Childhood exposure to non-persistent endocrine disruptors, glucocorticosteroids, and attentional function: A study based on the parametric g-formula

Abstract

Evidence suggests that endocrine disrupting chemicals (EDCs) may perturb the hypothalamic-pituitary-adrenocortical (HPA) axis, which has a major role in brain development. We aimed to evaluate the effects of childhood exposure to organophosphate pesticides, phenols, and phthalate metabolites, on urinary glucocorticosteroids and inattention in children using data from the Human Early-Life Exposome (HELIX) cohort. We used the parametric g-formula to estimate effects between EDCs, glucocorticosteroids, and hit reaction time standard error (HRT-SE), a measure of inattention from the Attention Network Test (ANT), and tested for possible effect modification by sex. We observed a positive marginal contrast (MC) for exposure increases from the 10th to the 90th percentile for methyl-paraben (MC: 0.042 and 95% confidence interval (CI): (0.013, 0.071)), and the phthalate metabolites oxo-MiNP (MC: 0.023 and 95% CI: (0.003, 0.044)), oh-MiNP (MC: 0.039 and 95% CI: (0.001, 0.076)), and MEHP (MC: 0.036 and 95% CI: (0.008, 0.063)), on HRT-SE, indicating lower attention. Several EDCs were also associated with a positive MC for cortisone, cortisol, and corticosterone production. Increased levels of the glucocorticosteroids had no effect on HRT-SE, although we found a possible effect modification by sex. Our results suggest that multiple EDCs might interfere with inattention in children and with the homeostasis of the HPA axis.

The prevalence of several neurodevelopmental disorders has increased in the pediatric population (1), and multiple environmental pollutants may play a role in the increased rates of these disorders (2). Multiple endocrine disrupting chemicals (EDCs), ubiquitous chemicals present in many every-day products and diet, are capable of interfering with the endocrine system, and have shown associations with childhood neurodevelopment and behavior (3–17). Although both pregnancy and early infancy 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).

One group of EDCs that may have a deleterious effect on neurodevelopment is the organophosphate pesticides (OP pesticides), although the few studies assessing exposure during childhood and through the use of biomarkers suffered from a series of limitations, including a small sample size (2). Exposure to phthalates and their metabolites during childhood and early adolescence has also been associated with several adverse neurodevelopmental outcomes, but these studies were limited to few phthalate metabolites and small study populations (2). The effects of exposure to bisphenol A (BPA) during childhood on cognitive functions are still unclear (2).

Moreover, little is known about the biological mechanisms of action (2). There is some toxicological evidence, however, that exposure to certain EDCs, specifically phthalates, might interfere with the hypothalamic-pituitary-adrenocortical (HPA) axis and might interact with the glucocorticoid receptor (18–20). The HPA axis, which can be activated by stress, is responsible for the production of glucocorticosteroids. The brain, and its proper functioning, is a potential target, due to the presence of receptors for these hormones (19,21). Glucocorticosteroids are necessary for brain maturation, although their under- or over-production might interfere with its normal development and ultimately lead to long-term impaired functioning (20,21).

Taken together, these results suggest that the negative influence of exposure to certain EDCs on neurodevelopmental outcomes might be mediated, at least partially, by disruption of the HPA axis' homeostasis. In the present study, we thus estimated cross-sectional associations between 1) non-persistent EDCs and attentional function, 2) non-persistent EDCs and glucocorticosteroids, and 3) glucocorticosteroids and attentional function, using the parametric g-formula and marginal contrasts (MCs), in children of a large network of cohorts in Europe.

