | 77 (38%) | 105 (39%) | 38 (19%) | 30 (14%) | | spring | 358 (28%) | 48 (24%) | 64 (32%) | 61 (30%) | 37 (14%) | 77 (39%) | 71 (32%) | | summer | 297 (23%) | 67 (33%) | 72 (36%) | 27 (13%) | 57 (21%) | 53 (27%) | 21 (9.6%) | | winter | 339 (26%) | 40 (20%) | 61 (31%) | 38 (19%) | 73 (27%) | 30 (15%) | 97 (44%) | | Unknown | 3 | 0 | 0 | 0 | 0 | 1 | 2 | | Child’s sex |  |  |  |  |  |  |  | | Male | 587 (45%) | 92 (45%) | 85 (43%) | 92 (45%) | 129 (47%) | 88 (44%) | 101 (46%) | | Female | 710 (55%) | 112 (55%) | 113 (57%) | 111 (55%) | 143 (53%) | 111 (56%) | 120 (54%) | | Imputed difference between blood time extraction and last meal time | 3.33 (2.80, 4.00) | 3.33 (2.75, 4.10) | 3.17 (2.80, 3.67) | 3.33 (2.83, 3.83) | 3.38 (2.83, 3.84) | 4.00 (3.29, 4.75) | 3.00 (2.58, 3.75) | | Creatinine in child in night sample (g / l) | 1.69 (0.88, 2.96) | 0.81 (0.57, 1.11) | 3.33 (1.98, 4.32) | 1.68 (0.95, 2.69) | 2.01 (1.19, 3.05) | 0.76 (0.40, 1.31) | 2.47 (1.52, 3.81) | | Unknown | 321 | 72 | 64 | 23 | 72 | 71 | 19 | | *1*Median (IQR); n (%) | | | | | | | | |

## Endocrine disruptors

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 2: Levels of unprocessed chemicals, by cohort and overall   | **Characteristic** | **Overall**, N = 976*1* | **BIB**, N = 132*1* | **EDEN**, N = 134*1* | **KANC**, N = 180*1* | **MOBA**, N = 200*1* | **RHEA**, N = 128*1* | **SAB**, N = 202*1* | | --- | --- | --- | --- | --- | --- | --- | --- | | mep | 33 (15, 76) | 44 (19, 114) | 46 (24, 89) | 27 (14, 55) | 13 (8, 21) | 27 (13, 54) | 91 (42, 169) | | mibp | 38 (23, 66) | 63 (38, 104) | 44 (27, 70) | 71 (42, 116) | 21 (13, 34) | 41 (29, 61) | 28 (18, 44) | | mnbp | 22 (14, 38) | 24 (16, 45) | 19 (13, 30) | 41 (26, 62) | 20 (14, 32) | 23 (13, 38) | 15 (10, 23) | | mbzp | 5 (3, 9) | 3 (1, 5) | 7 (5, 12) | 6 (3, 11) | 4 (2, 6) | 5 (3, 9) | 5 (3, 9) | | mehp | 2.8 (1.5, 5.0) | 3.2 (1.6, 5.9) | 2.2 (1.2, 3.8) | 3.2 (1.8, 4.8) | 1.7 (1.1, 2.7) | 4.7 (2.6, 7.6) | 3.4 (2.0, 6.0) | | Unknown | 32 | 5 | 3 | 5 | 16 | 3 | 0 | | mehhp | 19 (12, 32) | 22 (13, 38) | 13 (9, 21) | 26 (17, 38) | 11 (7, 17) | 33 (18, 57) | 21 (14, 37) | | Unknown | 3 | 0 | 0 | 0 | 3 | 0 | 0 | | meohp | 12 (7, 20) | 14 (8, 25) | 8 (5, 13) | 17 (11, 26) | 7 (4, 10) | 20 (12, 35) | 13 (9, 21) | | Unknown | 1 | 0 | 0 | 0 | 1 | 0 | 0 | | mecpp | 33 (20, 57) | 41 (23, 66) | 22 (15, 32) | 46 (33, 74) | 20 (14, 31) | 60 (30, 96) | 35 (24, 61) | | ohminp | 5 (3, 9) | 8 (4, 14) | 5 (3, 9) | 5 (3, 8) | 5 (3, 8) | 5 (3, 9) | 5 (3, 10) | | oxominp | 2.8 (1.7, 5.0) | 3.2 (1.9, 5.8) | 2.5 (1.5, 4.2) | 2.5 (1.5, 4.5) | 2.1 (1.3, 3.9) | 3.4 (2.1, 6.4) | 3.1 (2.1, 5.3) | | mepa | 6 (3, 25) | 10 (4, 59) | 6 (3, 22) | 7 (3, 31) | 3 (2, 7) | 5 (2, 9) | 14 (5, 63) | | Unknown | 2 | 0 | 0 | 0 | 2 | 0 | 0 | | etpa | 0.66 (0.40, 1.23) | 0.72 (0.39, 1.30) | 0.71 (0.49, 1.03) | 0.65 (0.34, 1.46) | 0.60 (0.39, 1.07) | 0.54 (0.30, 1.03) | 0.78 (0.45, 1.54) | | Unknown | 2 | 0 | 1 | 0 | 0 | 0 | 1 | | prpa | 0 (0, 2) | 1 (0, 6) | 0 (0, 0) | 0 (0, 1) | 0 (0, 0) | 0 (0, 1) | 1 (0, 8) | | Unknown | 11 | 4 | 2 | 2 | 0 | 1 | 2 | | bpa | 4 (2, 7) | 5 (2, 10) | 3 (2, 4) | 3 (2, 6) | 4 (3, 8) | 4 (2, 7) | 4 (2, 7) | | Unknown | 8 | 0 | 1 | 2 | 2 | 0 | 3 | | bupa | 0.08 (0.05, 0.14) | 0.06 (0.04, 0.10) | 0.05 (0.03, 0.07) | 0.09 (0.06, 0.19) | 0.08 (0.06, 0.13) | 0.07 (0.04, 0.14) | 0.10 (0.06, 0.23) | | Unknown | 4 | 1 | 1 | 0 | 2 | 0 | 0 | | oxbe | 2 (1, 6) | 4 (1, 12) | 1 (0, 2) | 2 (1, 6) | 3 (1, 7) | 2 (1, 9) | 2 (1, 6) | | trcs | 0.6 (0.3, 1.5) | 1.1 (0.6, 2.8) | 0.7 (0.4, 1.3) | 0.7 (0.4, 1.5) | 0.2 (0.1, 0.4) | 0.4 (0.2, 0.8) | 1.0 (0.4, 2.4) | | dmp | 0.4 (0.3, 4.4) | 0.3 (0.3, 3.3) | 0.4 (0.3, 6.2) | 0.3 (0.3, 2.3) | 1.4 (0.3, 4.4) | 2.1 (0.3, 5.7) | 0.4 (0.3, 5.8) | | Unknown | 4 | 0 | 0 | 1 | 1 | 1 | 1 | | dmtp | 2.8 (1.2, 6.2) | 2.1 (0.9, 5.2) | 4.0 (1.4, 8.9) | 2.5 (0.9, 4.6) | 2.3 (0.9, 5.0) | 3.2 (1.6, 6.4) | 3.4 (1.6, 7.9) | | Unknown | 1 | 0 | 0 | 1 | 0 | 0 | 0 | | dep | 1.5 (0.3, 4.1) | 3.2 (0.9, 8.9) | 1.7 (0.1, 3.4) | 0.7 (0.1, 2.1) | 1.6 (0.4, 4.8) | 1.5 (0.4, 5.5) | 1.6 (0.6, 3.6) | | Unknown | 2 | 0 | 0 | 0 | 0 | 1 | 1 | | detp | 0.12 (0.10, 1.52) | 0.12 (0.10, 1.27) | 0.13 (0.10, 1.74) | 0.12 (0.09, 0.35) | 0.12 (0.10, 1.26) | 0.63 (0.11, 3.05) | 0.13 (0.10, 1.96) | | Unknown | 14 | 4 | 5 | 2 | 1 | 2 | 0 | | *1*Median (IQR) | | | | | | | | |