1 Methods

1.1 Study population and design

The Human Early-Life Exposome (HELIX) project aims to characterize early-life exposures and their potential association with endogenous biomarkers and health outcomes (22). It consists of six existing population-based birth cohort studies across Europe: BiB (Born in Bradford, UK) (23), EDEN (Study of determinants of pre- and postnatal developmental, France) (24), INMA (Environment and Childhood, Spain) (25), KANC (Kaunas Cohort, Lithuania) (26), MoBa (The Norwegian Mother and

Child Cohort Study, Norway) (27), and Rhea (Mother–Child Cohort in Crete, Greece) (28). The HELIX subcohort of 1,301 mother-child pairs was fully characterized for the external and internal exposome, including exposure and omics biomarkers during childhood (29). 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. Ethical permission was obtained from the relevant authorities in the corresponding country.

1.2 Variables

1.2.1 Endocrine disrupting chemicals

Children were assessed between December 2013 and February 2016, and assessments 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 the urine samples 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 S1. Briefly, we analyzed a total of 7 phenols (bisphenol A (BPA), ethyl-paraben (ETPA), methyl-paraben (MEPA), n-butyl-paraben (BUPA), oxybenzone (OXBE), propyl-paraben (PRPA), triclosan (TRCS)), 6 non-specific organophosphate pesticide metabolites (diethyl dithiophosphate (DEDTP), diethyl phosphate (DEP), diethyl thiophosphate (DETP), dimethyl dithiophosphate (DMDTP), dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP)), and 10 phthalate metabolites (mono benzyl phthalate (MBzP), monoethyl phthalate (MEP), mono-2-ethyl 5-carboxypentyl phthalate (MECPP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), mono-4-methyl-7-hydroxyoctyl phthalate (oh-MiNP), mono-4-methyl-7-oxooctyl phthalate (oxo-MiNP), mono-iso-butyl phthalate (MiBP), mono-n-butyl phthalate (MnBP)) originating from 6 distinct phthalate parent compounds. The laboratory protocols for the analysis are described elsewhere (30).

1.2.2 Glucocorticosteroids

Urine samples of the night before the day of the visit were used to measure levels of the glucocorticosteroids. These included glucocorticosteroids, glucocorticosteroid metabolites, glucocorticosteroid precursors, glucocorticosteroid precursor metabolites, androgens, and androgen metabolites. A list of the glucocorticosteroids determined in urine samples and used for the present study is given in Table S2.

To assess the levels of glucocorticosteroids 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 (31,32).

Three additional markers, total cortisol production, total cortisone production, and total corticosterone production, were computed based on the following: cortisol production as the sum of cortisol and its metabolites (20 -dihydrocortisol (20aDHF), 20 -dihydrocortisol (20bDHF), 5 ,20 -cortol (5a20acortol), 5 ,20 -cortol (5a20bcortol), 5 -tetrahydrocortisol (5aTHF), 5 ,20 -cortol (5b20acortol), 5 ,20 -cortol (5b20bcortol), 5 -dihydrocortisol (5bDHF), 5 -tetrahydrocortisol (5bTHF), 6 -hydroxycortisol (6OHF)), cortisone production as the sum of cortisone and its metabolites (20 -dihydrocortisone (20aDHE), 20 -dihydrocortisone (20bDHE), 5 -tetrahydrocortisone (5aTHE), 5 ,20 -cortolone (5b20acortolone), 5 ,20 -cortolone (5b20bcortolone), 5 -tetrahydrocortisone (5bTHE), 6 -hydroxycortisone (6OHE)), and corticosterone production as the sum of 11-dehydrocorticosterone (A), 17-deoxycortolone (17-DO-cortolone), 5 -tetrahydrocorticosterone (5aTHB), 5 -tetrahydrocorticosterone (5bTHB).

1.2.3 Attentional function

Cognitive and motor function outcomes were assessed with standardized, non-linguistic, and culturally blind computer tests, including the Attention Network Test (ANT) (33), which provides a measure of efficiency of attentional function. The tests were administered in a standardized way, and with minimal interference from the field workers. Further information can be found in (29). The outcome of interest for the present study is the hit reaction time standard error (HRT-SE) (34), a measure of response speed consistency throughout the test. A high HRT-SE indicates highly variable reaction times, and is considered a measure of inattentiveness.