## Corticosteroids

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 3: Levels of unprocessed corticosteroids, by cohort and overall   | **Characteristic** | **Overall**, N = 976*1* | **BIB**, N = 132*1* | **EDEN**, N = 134*1* | **KANC**, N = 180*1* | **MOBA**, N = 200*1* | **RHEA**, N = 128*1* | **SAB**, N = 202*1* | | --- | --- | --- | --- | --- | --- | --- | --- | | F | 5.4 (3.1, 9.3) | 6.3 (3.9, 10.3) | 7.8 (4.2, 11.2) | 4.9 (2.7, 8.2) | 5.2 (3.0, 9.1) | 6.2 (3.4, 13.1) | 4.5 (2.8, 7.1) | | Unknown | 2 | 0 | 0 | 1 | 1 | 0 | 0 | | 20aDHF | 7 (3, 13) | 7 (4, 14) | 10 (6, 19) | 5 (2, 11) | 7 (4, 14) | 7 (3, 14) | 5 (3, 10) | | Unknown | 7 | 4 | 0 | 3 | 0 | 0 | 0 | | 20bDHF | 15 (9, 25) | 17 (11, 26) | 20 (12, 32) | 14 (9, 25) | 14 (8, 24) | 14 (8, 28) | 13 (8, 18) | | 5bDHF | 1.37 (0.90, 2.02) | 1.35 (0.92, 2.06) | 1.84 (1.26, 2.55) | 1.47 (1.08, 1.92) | 1.06 (0.59, 1.71) | 1.49 (1.02, 2.13) | 1.10 (0.62, 1.79) | | Unknown | 2 | 0 | 0 | 0 | 1 | 0 | 1 | | 5aTHF | 2,845 (1,660, 4,350) | 3,368 (2,216, 5,272) | 3,453 (1,842, 5,224) | 2,907 (1,656, 4,621) | 2,283 (1,260, 3,455) | 3,002 (1,652, 4,614) | 2,719 (1,548, 3,749) | | 5bTHF | 904 (543, 1,405) | 1,131 (656, 1,603) | 1,212 (723, 1,565) | 754 (389, 1,259) | 860 (493, 1,261) | 882 (565, 1,441) | 883 (542, 1,195) | | Unknown | 2 | 2 | 0 | 0 | 0 | 0 | 0 | | 6OHF | 42 (22, 76) | 52 (30, 92) | 55 (29, 79) | 37 (20, 69) | 46 (28, 83) | 42 (21, 93) | 32 (18, 53) | | 5a20acortol | 88 (52, 140) | 106 (57, 174) | 102 (57, 151) | 85 (47, 146) | 89 (54, 138) | 72 (47, 130) | 83 (46, 118) | | Unknown | 8 | 8 | 0 | 0 | 0 | 0 | 0 | | 5a20bcortol | 122 (70, 184) | 133 (67, 176) | 147 (107, 223) | 115 (63, 189) | 115 (68, 173) | 105 (73, 175) | 123 (69, 179) | | Unknown | 5 | 5 | 0 | 0 | 0 | 0 | 0 | | 5b20acortol | 147 (83, 223) | 178 (98, 297) | 169 (90, 251) | 143 (80, 230) | 144 (87, 204) | 138 (80, 220) | 140 (76, 187) | | Unknown | 10 | 10 | 0 | 0 | 0 | 0 | 0 | | 5b20bcortol | 192 (118, 300) | 243 (153, 357) | 224 (141, 357) | 156 (88, 270) | 186 (115, 269) | 178 (114, 302) | 198 (129, 288) | | Unknown | 3 | 3 | 0 | 0 | 0 | 0 | 0 | | 11OHAndros | 227 (128, 380) | 245 (141, 347) | 404 (221, 616) | 163 (81, 298) | 254 (152, 408) | 165 (96, 304) | 249 (141, 350) | | Unknown | 3 | 0 | 0 | 3 | 0 | 0 | 0 | | CortisoneE | 23 (13, 38) | 26 (14, 43) | 28 (14, 42) | 21 (12, 34) | 23 (14, 38) | 29 (19, 59) | 17 (10, 27) | | 20aDHE | 16 (10, 27) | 14 (7, 26) | 25 (15, 37) | 15 (8, 26) | 17 (12, 26) | 15 (9, 28) | 16 (10, 23) | | Unknown | 11 | 7 | 0 | 4 | 0 | 0 | 0 | | 20bDHE | 9 (6, 14) | 9 (5, 14) | 13 (10, 17) | 9 (5, 14) | 9 (6, 14) | 9 (5, 15) | 9 (7, 12) | | Unknown | 16 | 13 | 0 | 3 | 0 | 0 | 0 | | 5aTHE | 73 (39, 123) | 80 (52, 136) | 84 (41, 133) | 71 (40, 122) | 65 (36, 104) | 108 (51, 183) | 61 (32, 97) | | Unknown | 1 | 0 | 0 | 0 | 0 | 1 | 0 | | 5bTHE | 3,112 (1,868, 4,672) | 3,553 (2,323, 4,791) | 3,591 (2,235, 5,287) | 2,755 (1,448, 3,989) | 3,070 (1,785, 4,638) | 3,542 (2,010, 5,901) | 2,880 (1,605, 4,011) | | 6OHE | 12 (6, 18) | 13 (8, 21) | 12 (6, 17) | 13 (7, 20) | 11 (6, 18) | 14 (9, 24) | 9 (5, 14) | | 5b20acortolone | 641 (364, 969) | 637 (377, 1,008) | 877 (566, 1,277) | 518 (261, 870) | 581 (318, 902) | 629 (401, 962) | 654 (397, 888) | | 5b20bcortolone | 545 (335, 829) | 561 (334, 889) | 677 (452, 995) | 505 (272, 769) | 496 (289, 761) | 563 (328, 881) | 531 (367, 780) | | 5aTHB | 132 (75, 222) | 158 (104, 247) | 144 (88, 255) | 148 (83, 246) | 106 (61, 185) | 140 (75, 260) | 116 (73, 172) | | 5bTHB | 49 (28, 82) | 54 (28, 100) | 60 (34, 92) | 44 (28, 90) | 40 (25, 66) | 53 (28, 77) | 50 (29, 74) | | Unknown | 1 | 0 | 0 | 1 | 0 | 0 | 0 | | A | 4 (2, 8) | 5 (3, 9) | 5 (3, 9) | 4 (2, 7) | 4 (3, 8) | 6 (4, 15) | 3 (2, 6) | | Unknown | 1 | 0 | 0 | 0 | 0 | 0 | 1 | | 17DOcortolone | 57 (29, 100) | 54 (33, 96) | 76 (45, 133) | 44 (15, 93) | 56 (26, 92) | 51 (28, 94) | 61 (32, 102) | | Unknown | 2 | 0 | 0 | 1 | 0 | 1 | 0 | | S | 0.45 (0.26, 0.76) | 0.52 (0.29, 0.94) | 0.42 (0.25, 0.73) | 0.32 (0.22, 0.47) | 0.44 (0.25, 0.67) | 0.45 (0.22, 0.77) | 0.58 (0.37, 0.94) | | Unknown | 94 | 6 | 5 | 9 | 51 | 11 | 12 | | 5bDHS | 0.26 (0.17, 0.40) | 0.25 (0.17, 0.40) | 0.29 (0.19, 0.46) | 0.23 (0.18, 0.30) | 0.25 (0.17, 0.41) | 0.32 (0.18, 0.51) | 0.27 (0.16, 0.35) | | Unknown | 131 | 4 | 20 | 0 | 57 | 7 | 43 | | 5bTHS | 31 (18, 50) | 37 (21, 59) | 34 (19, 49) | 31 (19, 55) | 26 (14, 41) | 34 (20, 58) | 27 (17, 43) | | Unknown | 2 | 0 | 0 | 0 | 1 | 0 | 1 | | 17HP | 22 (15, 33) | 17 (11, 27) | 33 (24, 44) | 20 (11, 33) | 23 (17, 31) | 22 (16, 32) | 20 (13, 32) | | Unknown | 1 | 0 | 0 | 0 | 0 | 1 | 0 | | PT | 201 (114, 342) | 150 (87, 239) | 373 (230, 539) | 142 (82, 274) | 176 (113, 283) | 189 (105, 306) | 252 (149, 403) | | T | 0.53 (0.31, 0.95) | 0.66 (0.54, 0.92) | 1.00 (0.49, 1.86) | 0.35 (0.18, 0.57) | 0.41 (0.28, 0.74) | 0.38 (0.26, 0.69) | 0.57 (0.31, 1.01) | | Unknown | 75 | 0 | 5 | 29 | 24 | 14 | 3 | | Andros | 184 (78, 392) | 140 (70, 255) | 550 (297, 971) | 98 (40, 227) | 135 (63, 293) | 110 (62, 226) | 295 (131, 508) | | Unknown | 1 | 0 | 0 | 1 | 0 | 0 | 0 | | Etio | 111 (51, 237) | 73 (30, 138) | 369 (223, 555) | 75 (38, 123) | 91 (46, 184) | 76 (41, 147) | 168 (84, 304) | | Unknown | 1 | 0 | 0 | 1 | 0 | 0 | 0 | | AED | 0.23 (0.17, 0.35) | 0.23 (0.21, 0.26) | 0.34 (0.19, 0.54) | 0.18 (0.14, 0.26) | 0.19 (0.14, 0.27) | 0.20 (0.15, 1.05) | 0.22 (0.15, 0.39) | | Unknown | 406 | 0 | 34 | 117 | 106 | 77 | 72 | | *1*Median (IQR) | | | | | | | | |

# Main results

## Balancing weights

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 4: Effective number of observations   | exposure | Unadjusted*1* | Adjusted*1,2* | | --- | --- | --- | | Phenols | | | | etpa | 1,297 | 1,289 | | oxbe | 1,297 | 1,277 | | bupa | 1,297 | 1,276 | | prpa | 1,297 | 1,275 | | mepa | 1,297 | 1,266 | | trcs | 1,297 | 1,255 | | bpa | 1,297 | 1,137 | | OP pesticide metabolites | | | | detp | 1,297 | 1,222 | | dep | 1,297 | 1,222 | | dmtp | 1,297 | 1,219 | | dmp | 1,297 | 1,172 | | Phthalate metabolites | | | | oxominp | 1,297 | 1,199 | | ohminp | 1,297 | 1,172 | | mbzp | 1,297 | 1,113 | | mehp | 1,297 | 1,089 | | mep | 1,297 | 1,055 | | mnbp | 1,297 | 1,035 | | mehhp | 1,297 | 1,010 | | meohp | 1,297 | 1,001 | | mecpp | 1,297 | 980.1 | | mibp | 1,297 | 927.1 | | *1*N. | | | | *2*Truncated weights. | | | |

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| Table 5: Effective number of observations   | exposure | Unadjusted*1* | Adjusted*1,2* | | --- | --- | --- | | Phenols | | | | oxbe | 976.0 | 960.1 | | prpa | 976.0 | 955.8 | | mepa | 976.0 | 953.8 | | bupa | 976.0 | 952.5 | | etpa | 976.0 | 951.7 | | trcs | 976.0 | 943.0 | | bpa | 976.0 | 855.7 | | OP pesticide metabolites | | | | detp | 976.0 | 922.4 | | dep | 976.0 | 921.5 | | dmtp | 976.0 | 907.3 | | dmp | 976.0 | 892.5 | | Phthalate metabolites | | | | ohminp | 976.0 | 878.3 | | oxominp | 976.0 | 874.0 | | mbzp | 976.0 | 827.7 | | mehp | 976.0 | 827.4 | | mep | 976.0 | 795.7 | | mehhp | 976.0 | 783.7 | | mecpp | 976.0 | 767.4 | | meohp | 976.0 | 761.5 | | mnbp | 976.0 | 745.9 | | mibp | 976.0 | 689.8 | | *1*N. | | | | *2*Truncated weights. | | | |

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| Table 6: Effective number of observations   | exposure | Unadjusted*1* | Adjusted*1,2* | | --- | --- | --- | | cortisol metabolism | 976.0 | 872.0 | | 11bhsd | 976.0 | 866.6 | | cortisone metabolism | 976.0 | 859.5 | | cortisone production | 976.0 | 777.2 | | corticosterone production | 976.0 | 758.1 | | cortisol production | 976.0 | 751.6 | | *1*N. | | | | *2*Truncated weights. | | | |

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| Table 7: Weights   |  | Median (IQR) | Range | | --- | --- | --- | | **Characteristic***1* | **N = 1,297***1* | **N = 1,297***1* | | mep | 0.93 (0.61, 1.27) | 0.28, 1.77 | | mibp | 0.91 (0.46, 1.38) | 0.05, 1.93 | | mnbp | 0.98 (0.59, 1.33) | 0.19, 1.74 | | mbzp | 0.98 (0.66, 1.28) | 0.34, 1.62 | | mehp | 0.98 (0.64, 1.27) | 0.31, 1.68 | | mehhp | 0.96 (0.54, 1.35) | 0.16, 1.75 | | meohp | 0.96 (0.52, 1.35) | 0.15, 1.78 | | mecpp | 0.95 (0.50, 1.34) | 0.14, 1.84 | | ohminp | 1.01 (0.74, 1.24) | 0.47, 1.50 | | oxominp | 1.01 (0.78, 1.20) | 0.52, 1.43 | | mepa | 1.01 (0.90, 1.13) | 0.74, 1.25 | | etpa | 1.01 (0.96, 1.07) | 0.88, 1.14 | | prpa | 1.01 (0.92, 1.12) | 0.80, 1.23 | | bpa | 0.99 (0.70, 1.27) | 0.38, 1.57 | | bupa | 1.01 (0.91, 1.11) | 0.81, 1.22 | | oxbe | 1.01 (0.92, 1.10) | 0.79, 1.21 | | trcs | 1.01 (0.87, 1.13) | 0.68, 1.28 | | dmp | 0.98 (0.73, 1.25) | 0.49, 1.51 | | dmtp | 1.00 (0.81, 1.20) | 0.59, 1.39 | | dep | 1.01 (0.81, 1.19) | 0.59, 1.38 | | detp | 0.99 (0.81, 1.18) | 0.61, 1.41 | | *1*Truncated weights. | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 8: Weights   |  | Median (IQR) | Range | | --- | --- | --- | | **Characteristic***1* | **N = 976***1* | **N = 976***1* | | mep | 0.93 (0.60, 1.27) | 0.28, 1.74 | | mibp | 0.88 (0.43, 1.38) | 0.08, 1.98 | | mnbp | 0.97 (0.53, 1.36) | 0.14, 1.84 | | mbzp | 0.94 (0.68, 1.28) | 0.35, 1.69 | | mehp | 0.98 (0.64, 1.29) | 0.33, 1.63 | | mehhp | 0.98 (0.56, 1.35) | 0.21, 1.70 | | meohp | 0.98 (0.52, 1.35) | 0.18, 1.78 | | mecpp | 0.95 (0.55, 1.36) | 0.19, 1.77 | | ohminp | 1.00 (0.73, 1.25) | 0.46, 1.49 | | oxominp | 1.01 (0.71, 1.25) | 0.45, 1.52 | | mepa | 1.00 (0.90, 1.13) | 0.75, 1.26 | | etpa | 1.02 (0.90, 1.14) | 0.72, 1.24 | | prpa | 1.00 (0.92, 1.12) | 0.77, 1.26 | | bpa | 0.99 (0.70, 1.26) | 0.40, 1.58 | | bupa | 1.01 (0.89, 1.13) | 0.75, 1.27 | | oxbe | 1.01 (0.92, 1.10) | 0.78, 1.21 | | trcs | 1.01 (0.86, 1.13) | 0.69, 1.29 | | dmp | 0.99 (0.75, 1.23) | 0.51, 1.46 | | dmtp | 1.00 (0.79, 1.23) | 0.56, 1.41 | | dep | 0.99 (0.81, 1.19) | 0.63, 1.42 | | detp | 0.99 (0.82, 1.18) | 0.62, 1.41 | | *1*Truncated weights. | | | |