1.2.4 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` (35) and `ggdag` (36). The sets of covariates were selected to estimate the total effect of the exposure on the outcome. For effect estimation of the EDCs on glucocorticosteroids and of glucocorticosteroids on HRT-SE, these sets were also sufficient to estimate direct effects. Sample-specific creatinine values were used to adjust for possible dilution effects. 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. Common confounders were cohort, ethnicity, sex, age, height, weight, and head circumference of the child, consumption of fish, fruit, vegetables, organic food, anf fast food, maternal tobacco consumption, family financial situation and affluence scale (FAS). Models for estimating the effects of EDCs on HRT-SE were further adjusted for child breastfeeding, prenatal maternal active and passive smoking, urine creatinine, child mood and rest before assessment, child neuropsychological diagnosis, marital status, season, and fasting time before assessment. Models for estimating the effects of EDCs on glucocorticosteroids were further adjusted for urine creatinine, season, and fasting time before assessment. Models for estimating the effects of glucocorticosteroids on HRT-SE were further

adjusted for child breastfeeding, prenatal maternal active and passive smoking, marital status, EDCs, urine creatinine, child mood and rest before assessment, and child neuropsychological diagnosis. The adjustment sets are provided in the Supplementary Material as text files compatible with DAGitty. Codebooks for the used covariates, by research question, are provided in Supplementary Tables Table S3, Table S4, Table S5.

1.3 Statistical methods

1.3.1 Data pre-processing

Concentrations of the glucocorticosteroids 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 LOQ, for those metabolites that had less than 30% of missings within each cohort and 20% of missings overall. Information about the lower limit of quantification (LLOQ) for the glucocorticosteroids is provided in Table S6. The remaining missing values were imputed using kNN from the `VIM` R package (37), 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 (38). Values of total cortisol, cortisone, and corticosterone production were expressed in nanograms per millilitre (ng/ml).

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 (39). Information about the lower limits of detection can be found in (30). Chemicals with more than 70% of observations below the LOD were excluded from the present study. Remaining missing values were imputed similarly using kNN. Values of the chemicals were expressed in μgrams per litre (μg/L).

Missing values in the clinical outcome were imputed similarly using kNN. We natural log-transformed these 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 (g/L).

1.3.2 Estimation of balancing weights

To reduce the effect of measured confounders on the exposure-outcome association, stabilized balancing weights were estimated using the energy method available in the `WeightIt` R package (40). This method estimates weights by minimizing an energy statistic related to covariate balance (41), 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 (42). Specifically, we used *Love* plots to visualize covariate balance before and after adjusting.

1.3.3 G-computation

We estimated MCs 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 ($\mathbb{E}\left[Y^{d_1}\right] - \mathbb{E}\left[Y^{d_2}\right]$). 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).

To estimate the MCs, we used the `avg_comparisons` function from the `marginaleffects` R package (43). The two counterfactual datasets were obtained by setting the exposures levels to 90th percentile (d_1) and the 10th percentile (d_2), for each cohort separately. The MCs 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 (44,45). For each outcome, we report the results as differences between MCs.

The R code to reproduce analyses and results is available online (https://github.com/lorenzoFabbri/paper-helixSC-neuro).

1.3.4 Effect-modification analysis

We further estimated separate MCs 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 MCs were aggregated separately for each level of sex.

2 Results

Table 1 and Table S7 provide descriptive statistics for the outcome and covariates for the HELIX subcohort and for each cohort, respectively. Of the 1,301 children of the HELIX subcohort, 1,297 had measurements of the non-persistent EDCs. Measurements of the glucocorticosteroids were available for 1,004 children, of which 980 were matched to the HELIX subcohort. Measurements of both non-persistent EDCs and glucocorticosteroids were available for 976 children of the subcohort. A flowchart describing the sample size for each research question is presented in Figure S1. The sample consisted of 55% males. The median HRT-SE was 300 ms (interquartile range (IQR), 231-368), with lower median values for EDEN, MOBA, and INMA, 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%), and the largest minority were of Pakistani origin (6.2%).