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| Table 9: Weights   |  | Median (IQR) | Range | | --- | --- | --- | | **Characteristic***1* | **N = 976***1* | **N = 976***1* | | cortisol\_production | 1.00 (0.54, 1.40) | 0.14, 1.80 | | cortisol\_metabolism | 1.01 (0.73, 1.26) | 0.44, 1.52 | | cortisone\_production | 1.01 (0.58, 1.39) | 0.19, 1.73 | | cortisone\_metabolism | 0.98 (0.70, 1.29) | 0.43, 1.58 | | X11bHSD | 0.98 (0.70, 1.27) | 0.46, 1.55 | | corticosterone\_production | 0.98 (0.56, 1.39) | 0.16, 1.78 | | *1*Truncated weights. | | | |

## Marginal comparisons

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 10: Average comparisons   |  | hitrtse | | --- | --- | | **OP pesticide metabolites** | | | dmtp | 0.004 (-0.065, 0.072) | | dmp | 0.009 (-0.036, 0.054) | | detp | -0.026 (-0.054, 0.001) | | dep | -0.007 (-0.046, 0.031) | | **Phenols** | | | trcs | 0.018 (-0.028, 0.065) | | prpa | 0.01 (-0.04, 0.061) | | oxbe | 0.019 (-0.018, 0.056) | | mepa | **0.042 (0.013, 0.071)\*** | | etpa | 0.007 (-0.029, 0.043) | | bupa | 0.002 (-0.026, 0.029) | | bpa | 0.012 (-0.013, 0.036) | | **Phthalate metabolites** | | | oxominp | **0.023 (0.003, 0.044)\*** | | ohminp | **0.039 (0.001, 0.076)\*** | | mnbp | 0.008 (-0.033, 0.049) | | mibp | 0.02 (-0.049, 0.089) | | mep | -0.001 (-0.025, 0.023) | | meohp | 0.035 (-0.003, 0.074) | | mehp | **0.036 (0.008, 0.063)\*** | | mehhp | 0.026 (-0.006, 0.059) | | mecpp | 0.016 (-0.014, 0.047) | | mbzp | 0.024 (-0.003, 0.051) | | \*Significant results. | | |

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| Table 11: Average comparisons   |  | 11bhsd | corticosterone production | cortisol metabolism | cortisol production | cortisone metabolism | cortisone production | | --- | --- | --- | --- | --- | --- | --- | | **OP pesticide metabolites** | | | | | | | | dmtp | **0.073 (0.035, 0.111)\*** | 0.085 (-0.007, 0.177) | 0.022 (-0.042, 0.085) | **0.08 (0.023, 0.137)\*** | **0.092 (0.011, 0.173)\*** | **0.138 (0.072, 0.205)\*** | | dmp | **0.067 (0.028, 0.107)\*** | **0.084 (0.003, 0.165)\*** | 0.004 (-0.054, 0.061) | 0.051 (-0.033, 0.134) | **0.085 (0.039, 0.132)\*** | **0.109 (0.044, 0.173)\*** | | detp | 0.034 (-0.018, 0.086) | 0.061 (-0.033, 0.154) | 0.014 (-0.025, 0.054) | -0.002 (-0.093, 0.09) | 0.046 (-0.014, 0.107) | 0.033 (-0.068, 0.134) | | dep | 0.006 (-0.024, 0.035) | **0.167 (0.061, 0.274)\*** | **0.087 (0.044, 0.13)\*** | **0.159 (0.064, 0.253)\*** | **0.075 (0.049, 0.101)\*** | **0.136 (0.055, 0.216)\*** | | **Phenols** | | | | | | | | trcs | -0.005 (-0.07, 0.06) | 0.145 (-0.01, 0.3) | 0.056 (-0.046, 0.159) | 0.094 (-0.04, 0.228) | 0.052 (-0.044, 0.149) | 0.073 (-0.034, 0.179) | | prpa | 0.016 (-0.047, 0.078) | 0.048 (-0.047, 0.143) | 0.031 (-0.008, 0.07) | 0.034 (-0.04, 0.108) | **0.048 (0.015, 0.082)\*** | 0.044 (-0.031, 0.119) | | oxbe | -0.003 (-0.026, 0.021) | 0.005 (-0.081, 0.09) | 0.005 (-0.034, 0.044) | 0.015 (-0.092, 0.122) | 0.011 (-0.039, 0.061) | 0.01 (-0.086, 0.105) | | mepa | **0.055 (0.017, 0.092)\*** | 0.072 (-0.012, 0.156) | 0.004 (-0.039, 0.046) | **0.064 (0.011, 0.118)\*** | **0.068 (0.008, 0.128)\*** | **0.108 (0.031, 0.185)\*** | | etpa | 0.041 (-0.013, 0.094) | **0.186 (0.084, 0.289)\*** | 0.046 (-0.003, 0.095) | **0.151 (0.076, 0.226)\*** | **0.123 (0.079, 0.166)\*** | **0.165 (0.095, 0.234)\*** | | bupa | -0.022 (-0.075, 0.032) | -0.043 (-0.128, 0.043) | -0.01 (-0.067, 0.047) | -0.02 (-0.112, 0.072) | -0.026 (-0.081, 0.03) | -0.038 (-0.119, 0.043) | | bpa | **0.038 (0.017, 0.059)\*** | **0.285 (0.105, 0.466)\*** | **0.137 (0.038, 0.235)\*** | **0.275 (0.105, 0.444)\*** | **0.173 (0.054, 0.292)\*** | **0.264 (0.131, 0.397)\*** | | **Phthalate metabolites** | | | | | | | | oxominp | -0.007 (-0.045, 0.032) | **0.116 (0.051, 0.18)\*** | **0.123 (0.064, 0.181)\*** | **0.094 (0.002, 0.186)\*** | **0.115 (0.065, 0.165)\*** | **0.071 (0.002, 0.14)\*** | | ohminp | 0.017 (-0.02, 0.055) | **0.16 (0.046, 0.274)\*** | **0.151 (0.067, 0.236)\*** | **0.143 (0.016, 0.271)\*** | **0.168 (0.08, 0.256)\*** | **0.136 (0.039, 0.233)\*** | | mnbp | 0.011 (-0.038, 0.059) | 0.145 (-0.05, 0.339) | **0.154 (0.026, 0.281)\*** | 0.112 (-0.083, 0.307) | **0.137 (0.034, 0.24)\*** | 0.103 (-0.046, 0.253) | | mibp | **-0.084 (-0.147, -0.021)\*** | 0.13 (-0.002, 0.261) | **0.103 (0.055, 0.15)\*** | 0.066 (-0.062, 0.193) | 0.038 (-0.019, 0.094) | -0.029 (-0.132, 0.074) | | mep | 0.006 (-0.037, 0.049) | 0.059 (-0.01, 0.128) | 0.025 (-0.048, 0.098) | 0.035 (-0.078, 0.148) | 0.025 (-0.042, 0.091) | 0.034 (-0.079, 0.146) | | meohp | -0.004 (-0.054, 0.046) | 0.169 (-0.015, 0.353) | 0.121 (-0.001, 0.243) | 0.111 (-0.071, 0.292) | 0.07 (-0.044, 0.184) | 0.089 (-0.058, 0.235) | | mehp | **0.036 (0.008, 0.063)\*** | **0.251 (0.116, 0.385)\*** | **0.117 (0.019, 0.214)\*** | **0.2 (0.04, 0.36)\*** | **0.152 (0.022, 0.282)\*** | **0.2 (0.077, 0.323)\*** | | mehhp | 0.021 (-0.015, 0.058) | 0.179 (-0.02, 0.378) | **0.128 (0.001, 0.255)\*** | 0.124 (-0.086, 0.335) | 0.105 (-0.016, 0.225) | 0.125 (-0.046, 0.296) | | mecpp | 0.017 (-0.027, 0.061) | 0.209 (-0.016, 0.433) | **0.127 (0.017, 0.237)\*** | 0.144 (-0.054, 0.342) | 0.097 (-0.028, 0.221) | 0.138 (-0.044, 0.32) | | mbzp | 0.008 (-0.051, 0.068) | 0.097 (-0.112, 0.305) | 0.064 (-0.038, 0.166) | 0.055 (-0.135, 0.244) | 0.071 (-0.031, 0.174) | 0.054 (-0.107, 0.214) | | \*Significant results. | | | | | | | |

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| Table 12: Average comparisons   |  | hitrtse | | --- | --- | | **TMP** | | | X11bHSD | 0.015 (-0.009, 0.04) | | cortisone production | 0.003 (-0.04, 0.046) | | cortisone metabolism | 0.012 (-0.044, 0.068) | | cortisol production | -0.001 (-0.056, 0.054) | | cortisol metabolism | 0.003 (-0.037, 0.042) | | corticosterone production | -0.006 (-0.06, 0.048) | | \*Significant results. | | |