Levels of unprocessed non-persistent EDCs, after imputation of values below the LOD, and glucocorticosteroids, are presented in Table 2, Table 3, and Table S8. Supplementary Figures Figure S2 and Figure S3 provide information on the measurement classification of the EDCs and glucocorticosteroids by cohort, respectively.

The effective sample sizes before and after balancing weights estimation are presented in Supplementary Tables Table S9, Table S10, Table S11, while basic summary statistics of the estimated balancing weights are presented in Supplementary Tables Table S12, Table S13, Table S14. As expected, the median value of the weights for each exposure was close to 1.00.

Figure 1 presents the forest plot for the MCs on the logarithmic scale of the non-persistent EDCs on HRT-SE. For most EDCs, a cohort-specific increase in the levels of the exposures from the 10th to the 90th percentiles was associated with a positive MC, indicating an increase in the values of HRT-SE and thus lower attention. Most of the confidence intervals (CIs) included the null effect, though. Significant effects were observed for the paraben MEPA (MC: 0.042 and 95% CI: (0.013, 0.071)), and the phthalate metabolites oxo-MiNP (MC: 0.023 and 95% CI: (0.003, 0.044)), oh-MiNP (MC: 0.039 and 95% CI: (0.001, 0.076)), and MEHP (MC: 0.036 and 95% CI: (0.008, 0.063)). The organophosphate pesticide (OP pesticide) DETP was negatively associated with HRT-SE (MC: -0.026 and 95% CI: (-0.054, 0.001)).

Figure 2 presents the forest plot for the MCs on the logarithmic scale of the non-persistent EDCs on total cortisone, cortisol, and corticosterone production. For most

EDCs, a cohort-specific increase in the levels of the exposures from the 10th to the 90th percentiles was associated with a positive MC, indicating an increase in the total production of these metabolites. Exceptions were BUPA, which was associated with negative MCs for all three outcomes, and MiBP, which was associated with a negative MC for total cortisone production only. The majority of the effects for the phenols and phthalate metabolites included the null. The phenol BPA showed the largest MCs across all three outcomes (cortisone production, MC: 0.263 and 95% CI: (0.131, 0.394); cortisol production, MC: 0.274 and 95% CI: (0.107, 0.441); corticosterone production, MC: 0.285 and 95% CI: (0.106, 0.464)).

Figure 3 presents the forest plot for the MCs on the logarithmic scale of the glucocorticosteroids on HRT-SE. All MCs included the null, with no clear indication of directionality of the effect.

2.1 Effect modification by sex

Basic summary statistics of the estimated balancing weights for effect modification are presented in Supplementary Tables Table S15, Table S16, Table S17. As expected, the median value of the weights for each exposure was close to 1.00.

Table 4 presents the results of the difference between estimates of the MCs on the logarithmic scale for females and males, for the EDCs on the glucocorticosteroids and HRT-SE. For HRT-SE, significant differences were present for the phenol OXBE (MC: 0.032 and 95% CI: (0.004, 0.061)) and the phthalate metabolites MEP (MC: -0.053 and 95% CI: (-0.138, 0.033)) and MbZP (MC: -0.066 and 95% CI: (-0.126, -0.007)). For the glucocorticosteroids, significant differences were present across all three classes of EDCs and for all outcomes. The largest differences were attributable to the OP pesticides DMTP (cortisol production, MC: -0.21 and 95% CI: (-0.326, -0.094)) and DETP (corticosterone production, (MC: -0.16 and 95% CI: (-0.332, 0.011)); cortisone production, (MC: -0.097 and 95% CI: (-0.269, 0.076))). The forest plots of the individual MCs are presented in Supplementary Figures Figure S4 and Figure S5.

Table 5 presents the results of the difference between estimates of the MCs on the logarithmic scale for females and males, for the glucocorticosteroids on HRT-SE. Significant differences were present for cortisone production (MC: 0.14 and 95% CI: (0.019, 0.261)) and corticosterone production (MC: 0.126 and 95% CI: (0.009, 0.243)). Furthermore, for all exposures, the MCs had opposite sign (positive for males and negative for females). The forest plot of the individual MCs is presented in Figure S6.

3 Discussion

The impact of exposure to EDCs on human health has attracted considerable research interest. While research in this area has mainly investigated the effects of prenatal exposure on child neurodevelopment (2), little is still known about childhood exposure. In this study, consisting of 1,297 children from 6 European birth cohorts, we observed that short-term childhood exposure to certain non-persistent EDCs was associated with

attentional function (MEPA, MEHP, oh-MiNP, and oxo-MiNP), and with total production of cortisol, cortisone, and corticosterone (DEP, DMP, DMTP, BPA, ETPA, MEPA, MEHP, oh-MiNP, and oxo-MiNP). Increased production of these glucocorticosteroids did not seem to affect attentional function. Some of these effects differed for females and males, including significant differences for the effects of increased production of cortisone and corticosterone on HRT-SE. Specifically, an increased production of these glucocorticosteroids was associated with lower values of HRT-SE for females, and higher values for males. Taken together, these results suggest that these non-persistent EDCs might be responsible for perturbations of the HPA axis' homeostasis, and that higher levels of these glucocorticosteroids might interfere with different functions of attention in a sex-specific manner.

To the best of our knowledge, no other study has investigated the effects of childhood exposure to multiple classes of non-persistent EDCs in relation to attentional function. More generally, the literature on non-persistent EDCs and neurodevelopment in children has mostly focused on OP pesticides (3,4,6,8), phthalate metabolites (5,9,10,15,17,46–48), and BPA (7,13,14). González-Alzaga et al. and Cartier et al. evaluated cross-sectional associations between dialkylphosphate (DAP) metabolites and subtests of the Wechsler Intelligence Scale for Children (49) in European children with ages between 6 and 11 years. Higher levels of DAP metabolites (DMP, DMTP, DMDTP, DEP, DETP, and DEDTP) were associated with lower scores of intelligence quotient (IQ) and verbal comprehension, especially in boys (4), while higher levels of diethylphosphate metabolites (DEP, DETP, DEDTP) were associated with lower working memory scores (6). There is also preliminary evidence of a possible association between exposure to certain OP pesticides and Attention-Deficit / Hyperactivity Disorder (ADHD) in children (3,8). Specifically, Bouchard et al. found evidence of a cross-sectional association between dimethyl alkylphosphate metabolites (DMP, DMTP, and DMDTP) and ADHD in children aged 8 to 15 years from National Health and Nutrition Examination Survey (NHANES), while Yu et al. found a dose-response relationship between DMP and ADHD in Taiwanese children aged 4 to 15 years. Preliminary evidence is also available for several phthalate metabolites in relation to cognitive development in childhood. Higher levels of di(2-ethylhexyl) phthalate metabolites (including MEHP, MEHHP, and MEOHP) were associated with lower intelligence scores in children aged 2 to 12 years (5), lower scores of IQ and verbal intelligence, more omission errors (a measure of inattention), and higher scores of response time variability (a measure of sustained attention) in 6-year old Korean children (10), poorer fine motor skills in preadolescent boys (47), and lower intelligence scores in 7-year old children (17). Further associations were found for MEOHP with lower scores of IQ (5) and verbal intelligence in Taiwanese children aged 6 to 12 years (9), and for dibutyl phthalate metabolites (MnBP and MiBP) with impaired verbal intelligence (9). There is further preliminary evidence that associations between certain phthalate metabolites and cognitive abilities vary by timing of exposure assessment (46). Among phenols, some studies provide preliminary evidence of an association between BPA and ADHD in children aged 8 to 15 years (7) and in a case-control study of children aged 6 to 12 years (13), especially in boys. Except for working memory, there does not seem to be evidence of an association