# Other analyses

## Marginal hypothesis

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 13: Hypothesis testing for effect modification   |  | hitrtse | | --- | --- | | **OP pesticide metabolites** | | | dmtp | -0.002 (-0.1, 0.097) | | dmp | 0.027 (-0.031, 0.085) | | detp | -0.024 (-0.12, 0.072) | | dep | -0.006 (-0.033, 0.021) | | **Phenols** | | | trcs | -0.001 (-0.035, 0.033) | | prpa | -0.021 (-0.081, 0.04) | | oxbe | **-0.032 (-0.059, -0.004)\*** | | mepa | -0.032 (-0.095, 0.031) | | etpa | -0.015 (-0.056, 0.026) | | bupa | 0.022 (-0.024, 0.067) | | bpa | -0.038 (-0.095, 0.019) | | **Phthalate metabolites** | | | oxominp | 0.02 (-0.016, 0.055) | | ohminp | -0.053 (-0.112, 0.007) | | mnbp | 0.026 (-0.09, 0.143) | | mibp | 0.025 (-0.089, 0.14) | | mep | **0.092 (0.017, 0.167)\*** | | meohp | -0.005 (-0.086, 0.076) | | mehp | -0.009 (-0.105, 0.086) | | mehhp | -0.017 (-0.113, 0.079) | | mecpp | -0.005 (-0.087, 0.077) | | mbzp | **0.063 (0.002, 0.124)\*** | | \*Significant results. | | |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 14: Hypothesis testing for effect modification   |  | 11bhsd | corticosterone production | cortisol metabolism | cortisol production | cortisone metabolism | cortisone production | | --- | --- | --- | --- | --- | --- | --- | | **OP pesticide metabolites** | | | | | | | | dmtp | -0.022 (-0.146, 0.101) | 0.045 (-0.092, 0.182) | **0.13 (0.03, 0.231)\*** | **0.211 (0.088, 0.333)\*** | 0.102 (-0.049, 0.252) | 0.15 (-0.038, 0.338) | | dmp | 0.037 (-0.08, 0.155) | -0.002 (-0.187, 0.184) | -0.026 (-0.109, 0.057) | 0.033 (-0.063, 0.13) | -0.002 (-0.142, 0.139) | 0.065 (-0.1, 0.23) | | detp | **0.068 (0.008, 0.127)\*** | **0.233 (0.033, 0.433)\*** | 0.045 (-0.077, 0.167) | 0.178 (-0.024, 0.379) | 0.092 (-0.018, 0.202) | **0.214 (0.048, 0.381)\*** | | dep | **-0.037 (-0.073, -0.001)\*** | 0.009 (-0.179, 0.198) | 0.033 (-0.054, 0.121) | 0.102 (-0.123, 0.327) | 0.006 (-0.112, 0.123) | 0.046 (-0.162, 0.254) | | **Phenols** | | | | | | | | trcs | 0.051 (-0.03, 0.132) | 0.041 (-0.113, 0.195) | -0.004 (-0.099, 0.09) | 0.049 (-0.091, 0.19) | 0.039 (-0.033, 0.112) | **0.092 (0.039, 0.144)\*** | | prpa | 0.038 (-0.06, 0.137) | 0.108 (-0.018, 0.233) | -0.064 (-0.136, 0.008) | 0.086 (-0.103, 0.274) | 0.019 (-0.07, 0.109) | 0.109 (-0.008, 0.227) | | oxbe | 0.002 (-0.114, 0.118) | 0.213 (-0.058, 0.484) | 0 (-0.128, 0.127) | 0.078 (-0.149, 0.306) | 0.079 (-0.027, 0.185) | 0.067 (-0.133, 0.267) | | mepa | -0.014 (-0.074, 0.046) | **0.106 (0.002, 0.211)\*** | -0.022 (-0.125, 0.08) | **0.142 (0.012, 0.272)\*** | 0.012 (-0.076, 0.1) | **0.103 (0.016, 0.191)\*** | | etpa | 0.046 (-0.049, 0.141) | 0.133 (-0.011, 0.277) | -0.009 (-0.129, 0.111) | 0.089 (-0.108, 0.287) | 0.023 (-0.139, 0.185) | 0.119 (-0.101, 0.339) | | bupa | **-0.097 (-0.163, -0.031)\*** | 0.111 (-0.019, 0.241) | 0.061 (-0.004, 0.126) | **0.126 (0.041, 0.211)\*** | 0.016 (-0.031, 0.063) | 0.007 (-0.095, 0.109) | | bpa | -0.019 (-0.159, 0.122) | **0.142 (0.027, 0.257)\*** | -0.018 (-0.124, 0.088) | 0.111 (-0.023, 0.245) | -0.023 (-0.146, 0.1) | 0.073 (-0.059, 0.205) | | **Phthalate metabolites** | | | | | | | | oxominp | 0.003 (-0.124, 0.13) | 0.066 (-0.1, 0.232) | 0.017 (-0.117, 0.151) | 0.107 (-0.069, 0.283) | 0.04 (-0.036, 0.117) | 0.091 (-0.019, 0.201) | | ohminp | 0.016 (-0.062, 0.093) | 0.098 (-0.07, 0.267) | 0.017 (-0.086, 0.121) | **0.146 (0.004, 0.288)\*** | 0.031 (-0.071, 0.132) | 0.137 (-0.001, 0.274) | | mnbp | 0.065 (-0.054, 0.184) | 0.092 (-0.188, 0.372) | 0.003 (-0.142, 0.148) | 0.053 (-0.189, 0.295) | 0.063 (-0.009, 0.136) | 0.11 (-0.054, 0.273) | | mibp | -0.018 (-0.153, 0.117) | -0.027 (-0.247, 0.193) | 0.042 (-0.139, 0.223) | 0.047 (-0.189, 0.284) | 0.066 (-0.097, 0.229) | 0.022 (-0.126, 0.169) | | mep | 0.066 (-0.045, 0.176) | -0.124 (-0.289, 0.041) | -0.026 (-0.13, 0.079) | **-0.118 (-0.201, -0.035)\*** | 0.022 (-0.129, 0.172) | -0.029 (-0.185, 0.127) | | meohp | -0.07 (-0.174, 0.034) | 0.1 (-0.086, 0.286) | **0.078 (0.01, 0.146)\*** | **0.1 (0.01, 0.191)\*** | 0.028 (-0.011, 0.067) | 0.014 (-0.066, 0.093) | | mehp | -0.003 (-0.119, 0.113) | **0.144 (0.045, 0.244)\*** | **0.075 (0.028, 0.123)\*** | **0.178 (0.084, 0.272)\*** | 0.055 (-0.078, 0.187) | **0.144 (0.032, 0.255)\*** | | mehhp | -0.066 (-0.161, 0.029) | 0.079 (-0.125, 0.282) | 0.079 (-0.006, 0.164) | 0.105 (-0.008, 0.218) | 0.032 (-0.005, 0.068) | 0.022 (-0.056, 0.101) | | mecpp | -0.043 (-0.148, 0.061) | 0.06 (-0.12, 0.24) | 0.052 (-0.015, 0.118) | **0.072 (0.005, 0.139)\*** | 0.013 (-0.055, 0.08) | 0.017 (-0.078, 0.112) | | mbzp | 0.067 (-0.066, 0.201) | 0.01 (-0.053, 0.073) | **-0.079 (-0.135, -0.023)\*** | 0.003 (-0.115, 0.12) | -0.031 (-0.122, 0.06) | 0.07 (-0.041, 0.181) | | \*Significant results. | | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 15: Hypothesis testing for effect modification   |  | hitrtse | | --- | --- | | **TMP** | | | X11bHSD | -0.102 (-0.239, 0.036) | | cortisone production | **-0.135 (-0.241, -0.028)\*** | | cortisone metabolism | 0.024 (-0.121, 0.17) | | cortisol production | -0.1 (-0.238, 0.039) | | cortisol metabolism | -0.002 (-0.138, 0.134) | | corticosterone production | **-0.13 (-0.253, -0.006)\*** | | \*Significant results. | | |

* Figure titles and legends should be submitted as single paragraph.

# Main results

## Marginal comparisons

|  |
| --- |
| Figure 1: Average comparisons |

|  |
| --- |
| Figure 2: Average comparisons |

|  |
| --- |
| Figure 3: Average comparisons |

* Files for supplementary data must be accompanied by a summary of the file names and types.

# Supplementary information

## Directed Acyclic Graphs

dag {  
age\_child  
biomarker  
breastfeeding  
bw  
characteristics\_child  
chemical [exposure]  
child\_diet  
child\_smoking  
cohort  
creatinine  
envFactors\_visit  
ethnicity\_child  
ethnicity\_mother  
familySEP  
gestational\_age  
maternalAlcohol\_preg  
maternalDiet\_preg  
maternalSEP\_preg  
maternalSmoking\_preg  
neuropsychologicalDiagnosis\_child  
outcome [outcome]  
paternalSEP\_preg  
season\_visit  
sex\_child  
time\_lastMeal  
type\_sample  
age\_child -> biomarker  
age\_child -> characteristics\_child  
age\_child -> creatinine  
age\_child -> outcome  
age\_child -> type\_sample  
biomarker -> outcome  
breastfeeding -> neuropsychologicalDiagnosis\_child  
breastfeeding -> outcome  
bw -> characteristics\_child  
bw -> neuropsychologicalDiagnosis\_child  
characteristics\_child -> biomarker  
characteristics\_child -> chemical  
characteristics\_child -> creatinine  
characteristics\_child -> outcome  
chemical -> biomarker  
chemical -> outcome  
child\_diet -> biomarker  
child\_diet -> characteristics\_child  
child\_diet -> chemical  
child\_diet -> outcome  
child\_smoking -> biomarker  
child\_smoking -> characteristics\_child  
child\_smoking -> creatinine  
child\_smoking -> outcome  
cohort -> biomarker  
cohort -> bw  
cohort -> characteristics\_child  
cohort -> chemical  
cohort -> child\_diet  
cohort -> creatinine  
cohort -> outcome  
creatinine -> biomarker  
creatinine -> chemical  
creatinine -> outcome  
envFactors\_visit -> outcome  
ethnicity\_child -> biomarker  
ethnicity\_child -> bw  
ethnicity\_child -> characteristics\_child  
ethnicity\_child -> chemical  
ethnicity\_child -> child\_diet  
ethnicity\_child -> child\_smoking  
ethnicity\_child -> creatinine  
ethnicity\_child -> neuropsychologicalDiagnosis\_child  
ethnicity\_child -> outcome  
ethnicity\_mother -> biomarker  
ethnicity\_mother -> breastfeeding  
ethnicity\_mother -> bw  
ethnicity\_mother -> characteristics\_child  
ethnicity\_mother -> child\_diet  
ethnicity\_mother -> familySEP  
ethnicity\_mother -> maternalAlcohol\_preg  
ethnicity\_mother -> maternalDiet\_preg  
ethnicity\_mother -> maternalSEP\_preg  
ethnicity\_mother -> maternalSmoking\_preg  
ethnicity\_mother -> neuropsychologicalDiagnosis\_child  
ethnicity\_mother -> outcome  
familySEP -> biomarker  
familySEP -> characteristics\_child  
familySEP -> chemical  
familySEP -> child\_diet  
familySEP -> child\_smoking  
familySEP -> creatinine  
familySEP -> outcome  
gestational\_age -> bw  
gestational\_age -> characteristics\_child  
gestational\_age -> neuropsychologicalDiagnosis\_child  
maternalAlcohol\_preg -> bw  
maternalAlcohol\_preg -> characteristics\_child  
maternalAlcohol\_preg -> neuropsychologicalDiagnosis\_child  
maternalAlcohol\_preg -> outcome  
maternalDiet\_preg -> characteristics\_child  
maternalDiet\_preg -> neuropsychologicalDiagnosis\_child  
maternalDiet\_preg -> outcome  
maternalSEP\_preg -> breastfeeding  
maternalSEP\_preg -> bw  
maternalSEP\_preg -> characteristics\_child  
maternalSEP\_preg -> familySEP  
maternalSEP\_preg -> maternalAlcohol\_preg  
maternalSEP\_preg -> maternalDiet\_preg  
maternalSEP\_preg -> maternalSmoking\_preg  
maternalSEP\_preg -> neuropsychologicalDiagnosis\_child  
maternalSEP\_preg -> outcome  
maternalSmoking\_preg -> bw  
maternalSmoking\_preg -> characteristics\_child  
maternalSmoking\_preg -> neuropsychologicalDiagnosis\_child  
maternalSmoking\_preg -> outcome  
neuropsychologicalDiagnosis\_child -> outcome  
paternalSEP\_preg -> breastfeeding  
paternalSEP\_preg -> bw  
paternalSEP\_preg -> characteristics\_child  
paternalSEP\_preg -> familySEP  
paternalSEP\_preg -> maternalAlcohol\_preg  
paternalSEP\_preg -> maternalDiet\_preg  
paternalSEP\_preg -> maternalSmoking\_preg  
paternalSEP\_preg -> neuropsychologicalDiagnosis\_child  
paternalSEP\_preg -> outcome  
season\_visit -> biomarker  
season\_visit -> chemical  
sex\_child -> biomarker  
sex\_child -> characteristics\_child  
sex\_child -> chemical  
sex\_child -> child\_diet  
sex\_child -> child\_smoking  
sex\_child -> creatinine  
sex\_child -> neuropsychologicalDiagnosis\_child  
sex\_child -> outcome  
sex\_child -> type\_sample  
time\_lastMeal -> biomarker  
time\_lastMeal -> chemical  
type\_sample -> chemical  
type\_sample -> creatinine  
}

dag {  
age\_child  
biomarker [outcome]  
breastfeeding  
bw  
characteristics\_child  
chemical [exposure]  
child\_diet  
child\_smoking  
cohort  
creatinine  
envFactors\_visit  
ethnicity\_child  
ethnicity\_mother  
familySEP  
gestational\_age  
maternalAlcohol\_preg  
maternalDiet\_preg  
maternalSEP\_preg  
maternalSmoking\_preg  
neuropsychologicalDiagnosis\_child  
outcome  
paternalSEP\_preg  
season\_visit  
sex\_child  
time\_lastMeal  
type\_sample  
age\_child -> biomarker  
age\_child -> characteristics\_child  
age\_child -> creatinine  
age\_child -> outcome  
age\_child -> type\_sample  
biomarker -> outcome  
breastfeeding -> neuropsychologicalDiagnosis\_child  
breastfeeding -> outcome  
bw -> characteristics\_child  
bw -> neuropsychologicalDiagnosis\_child  
characteristics\_child -> biomarker  
characteristics\_child -> chemical  
characteristics\_child -> creatinine  
characteristics\_child -> outcome  
chemical -> biomarker  
chemical -> outcome  
child\_diet -> biomarker  
child\_diet -> characteristics\_child  
child\_diet -> chemical  
child\_diet -> outcome  
child\_smoking -> biomarker  
child\_smoking -> characteristics\_child  
child\_smoking -> creatinine  
child\_smoking -> outcome  
cohort -> biomarker  
cohort -> bw  
cohort -> characteristics\_child  
cohort -> chemical  
cohort -> child\_diet  
cohort -> creatinine  
cohort -> outcome  
creatinine -> biomarker  
creatinine -> chemical  
creatinine -> outcome  
envFactors\_visit -> outcome  
ethnicity\_child -> biomarker  
ethnicity\_child -> bw  
ethnicity\_child -> characteristics\_child  
ethnicity\_child -> chemical  
ethnicity\_child -> child\_diet  
ethnicity\_child -> child\_smoking  
ethnicity\_child -> creatinine  
ethnicity\_child -> neuropsychologicalDiagnosis\_child  
ethnicity\_child -> outcome  
ethnicity\_mother -> biomarker  
ethnicity\_mother -> breastfeeding  
ethnicity\_mother -> bw  
ethnicity\_mother -> characteristics\_child  
ethnicity\_mother -> child\_diet  
ethnicity\_mother -> familySEP  
ethnicity\_mother -> maternalAlcohol\_preg  
ethnicity\_mother -> maternalDiet\_preg  
ethnicity\_mother -> maternalSEP\_preg  
ethnicity\_mother -> maternalSmoking\_preg  
ethnicity\_mother -> neuropsychologicalDiagnosis\_child  
ethnicity\_mother -> outcome  
familySEP -> biomarker  
familySEP -> characteristics\_child  
familySEP -> chemical  
familySEP -> child\_diet  
familySEP -> child\_smoking  
familySEP -> creatinine  
familySEP -> outcome  
gestational\_age -> bw  
gestational\_age -> characteristics\_child  
gestational\_age -> neuropsychologicalDiagnosis\_child  
maternalAlcohol\_preg -> bw  
maternalAlcohol\_preg -> characteristics\_child  
maternalAlcohol\_preg -> neuropsychologicalDiagnosis\_child  
maternalAlcohol\_preg -> outcome  
maternalDiet\_preg -> characteristics\_child  
maternalDiet\_preg -> neuropsychologicalDiagnosis\_child  
maternalDiet\_preg -> outcome  
maternalSEP\_preg -> breastfeeding  
maternalSEP\_preg -> bw  
maternalSEP\_preg -> characteristics\_child  
maternalSEP\_preg -> familySEP  
maternalSEP\_preg -> maternalAlcohol\_preg  
maternalSEP\_preg -> maternalDiet\_preg  
maternalSEP\_preg -> maternalSmoking\_preg  
maternalSEP\_preg -> neuropsychologicalDiagnosis\_child  
maternalSEP\_preg -> outcome  
maternalSmoking\_preg -> bw  
maternalSmoking\_preg -> characteristics\_child  
maternalSmoking\_preg -> neuropsychologicalDiagnosis\_child  
maternalSmoking\_preg -> outcome  
neuropsychologicalDiagnosis\_child -> outcome  
paternalSEP\_preg -> breastfeeding  
paternalSEP\_preg -> bw  
paternalSEP\_preg -> characteristics\_child  
paternalSEP\_preg -> familySEP  
paternalSEP\_preg -> maternalAlcohol\_preg  
paternalSEP\_preg -> maternalDiet\_preg  
paternalSEP\_preg -> maternalSmoking\_preg  
paternalSEP\_preg -> neuropsychologicalDiagnosis\_child  
paternalSEP\_preg -> outcome  
season\_visit -> biomarker  
season\_visit -> chemical  
sex\_child -> biomarker  
sex\_child -> characteristics\_child  
sex\_child -> chemical  
sex\_child -> child\_diet  
sex\_child -> child\_smoking  
sex\_child -> creatinine  
sex\_child -> neuropsychologicalDiagnosis\_child  
sex\_child -> outcome  
sex\_child -> type\_sample  
time\_lastMeal -> biomarker  
time\_lastMeal -> chemical  
type\_sample -> chemical  
type\_sample -> creatinine  
}

dag {  
age\_child  
biomarker [exposure]  
breastfeeding  
bw  
characteristics\_child  
chemical  
child\_diet  
child\_smoking  
cohort  
creatinine  
envFactors\_visit  
ethnicity\_child  
ethnicity\_mother  
familySEP  
gestational\_age  
maternalAlcohol\_preg  
maternalDiet\_preg  
maternalSEP\_preg  
maternalSmoking\_preg  
neuropsychologicalDiagnosis\_child  
outcome [outcome]  
paternalSEP\_preg  
season\_visit  
sex\_child  
time\_lastMeal  
type\_sample  
age\_child -> biomarker  
age\_child -> characteristics\_child  
age\_child -> creatinine  
age\_child -> outcome  
age\_child -> type\_sample  
biomarker -> outcome  
breastfeeding -> neuropsychologicalDiagnosis\_child  
breastfeeding -> outcome  
bw -> characteristics\_child  
bw -> neuropsychologicalDiagnosis\_child  
characteristics\_child -> biomarker  
characteristics\_child -> chemical  
characteristics\_child -> creatinine  
characteristics\_child -> outcome  
chemical -> biomarker  
chemical -> outcome  
child\_diet -> biomarker  
child\_diet -> characteristics\_child  
child\_diet -> chemical  
child\_diet -> outcome  
child\_smoking -> biomarker  
child\_smoking -> characteristics\_child  
child\_smoking -> creatinine  
child\_smoking -> outcome  
cohort -> biomarker  
cohort -> bw  
cohort -> characteristics\_child  
cohort -> chemical  
cohort -> child\_diet  
cohort -> creatinine  
cohort -> outcome  
creatinine -> biomarker  
creatinine -> chemical  
creatinine -> outcome  
envFactors\_visit -> outcome  
ethnicity\_child -> biomarker  
ethnicity\_child -> bw  
ethnicity\_child -> characteristics\_child  
ethnicity\_child -> chemical  
ethnicity\_child -> child\_diet  
ethnicity\_child -> child\_smoking  
ethnicity\_child -> creatinine  
ethnicity\_child -> neuropsychologicalDiagnosis\_child  
ethnicity\_child -> outcome  
ethnicity\_mother -> biomarker  
ethnicity\_mother -> breastfeeding  
ethnicity\_mother -> bw  
ethnicity\_mother -> characteristics\_child  
ethnicity\_mother -> child\_diet  
ethnicity\_mother -> familySEP  
ethnicity\_mother -> maternalAlcohol\_preg  
ethnicity\_mother -> maternalDiet\_preg  
ethnicity\_mother -> maternalSEP\_preg  
ethnicity\_mother -> maternalSmoking\_preg  
ethnicity\_mother -> neuropsychologicalDiagnosis\_child  
ethnicity\_mother -> outcome  
familySEP -> biomarker  
familySEP -> characteristics\_child  
familySEP -> chemical  
familySEP -> child\_diet  
familySEP -> child\_smoking  
familySEP -> creatinine  
familySEP -> outcome  
gestational\_age -> bw  
gestational\_age -> characteristics\_child  
gestational\_age -> neuropsychologicalDiagnosis\_child  
maternalAlcohol\_preg -> bw  
maternalAlcohol\_preg -> characteristics\_child  
maternalAlcohol\_preg -> neuropsychologicalDiagnosis\_child  
maternalAlcohol\_preg -> outcome  
maternalDiet\_preg -> characteristics\_child  
maternalDiet\_preg -> neuropsychologicalDiagnosis\_child  
maternalDiet\_preg -> outcome  
maternalSEP\_preg -> breastfeeding  
maternalSEP\_preg -> bw  
maternalSEP\_preg -> characteristics\_child  
maternalSEP\_preg -> familySEP  
maternalSEP\_preg -> maternalAlcohol\_preg  
maternalSEP\_preg -> maternalDiet\_preg  
maternalSEP\_preg -> maternalSmoking\_preg  
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maternalSEP\_preg -> outcome  
maternalSmoking\_preg -> bw  
maternalSmoking\_preg -> characteristics\_child  
maternalSmoking\_preg -> neuropsychologicalDiagnosis\_child  
maternalSmoking\_preg -> outcome  
neuropsychologicalDiagnosis\_child -> outcome  
paternalSEP\_preg -> breastfeeding  
paternalSEP\_preg -> bw  
paternalSEP\_preg -> characteristics\_child  
paternalSEP\_preg -> familySEP  
paternalSEP\_preg -> maternalAlcohol\_preg  
paternalSEP\_preg -> maternalDiet\_preg  
paternalSEP\_preg -> maternalSmoking\_preg  
paternalSEP\_preg -> neuropsychologicalDiagnosis\_child  
paternalSEP\_preg -> outcome  
season\_visit -> biomarker  
season\_visit -> chemical  
sex\_child -> biomarker  
sex\_child -> characteristics\_child  
sex\_child -> chemical  
sex\_child -> child\_diet  
sex\_child -> child\_smoking  
sex\_child -> creatinine  
sex\_child -> neuropsychologicalDiagnosis\_child  
sex\_child -> outcome  
sex\_child -> type\_sample  
time\_lastMeal -> biomarker  
time\_lastMeal -> chemical  
type\_sample -> chemical  
type\_sample -> creatinine  
}