between BPA and cognitive abilities in Spanish boys aged 9 to 11 years (14). Few studies have looked into different classes of non-persistent EDCs. Shoaff et al., for instance, investigated cross-sectional associations between multiple EDCs and ADHD-related behaviors in 15-year old adolescents, finding a higher risk of ADHD-related behavior problems with higher levels of antiandrogenic phthalate metabolites (MEHP, MEHHP, MEOHP, MECPP, MnBP, MiBP, MBzP, monohydroxyisobutyl phthalate (MHiBP), monocarboxyoctyl phthalate (MCOP), monoisononyl phthalate (MNP), and monohydroxybutyl phthalate (MHBP)), especially in boys (15).

We are not aware of other epidemiological studies investigating childhood exposure to phthalates metabolites, phenols, and OP pesticides, in relation to urinary glucocorticosteroid levels in childhood. Prior epidemiological research provides preliminary evidence for an association between certain non-persistent EDCs with higher levels of glucocorticoids (18–20). Repeated measures up to 15 months of age of the phthalate metabolites MEHHP, MEOHP, MiBP, and MnBP showed positive associations with free cortisol in Korean children, with no effect modification by sex (18). In a cohort of Chinese pregnant women, phthalate metabolites were measured at 14, 24, and 36 weeks of gestation, and the glucocorticoids cortisol and cortisone were measured in cord blood. Third-trimester levels of MEHP were positively associated with cortisol, while MECPP and MEOHP were negatively associated with cortisone (19). Time- and chemical-dependent sex differences were also found: during the third trimester, MEHHP and MEOHP were positively associated with cortisol in females, while negatively associated in males (19). In a longitudinal study, a mixture of several phthalate metabolites, driven by MEP, MiBP, and MBzP, measured in childhood, showed a positive association with hair cortisol measured at 12 years of age (20). While in the present study we did find positive MCs between some phthalate metabolites (MEHP, oh-MiNP, and oxo-MiNP) and the glucocorticosteroids, there are important differences with the previous studies. First, exposure assessment was performed during gestation (19) or the first 15 months of life (18), not during childhood. Second, the glucocorticosteroids were measured in other matrices, specifically in cord blood (19) or hair (20). Finally, (20) investigated mixture effects. Contrary to these studies (18,20), we did find effect modification by sex.

Adding to these epidemiological studies, previous toxicological research provide evidence for the inhibition by phthalates of human 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) activity, responsible for the conversion of active cortisol into inactive cortisone (50,51). There is also *in silico* evidence suggesting that BPA, a phenol, and Triazophos (TAP), a organophosphorus insecticide, can bind to the human glucocorticoid receptor (52,53).

We are also not aware of prior epidemiological studies specifically investigating the effects of elevated levels of glucocorticosteroids in relation to attentional function, although there is evidence that under- or over-production of glucocorticosteroids interfere with the normal development of the brain (21). While we did find sex-specific evidence of an effect, their clinical relevance is questionable.

Our findings should be interpreted in light of the following limitations and strengths.

Limitations include the cross-sectional design of the present study. Importantly, the non-persistent EDCs were measured in a pool of night and morning urine samples before the clinical visit, to represent exposure over the previous day, whereas the glucocorticosteroids were measured in the night urine sample. Although we included a wide range of confounders there is the possibility, as with other observational studies, of residual confounding, which might lead to a bias away from the null. Some of the confounders indicated in the adjustment sets had to be removed due to large fractions of missing values. There is further the possibility of misspecification of the outcome model, although we included a spline of the exposure to relax some of the linearity assumptions. The use of more data-adaptive learners was excluded due to the relatively small sample size. We finally acknowledge the possibility that some of chemicals might not act independently (mixture effect). Further research is thus warranted.