# Supplementary tables

## Descriptive data

### Study populations

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| |  | type | description | coding | labels | remarks | comments | included*1* | | --- | --- | --- | --- | --- | --- | --- | --- | | **age\_child** | | | | | | | | | hs\_age\_years | numerical | Age of the child at clinical assessment |  |  |  | years | TRUE | | **breastfeeding** | | | | | | | | | hs\_bf | categorical | Child breastfeeding | 0,1 | No, Yes |  |  | TRUE | | **characteristics\_child** | | | | | | | | | hs\_c\_height | numerical | Height of the child |  |  |  | m | TRUE | | hs\_c\_weight | numerical | Weight of the child |  |  |  | kg | TRUE | | hs\_head\_circ | numerical | Head circumference of the child |  |  |  | cm | TRUE | | **child\_diet** | | | | | | | | | hs\_fastfood | numerical | Visits a fast food restaurant/take away |  |  |  | Times / week | TRUE | | hs\_org\_food | numerical | Eats organic food |  |  |  | Times / week | TRUE | | hs\_total\_fish | numerical | Food group: fish and seafood (hs\_canfish+hs\_oilyfish+hs\_whfish+hs\_seafood) |  |  |  | Times / week | TRUE | | hs\_total\_fruits | numerical | Food group: fruits (hs\_canfruit+hs\_dryfruit+hs\_freshjuice+hs\_fruits) |  |  |  | Times / week | TRUE | | hs\_total\_veg | numerical | Food group: vegetables (hs\_cookveg+hs\_rawveg) |  |  |  | Times / week | TRUE | | **child\_smoking** | | | | | | | | | hs\_tob | categorical | Which of the following best describes your consumption of tobacco? | 1,2,3,4,5 | Non-smoker and has never smoked, Non-smoker but previously smoked although not daily, Non-smoker but previously smoked daily, Smoker but not daily, Daily smoker |  |  | TRUE | | **cohort** | | | | | | | | | cohort | character | Cohort name | SAB,EDEN,BIB,RHEA,KANC,MOBA | SAB, EDEN, BIB, RHEA, KANC, MOBA |  |  | TRUE | | **creatinine** | | | | | | | | | hs\_creatinine\_cg | numerical | Creatinine in child in pooled sample |  |  | Values below the limit of detection imputed | G / L | TRUE | | **envFactors\_visit** | | | | | | | | | hs\_mood | categorical | Mood of the child in the last few days before assessment | 1,2 | Usual, Not usual |  |  | TRUE | | hs\_rest\_nth | categorical | Child rested the night before assessment | 1,2 | Yes, Not as well as usual |  |  | TRUE | | **ethnicity\_child** | | | | | | | | | h\_ethnicity\_c | character | Which is the ethnicity of the child? | 1,2,3,4,5,6,7 | African, Asian, Caucasian, Native American, Other, Pakistani, White non European |  |  | TRUE | | **ethnicity\_mother** | | | | | | | | | h\_ethnicity\_m | integer | Which is the ethnicity of the mother? | 1,2,3,4,5,6,7 | White European, Pakistani, Asian, African, Other, Native American, White non European |  |  | FALSE | | **familySEP** | | | | | | | | | FAS\_score | numerical | Family Affluence Scale (FAS II) continuous |  |  |  |  | TRUE | | hs\_finance | categorical | How well would you say your family is managing financially these days? | 1,2,3,4,5,6 | Living comfortably, Doing alright, Getting by, Finding it quite difficult, Finding it very difficult, Does not wish to answer |  |  | TRUE | | **maternalAlcohol\_preg** | | | | | | | | | e3\_alcpreg\_g | numerical | Alcool during pregnancy |  |  |  | Glasses / week | FALSE | | **maternalDiet\_preg** | | | | | | | | | h\_cereal\_preg | numerical | Cereal consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_dairy\_preg | numerical | Dairy consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_fastfood\_preg | numerical | Fast food consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_fish\_preg | numerical | Fish consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_fruit\_preg | numerical | Fruit consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_legume\_preg | numerical | Legume consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_meat\_preg | numerical | Meat consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_veg\_preg | numerical | Vegetables consumption during pregnancy |  |  |  | Times / week | FALSE | | **maternalSEP\_preg** | | | | | | | | | e3\_edum | categorical | Maternal education | 0,1,2 | Primary school, Secondary school, University degree or higher |  |  | FALSE | | e3\_marital | categorical | Marital status | 0,1,2 | Living with the father, Living alone, Other situation |  |  | TRUE | | e3\_ses | categorical | Socioeconomic status of the parents | 1,2,3 | Low income, Medium income, High income |  |  | FALSE | | **maternalSmoking\_preg** | | | | | | | | | e3\_asmokyn\_p | categorical | Maternal active smoking during pregnancy | 0,1 | No, Yes |  |  | TRUE | | e3\_psmokanyt | categorical | Maternal passive smoking during pregnancy | 0,1 | No, Yes |  |  | TRUE | | **neuropsychologicalDiagnosis\_child** | | | | | | | | | hs\_neuro\_diag | categorical | Any previous child neuropsychological diagnosis? | 1,2 | No, Yes |  |  | TRUE | | **paternalSEP\_preg** | | | | | | | | | e3\_eduf | categorical | Paternal education | 0,1,2 | Primary school, Secondary school, University degree or higher |  |  | FALSE | | **season\_visit** | | | | | | | | | hs\_date\_neu | date | Date of test |  |  |  | season | TRUE | | **sex\_child** | | | | | | | | | e3\_sex | categorical | Child’s sex | 0,1 | Male, Female |  |  | TRUE | | **time\_lastMeal** | | | | | | | | | hs\_dift\_mealblood\_imp | numerical | Imputed difference between blood time extraction and last meal time |  |  |  |  | TRUE | | *1*Percentage of confounders included in the models: 65.79%. | | | | | | | |   Table S1: Codebook for covariates used in RQ1 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| |  | type | description | coding | labels | remarks | comments | included*1* | | --- | --- | --- | --- | --- | --- | --- | --- | | **age\_child** | | | | | | | | | hs\_age\_years | numerical | Age of the child at clinical assessment |  |  |  | years | TRUE | | **characteristics\_child** | | | | | | | | | hs\_c\_height | numerical | Height of the child |  |  |  | m | TRUE | | hs\_c\_weight | numerical | Weight of the child |  |  |  | kg | TRUE | | hs\_head\_circ | numerical | Head circumference of the child |  |  |  | cm | TRUE | | **child\_diet** | | | | | | | | | hs\_fastfood | numerical | Visits a fast food restaurant/take away |  |  |  | Times / week | TRUE | | hs\_org\_food | numerical | Eats organic food |  |  |  | Times / week | TRUE | | hs\_total\_fish | numerical | Food group: fish and seafood (hs\_canfish+hs\_oilyfish+hs\_whfish+hs\_seafood) |  |  |  | Times / week | TRUE | | hs\_total\_fruits | numerical | Food group: fruits (hs\_canfruit+hs\_dryfruit+hs\_freshjuice+hs\_fruits) |  |  |  | Times / week | TRUE | | hs\_total\_veg | numerical | Food group: vegetables (hs\_cookveg+hs\_rawveg) |  |  |  | Times / week | TRUE | | **child\_smoking** | | | | | | | | | hs\_tob | categorical | Which of the following best describes your consumption of tobacco? | 1,2,3,4,5 | Non-smoker and has never smoked, Non-smoker but previously smoked although not daily, Non-smoker but previously smoked daily, Smoker but not daily, Daily smoker |  |  | TRUE | | **cohort** | | | | | | | | | cohort | character | Cohort name | SAB,EDEN,BIB,RHEA,KANC,MOBA | SAB, EDEN, BIB, RHEA, KANC, MOBA |  |  | TRUE | | **creatinine** | | | | | | | | | creatinine\_to\_helix | numerical | Creatinine in child in night sample |  |  |  | G / L | TRUE | | hs\_creatinine\_cg | numerical | Creatinine in child in pooled sample |  |  | Values below the limit of detection imputed | G / L | TRUE | | **ethnicity\_child** | | | | | | | | | h\_ethnicity\_c | character | Which is the ethnicity of the child? | 1,2,3,4,5,6,7 | African, Asian, Caucasian, Native American, Other, Pakistani, White non European |  |  | TRUE | | **ethnicity\_mother** | | | | | | | | | h\_ethnicity\_m | integer | Which is the ethnicity of the mother? | 1,2,3,4,5,6,7 | White European, Pakistani, Asian, African, Other, Native American, White non European |  |  | FALSE | | **familySEP** | | | | | | | | | FAS\_score | numerical | Family Affluence Scale (FAS II) continuous |  |  |  |  | TRUE | | hs\_finance | categorical | How well would you say your family is managing financially these days? | 1,2,3,4,5,6 | Living comfortably, Doing alright, Getting by, Finding it quite difficult, Finding it very difficult, Does not wish to answer |  |  | TRUE | | **season\_visit** | | | | | | | | | hs\_date\_neu | date | Date of test |  |  |  | season | TRUE | | **sex\_child** | | | | | | | | | e3\_sex | categorical | Child’s sex | 0,1 | Male, Female |  |  | TRUE | | **time\_lastMeal** | | | | | | | | | hs\_dift\_mealblood\_imp | numerical | Imputed difference between blood time extraction and last meal time |  |  |  |  | TRUE | | *1*Percentage of confounders included in the models: 95%. | | | | | | | |   Table S2: Codebook for covariates used in RQ2 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| |  | type | description | coding | labels | remarks | comments | included*1* | | --- | --- | --- | --- | --- | --- | --- | --- | | **age\_child** | | | | | | | | | hs\_age\_years | numerical | Age of the child at clinical assessment |  |  |  | years | TRUE | | **breastfeeding** | | | | | | | | | hs\_bf | categorical | Child breastfeeding | 0,1 | No, Yes |  |  | TRUE | | **characteristics\_child** | | | | | | | | | hs\_c\_height | numerical | Height of the child |  |  |  | m | TRUE | | hs\_c\_weight | numerical | Weight of the child |  |  |  | kg | TRUE | | hs\_head\_circ | numerical | Head circumference of the child |  |  |  | cm | TRUE | | **chemical** | | | | | | | | | hs\_bpa\_c | numerical | Bisphenol A (BPA) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_bupa\_c | numerical | N-Butyl paraben (BUPA) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_dedtp\_cadj | numerical | Diethyl dithiophosphate (DEDTP) adjusted for creatinine |  |  | Values below the limit of detection imputed | microg / g | FALSE | | hs\_dep\_c | numerical | Diethyl phosphate (DEP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_detp\_c | numerical | Diethyl thiophosphate (DETP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_dmdtp\_craw | numerical | Dimethyl dithiophosphate (DMDTP) |  |  | Values below the limit of detection imputed | microg / L | FALSE | | hs\_dmp\_c | numerical | Dimethyl phosphate (DMP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_dmtp\_c | numerical | Dimethyl thiophosphate (DMTP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_etpa\_c | numerical | Ethyl paraben (ETPA) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_mbzp\_c | numerical | Mono benzyl phthalate (MbzP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_mecpp\_c | numerical | Mono-2-ethyl 5-carboxypentyl phthalate (MECPP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_mehhp\_c | numerical | Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_mehp\_c | numerical | Mono-2-ethylhexyl phthalate (MEHP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_meohp\_c | numerical | Mono-2-ethyl-5-oxohexyl phthalate (MEOHP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_mep\_c | numerical | Monoethyl phthalate (MEP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_mepa\_c | numerical | Methyl paraben (MEPA) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_mibp\_c | numerical | Mono-iso-butyl phthalate (MiBP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_mnbp\_c | numerical | Mono-n-butyl phthalate (MnBP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_ohminp\_c | numerical | Mono-4-methyl-7-hydroxyoctyl phthalate (OHMiNP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_oxbe\_c | numerical | Oxybenzone (OXBE) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_oxominp\_c | numerical | Mono-4-methyl-7-oxooctyl phthalate (OXOMiNP) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_prpa\_c | numerical | Propyl paraben (PRPA) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | hs\_trcs\_c | numerical | Triclosan (TRCS) |  |  | Values below the limit of detection imputed | microg / L | TRUE | | **child\_diet** | | | | | | | | | hs\_fastfood | numerical | Visits a fast food restaurant/take away |  |  |  | Times / week | TRUE | | hs\_org\_food | numerical | Eats organic food |  |  |  | Times / week | TRUE | | hs\_total\_fish | numerical | Food group: fish and seafood (hs\_canfish+hs\_oilyfish+hs\_whfish+hs\_seafood) |  |  |  | Times / week | TRUE | | hs\_total\_fruits | numerical | Food group: fruits (hs\_canfruit+hs\_dryfruit+hs\_freshjuice+hs\_fruits) |  |  |  | Times / week | TRUE | | hs\_total\_veg | numerical | Food group: vegetables (hs\_cookveg+hs\_rawveg) |  |  |  | Times / week | TRUE | | **child\_smoking** | | | | | | | | | hs\_tob | categorical | Which of the following best describes your consumption of tobacco? | 1,2,3,4,5 | Non-smoker and has never smoked, Non-smoker but previously smoked although not daily, Non-smoker but previously smoked daily, Smoker but not daily, Daily smoker |  |  | TRUE | | **cohort** | | | | | | | | | cohort | character | Cohort name | SAB,EDEN,BIB,RHEA,KANC,MOBA | SAB, EDEN, BIB, RHEA, KANC, MOBA |  |  | TRUE | | **creatinine** | | | | | | | | | creatinine\_to\_helix | numerical | Creatinine in child in night sample |  |  |  | G / L | TRUE | | **envFactors\_visit** | | | | | | | | | hs\_mood | categorical | Mood of the child in the last few days before assessment | 1,2 | Usual, Not usual |  |  | TRUE | | hs\_rest\_nth | categorical | Child rested the night before assessment | 1,2 | Yes, Not as well as usual |  |  | TRUE | | **ethnicity\_child** | | | | | | | | | h\_ethnicity\_c | character | Which is the ethnicity of the child? | 1,2,3,4,5,6,7 | African, Asian, Caucasian, Native American, Other, Pakistani, White non European |  |  | TRUE | | **ethnicity\_mother** | | | | | | | | | h\_ethnicity\_m | integer | Which is the ethnicity of the mother? | 1,2,3,4,5,6,7 | White European, Pakistani, Asian, African, Other, Native American, White non European |  |  | FALSE | | **familySEP** | | | | | | | | | FAS\_score | numerical | Family Affluence Scale (FAS II) continuous |  |  |  |  | TRUE | | hs\_finance | categorical | How well would you say your family is managing financially these days? | 1,2,3,4,5,6 | Living comfortably, Doing alright, Getting by, Finding it quite difficult, Finding it very difficult, Does not wish to answer |  |  | TRUE | | **maternalAlcohol\_preg** | | | | | | | | | e3\_alcpreg\_g | numerical | Alcool during pregnancy |  |  |  | Glasses / week | FALSE | | **maternalDiet\_preg** | | | | | | | | | h\_cereal\_preg | numerical | Cereal consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_dairy\_preg | numerical | Dairy consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_fastfood\_preg | numerical | Fast food consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_fish\_preg | numerical | Fish consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_fruit\_preg | numerical | Fruit consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_legume\_preg | numerical | Legume consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_meat\_preg | numerical | Meat consumption during pregnancy |  |  |  | Times / week | FALSE | | h\_veg\_preg | numerical | Vegetables consumption during pregnancy |  |  |  | Times / week | FALSE | | **maternalSEP\_preg** | | | | | | | | | e3\_edum | categorical | Maternal education | 0,1,2 | Primary school, Secondary school, University degree or higher |  |  | FALSE | | e3\_marital | categorical | Marital status | 0,1,2 | Living with the father, Living alone, Other situation |  |  | TRUE | | e3\_ses | categorical | Socioeconomic status of the parents | 1,2,3 | Low income, Medium income, High income |  |  | FALSE | | **maternalSmoking\_preg** | | | | | | | | | e3\_asmokyn\_p | categorical | Maternal active smoking during pregnancy | 0,1 | No, Yes |  |  | TRUE | | e3\_psmokanyt | categorical | Maternal passive smoking during pregnancy | 0,1 | No, Yes |  |  | TRUE | | **neuropsychologicalDiagnosis\_child** | | | | | | | | | hs\_neuro\_diag | categorical | Any previous child neuropsychological diagnosis? | 1,2 | No, Yes |  |  | TRUE | | **paternalSEP\_preg** | | | | | | | | | e3\_eduf | categorical | Paternal education | 0,1,2 | Primary school, Secondary school, University degree or higher |  |  | FALSE | | **sex\_child** | | | | | | | | | e3\_sex | categorical | Child’s sex | 0,1 | Male, Female |  |  | TRUE | | *1*Percentage of confounders included in the models: 74.58%. | | | | | | | |   Table S3: Codebook for covariates used in RQ3 |