Strengths of the present study include the use of pooled urine samples for chemical assessment to obtain more representative long-term exposures, since it is known that these specific EDCs have very short half-lives (54,55). We decided to model both the *treatment* mechanisms, for the estimation of balancing weights, and the outcomes, with traditional covariates adjustment, to try to obtain *doubly robust* effect estimates. Finally, we decided not to interpret our results by focusing on the estimated coefficients of possibly misspecified regression models, but by making use of the g-computation procedure and estimate MCs.

In conclusion, in a study of 1,297 children from 6 European birth cohorts, we observed that (i) exposure to non-persistent EDCs in childhood might have short-term effects on HRT-SE in childhood, (ii) exposure to non-persistent EDCs in childhood might disrupt the HPA axis in childhood, and (iii) disruption of the HPA axis in childhood might have short-term, sex-specific effects on HRT-SE. Future studies should investigate how glucocorticosteroids might mediate the adverse effects of exposure to non-persistent EDCs on childhood neurodevelopment (too broad) in larger populations.

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4 Tables for descriptive data

4.1 Study populations

Table 1: **Participant characteristics (HELIX subcohort; 2013-2016).**

Characteristic	**N = 1,297**[a]
Child age (years)	8.1 (6.5, 8.9)
Child breastfeeding	1,093.0 (84.7%)
Unknown	6
Child ethnicity	
Caucasian	1,157.0 (90.0%)
Pakistani	80.0 (6.2%)
Asian	21.0 (1.6%)
Other	19.0 (1.5%)
African	7.0 (0.5%)
Native American	2.0 (0.2%)
White non European	0.0 (0.0%)
Unknown	11
Child head circumference (cm)	51.8 (50.6, 52.9)
Unknown	3
Child height (m)	1.3 (1.2, 1.4)
Child neuropsychological diagnosis	95.0 (7.3%)
Child rest before assessment	
Yes	1,209.0 (93.3%)
Not as well as usual	87.0 (6.7%)
Unknown	1
Child sex	
Male	710.0 (54.7%)
Female	587.0 (45.3%)
Child weight (kg)	26.9 (22.9, 32.6)
Chiod mood before assessment	
Usual	1,232.0 (95.1%)
Not usual	64.0 (4.9%)
Unknown	1
Cohort	
MOBA	272.0 (21.0%)
INMA	221.0 (17.0%)
BIB	204.0 (15.7%)
KANC	203.0 (15.7%)
RHEA	199.0 (15.3%)
EDEN	198.0 (15.3%)
Creatinine night sample (g/l)	1.7 (0.9, 3.0)
Unknown	321

Creatinine pooled sample (g/l)	1.0 (0.8, 1.2)
Date of test (season)	
Spring	358.0 (27.7%)
Winter	339.0 (26.2%)
Autumn	300.0 (23.2%)
Summer	297.0 (23.0%)
Unknown	3
Family affluence scale	
6	410.0 (31.7%)
5	325.0 (25.1%)
7	248.0 (19.2%)
4	174.0 (13.4%)
3	92.0 (7.1%)
2	28.0 (2.2%)
1	12.0 (0.9%)
0	6.0 (0.5%)
Unknown	2
Fast food/take away (times/week)	0.1 (0.1, 0.5)
Unknown	7
Fasting time before visit (hours)	3.3 (2.8, 4.0)
Financial situation of the parents	
Doing alright	414.0 (32.1%)
Living comfortably	412.0 (31.9%)
Getting by	331.0 (25.6%)
Finding it quite difficult	86.0 (6.7%)
Finding it very difficult	40.0 (3.1%)
Does not wish to answer	8.0 (0.6%)
Unknown	6
Fish and seafood (times/week)	2.0 (1.1, 3.5)
Unknown	5
Fruits (times/week)	9.0 (5.9, 18.0)
Unknown	7
Hit reaction time standard error (ms)	299.6 (231.3, 368.2)
Unknown	18
Marital status	
Living with the father	1,212.0 (94.5%)
Living alone	39.0 (3.0%)
Other situation	31.0 (2.4%)
Unknown	15
Maternal tobacco consumption	
Non-smoker and has never smoked	681.0 (52.6%)
Daily smoker	200.0 (15.5%)
Non-smoker but previously smoked daily	186.0 (14.4%)
Non-smoker but previously smoked although not daily	163.0 (12.6%)
Smoker but not daily	64.0 (4.9%)