### Description of chemicals

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| | Compound | Symbol | Variable name | PubChem CID | Parental compound | | --- | --- | --- | --- | --- | | **OP pesticide metabolites** | | | | | | diethyl dithiophosphate | DEDTP | dedtp | 9274 |  | | diethyl phosphate | DEP | dep | 654 |  | | diethyl thiophosphate | DETP | detp | 3683036 |  | | dimethyl dithiophosphate | DMDTP | dmdtp |  |  | | dimethyl phosphate | DMP | dmp | 13134 |  | | dimethyl thiophosphate | DMTP | dmtp | 168140 |  | | **Phenols** | | | | | | bisphenol A | BPA | bpa | 6623 |  | | ethyl-paraben | ETPA | etpa | 8434 |  | | methyl-paraben | MEPA | mepa | 7456 |  | | n‑butyl‑paraben | BUPA | bupa | 7184 |  | | oxybenzone | OXBE | oxbe | 4632 |  | | propyl-paraben | PRPA | prpa | 7175 |  | | triclosan | TRCS | trcs | 5564 |  | | **Phthalate metabolites** | | | | | | mono benzyl phthalate | MBzP | mbzp | 31736 | BzBP | | mono‑2‑ethyl 5‑carboxypentyl phthalate | MECPP | mecpp | 148386 | DEHP | | mono‑2‑ethyl‑5‑hydroxyhexyl phthalate | MEHHP | mehhp | 170295 | DEHP | | mono‑2‑ethyl‑5‑oxohexyl phthalate | MEOHP | meohp | 119096 | DEHP | | mono‑2‑ethylhexyl phthalate | MEHP | mehp | 21924291 | DEHP | | mono‑4‑methyl‑7‑hydroxyoctyl phthalate | oh-MiNP | ohminp | 102401880 |  | | mono‑4‑methyl‑7‑oxooctyl phthalate | oxo-MiNP | oxominp | 102401881 |  | | mono‑iso‑butyl phthalate | MiBP | mibp | 92272 | DiBP | | mono‑n‑butyl phthalate | MnBP | mnbp | 8575 |  | | monoethyl phthalate | MEP | mep | 75318 | DEP |   Table S4: Information about non-persistent EDCs |

### Description of metabolites

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Metabolite | Symbol | HMDB ID*1* | CAS number*2* | | --- | --- | --- | --- | | **Glucocorticosteroid** | | | | | Cortisol | F | HMDB0000063 | 50-23-7 | | Cortisone | E | HMDB0002802 | 53-06-5 | | Corticosterone | B | HMDB0001547 | 50-22-6 | | 11-dehydrocorticosterone | A | HMDB0004029 | 72-23-1 | | **Glucocorticosteroid metabolite** | | | | | 20α-dihydrocortisol | 20aDHF | NA | NA | | 20β-dihydrocortisol | 20bDHF | NA | NA | | 5β-dihydrocortisol | 5bDHF | HMDB0003259 | 1482-50-4 | | 5α-tetrahydrocortisol | 5aTHF | HMDB0000526 | 302-91-0 | | 5β-tetrahydrocortisol | 5bTHF | HMDB0000949 | 1953-02-01 | | 5α,20α-cortol | 5a20acortol | HMDB0003180 | 516-38-1 | | 5α,20β-cortol | 5a20bcortol | HMDB0005821 | 667-65-2 | | 5β,20α-cortol | 5b20acortol | HMDB0003180 | 516-38-1 | | 5β,20β-cortol | 5b20bcortol | HMDB0005821 | 667-65-2 | | 6β-hydroxycortisol | 6OHF | HMDB0247074 |  | | 11β-hydroxyandrosterone | 11OHAndros | HMDB0002984 | 57-61-4 | | 20α-dihydrocortisone | 20aDHE | NA | NA | | 20β-dihydrocortisone | 20bDHE | NA | NA | | 5α-tetrahydrocortisone | 5aTHE | NA | NA | | 5β-tetrahydrocortisone | 5bTHE | NA | NA | | 5β,20α-cortolone | 5b20acortolone | HMDB0003128 | 516-42-7 | | 5β,20β-cortolone | 5b20bcortolone | NA | NA | | 6β-hydroxycortisone | 6OHE | NA | NA | | 5α-tetrahydrocorticosterone | 5aTHB | HMDB0000449 | 600-63-5 | | 5β-tetrahydrocorticosterone | 5bTHB | HMDB0000268 | 68-42-8 | | 17-deoxycortolone | 17-DO-cortolone | NA | NA | | **Glucocorticosteroid precursor** | | | | | Deoxycorticosterone | DOC | HMDB0000016 | 64-85-7 | | Cortexolone | S | HMDB0000015 | 152-58-9 | | 17-hydroxyprogesterone | 17OHP | HMDB0000374 | 68-96-2 | | **Glucocorticosteroid precursor metabolite** | | | | | Tetrahydrocortexolone | THS | HMDB0005972 | 68-60-0 | | Pregnantriol | PT | NA | 1098-45-9 | | 17-hydroxypregnanolone | 17HP | HMDB0000363 | 387-79-1 | | **Androgen** | | | | | Testosterone | T | HMDB0000234 | 58-22-0 | | Androsternedione | AED | HMDB0000053 | 63-05-8 | | **Androgen metabolite** | | | | | Androsterone | Andros | HMDB0000031 | 53-41-8 | | Etiocholanolone | Etio | HMDB0000490 | 53-42-9 | | *1*Human Metabolome Database | | | | | *2*Chemical Abstracts Service | | | |   Table S5: Information about metabolites |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | metabolite | lloq*1* | | --- | --- | | 11OHAndros | 2.00 | | 17DOcortolone | 0.50 | | 17HP | 2.00 | | 20aDHE | 0.50 | | 20aDHF | 0.25 | | 20bDHE | 0.50 | | 20bDHF | 0.50 | | 5a20acortol | 2.50 | | 5a20bcortol | 2.50 | | 5aTHB | 0.50 | | 5aTHE | 0.50 | | 5aTHF | 5.00 | | 5b20acortol | 2.50 | | 5b20acortolone | 5.00 | | 5b20bcortol | 2.50 | | 5b20bcortolone | 5.00 | | 5bDHF | 0.10 | | 5bDHS | 0.10 | | 5bTHB | 0.50 | | 5bTHE | 5.00 | | 5bTHF | 0.50 | | 5bTHS | 0.50 | | 6OHE | 0.50 | | 6OHF | 0.50 | | A | 0.10 | | AED | 0.10 | | Andros | 0.50 | | E | 0.50 | | Etio | 0.50 | | F | 0.25 | | PT | 2.00 | | S | 0.10 | | T | 0.10 | | *1*Lower limit of quantification expressed in nanograms per millilitre. | |   Table S6: Lower limits of quantification for the corticosteroids |

## Other results

### Balancing weights for effect modification

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  | Median (IQR) | | Range | | | --- | --- | --- | --- | --- | | **Characteristic***1* | **females**, N = 587*1* | **males**, N = 710*1* | **females**, N = 587*1* | **males**, N = 710*1* | | mep | 0.96 (0.67, 1.26) | 0.93 (0.61, 1.30) | 0.31, 1.67 | 0.31, 1.67 | | mibp | 0.93 (0.51, 1.39) | 0.96 (0.52, 1.40) | 0.16, 1.85 | 0.16, 1.85 | | mnbp | 1.00 (0.62, 1.33) | 0.98 (0.59, 1.35) | 0.28, 1.68 | 0.28, 1.68 | | mbzp | 1.00 (0.71, 1.27) | 0.99 (0.69, 1.28) | 0.40, 1.57 | 0.40, 1.57 | | mehp | 1.02 (0.69, 1.27) | 0.98 (0.62, 1.32) | 0.33, 1.62 | 0.33, 1.62 | | mehhp | 1.01 (0.60, 1.29) | 0.95 (0.55, 1.36) | 0.26, 1.72 | 0.26, 1.72 | | meohp | 1.00 (0.63, 1.29) | 0.95 (0.53, 1.41) | 0.23, 1.74 | 0.23, 1.74 | | mecpp | 1.00 (0.59, 1.33) | 0.95 (0.50, 1.38) | 0.23, 1.76 | 0.23, 1.76 | | ohminp | 1.02 (0.78, 1.22) | 1.00 (0.76, 1.23) | 0.51, 1.46 | 0.51, 1.46 | | oxominp | 1.02 (0.84, 1.17) | 1.01 (0.77, 1.21) | 0.58, 1.39 | 0.58, 1.39 | | mepa | 1.02 (0.89, 1.15) | 1.02 (0.94, 1.11) | 0.76, 1.23 | 0.76, 1.23 | | etpa | 1.02 (0.96, 1.08) | 1.01 (0.97, 1.06) | 0.91, 1.12 | 0.91, 1.12 | | prpa | 1.02 (0.92, 1.13) | 1.02 (0.95, 1.10) | 0.82, 1.21 | 0.82, 1.21 | | bpa | 1.02 (0.73, 1.28) | 1.02 (0.74, 1.25) | 0.41, 1.50 | 0.41, 1.50 | | bupa | 1.02 (0.95, 1.10) | 1.01 (0.81, 1.19) | 0.67, 1.29 | 0.67, 1.29 | | oxbe | 1.03 (0.92, 1.12) | 1.02 (0.94, 1.09) | 0.80, 1.19 | 0.80, 1.19 | | trcs | 1.03 (0.92, 1.13) | 1.01 (0.89, 1.12) | 0.74, 1.25 | 0.74, 1.25 | | dmp | 0.99 (0.74, 1.25) | 1.00 (0.74, 1.25) | 0.53, 1.46 | 0.53, 1.46 | | dmtp | 1.00 (0.79, 1.22) | 1.01 (0.82, 1.20) | 0.58, 1.38 | 0.58, 1.38 | | dep | 1.01 (0.82, 1.19) | 1.02 (0.84, 1.17) | 0.64, 1.36 | 0.64, 1.36 | | detp | 1.00 (0.77, 1.22) | 1.01 (0.82, 1.20) | 0.57, 1.39 | 0.57, 1.39 | | *1*Truncated weights. | | | | |   Table S7: Weights |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  | Median (IQR) | | Range | | | --- | --- | --- | --- | --- | | **Characteristic***1* | **females**, N = 434*1* | **males**, N = 542*1* | **females**, N = 434*1* | **males**, N = 542*1* | | mep | 0.99 (0.70, 1.24) | 0.95 (0.55, 1.30) | 0.31, 1.68 | 0.31, 1.68 | | mibp | 0.92 (0.46, 1.40) | 0.92 (0.54, 1.38) | 0.15, 1.85 | 0.15, 1.85 | | mnbp | 0.97 (0.51, 1.40) | 0.98 (0.56, 1.33) | 0.21, 1.78 | 0.21, 1.78 | | mbzp | 1.00 (0.70, 1.26) | 0.98 (0.66, 1.31) | 0.38, 1.58 | 0.38, 1.58 | | mehp | 1.01 (0.72, 1.28) | 0.99 (0.61, 1.34) | 0.37, 1.57 | 0.37, 1.57 | | mehhp | 1.02 (0.65, 1.31) | 1.00 (0.59, 1.34) | 0.30, 1.62 | 0.30, 1.62 | | meohp | 1.00 (0.62, 1.31) | 1.01 (0.50, 1.41) | 0.24, 1.68 | 0.24, 1.68 | | mecpp | 0.98 (0.62, 1.32) | 0.99 (0.53, 1.39) | 0.29, 1.67 | 0.29, 1.67 | | ohminp | 1.00 (0.73, 1.26) | 1.00 (0.77, 1.24) | 0.49, 1.45 | 0.49, 1.45 | | oxominp | 1.03 (0.73, 1.27) | 1.02 (0.77, 1.23) | 0.48, 1.45 | 0.48, 1.45 | | mepa | 1.01 (0.88, 1.17) | 1.03 (0.94, 1.11) | 0.73, 1.26 | 0.73, 1.26 | | etpa | 1.04 (0.92, 1.12) | 1.02 (0.92, 1.12) | 0.78, 1.22 | 0.78, 1.22 | | prpa | 1.03 (0.87, 1.16) | 1.02 (0.96, 1.10) | 0.74, 1.24 | 0.74, 1.24 | | bpa | 1.00 (0.71, 1.28) | 1.01 (0.75, 1.24) | 0.44, 1.52 | 0.44, 1.52 | | bupa | 1.02 (0.95, 1.11) | 1.01 (0.80, 1.19) | 0.64, 1.30 | 0.64, 1.30 | | oxbe | 1.03 (0.86, 1.16) | 1.02 (0.95, 1.09) | 0.76, 1.23 | 0.76, 1.23 | | trcs | 1.03 (0.92, 1.13) | 1.01 (0.88, 1.14) | 0.73, 1.25 | 0.73, 1.25 | | dmp | 0.98 (0.76, 1.23) | 1.01 (0.75, 1.21) | 0.57, 1.45 | 0.57, 1.45 | | dmtp | 1.03 (0.78, 1.22) | 1.01 (0.79, 1.23) | 0.56, 1.40 | 0.56, 1.40 | | dep | 1.01 (0.85, 1.16) | 1.00 (0.84, 1.19) | 0.67, 1.36 | 0.67, 1.36 | | detp | 1.00 (0.77, 1.23) | 1.00 (0.86, 1.17) | 0.57, 1.40 | 0.57, 1.40 | | *1*Truncated weights. | | | | |   Table S8: Weights |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  | Median (IQR) | | Range | | | --- | --- | --- | --- | --- | | **Characteristic***1* | **females**, N = 434*1* | **males**, N = 542*1* | **females**, N = 434*1* | **males**, N = 542*1* | | cortisol\_production | 0.98 (0.57, 1.40) | 1.02 (0.59, 1.34) | 0.23, 1.71 | 0.23, 1.71 | | cortisol\_metabolism | 1.01 (0.68, 1.27) | 1.01 (0.69, 1.28) | 0.44, 1.54 | 0.44, 1.54 | | cortisone\_production | 1.00 (0.60, 1.40) | 1.00 (0.60, 1.38) | 0.27, 1.69 | 0.27, 1.69 | | cortisone\_metabolism | 0.99 (0.70, 1.28) | 0.98 (0.68, 1.27) | 0.40, 1.59 | 0.40, 1.59 | | X11bHSD | 1.00 (0.65, 1.30) | 0.98 (0.71, 1.29) | 0.42, 1.57 | 0.42, 1.57 | | corticosterone\_production | 1.01 (0.61, 1.39) | 1.03 (0.56, 1.37) | 0.22, 1.70 | 0.22, 1.70 | | *1*Truncated weights. | | | | |   Table S9: Weights |

# Supplementary figures

## Descriptive data

### Description of chemicals

|  |
| --- |
| Figure S1: Description of chemicals |

### Description of metabolites

|  |
| --- |
| Figure S2: Description of metabolites |

## Main results

### Average dose-response functions for significant results

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| --- |
| Figure S3: Average dose-response functions for RQ3 |

## Other results

### Marginal comparisons for effect modification

|  |
| --- |
| Figure S4: Average comparisons for effect modification |

|  |
| --- |
| Figure S5: Average comparisons for effect modification |

|  |
| --- |
| Figure S6: Average comparisons for effect modification |