Unknown	3
Organic food (times/week)	0.5 (0.0, 3.0)
Unknown	7
Pregnancy maternal active smoking	190.0 (15.1%)
Unknown	40
Pregnancy maternal passive smoking	514.0 (40.3%)
Unknown	21
Vegetables (times/week)	6.5 (4.0, 10.0)
Unknown	6

[a] n (%); Median (IQR)

4.2 Endocrine disruptors

Table 2: **Participants endocrine disruptors concentrations expressed in μgrams/L (HELIX subcohort; 2013-2016).**

Characteristic	**N = 1,297**[a]	**N = 1,297**[b]
OP pesticide metabolites		
DEP	1.8 (0.4, 4.6)	2.0 (0.2)
DETP	0.1 (0.1, 1.7)	21.0 (1.6)
DMP	0.4 (0.3, 4.6)	6.0 (0.5)
DMTP	2.8 (1.2, 6.3)	1.0 (0.1)
Phenols		
BPA	3.8 (2.3, 7.0)	12.0 (0.9)
BUPA	0.1 (0.0, 0.1)	5.0 (0.4)
ETPA	0.7 (0.4, 1.2)	3.0 (0.2)
MEPA	6.3 (3.1, 24.1)	2.0 (0.2)
OXBE	2.0 (0.8, 6.6)	0.0 (0.0)
PRPA	0.2 (0.0, 1.6)	17.0 (1.3)
TRCS	0.6 (0.3, 1.5)	0.0 (0.0)
Phthalate metabolites		
MBzP	4.8 (2.7, 8.7)	1.0 (0.1)
MECPP	32.8 (19.9, 57.6)	1.0 (0.1)
MEHHP	19.3 (11.4, 33.1)	3.0 (0.2)
MEHP	2.8 (1.6, 5.1)	41.0 (3.2)
MEOHP	12.2 (7.1, 20.4)	1.0 (0.1)
MEP	32.5 (15.0, 79.2)	0.0 (0.0)
MiBP	40.2 (24.5, 71.1)	0.0 (0.0)
MnBP	22.7 (14.5, 38.8)	0.0 (0.0)
oh-MiNP	5.0 (3.1, 9.3)	0.0 (0.0)

oxo-MiNP	2.7 (1.7, 5.0)	0.0 (0.0)

[a]Median (IQR)
[b]N missing (% missing)

4.3 Glucocorticosteroids

Table 3: **Participants derived glucocorticosteroids concentrations expressed in ng/ml (HELIX subcohort; 2013-2016).**

Characteristic	**N = 1,004**[a]	**N = 976**[a,b]
cortisol production	4,607.9 (2,860.5, 6,787.6); 18.0 (1.8)	4,559.5 (2,834.5, 6,731.7); 17.0 (1.7)
cortisone production	4,608.1 (2,920.8, 6,843.9); 19.0 (1.9)	4,580.7 (2,899.3, 6,800.5); 18.0 (1.8)
corticosterone production	257.8 (157.9, 410.5); 3.0 (0.3)	256.7 (157.5, 409.7); 3.0 (0.3)

[a]Median (IQR); N missing (% missing)
[b]Measurements available for the HELIX subcohort.

5 Tables for other analyses

5.1 Marginal hypotheses for effect modification

Table 4: **Pairwise differences between marginal contrasts on the logarithmic scale of males and females, for the effect of a increase from the 10th to the 90th percentile of endocrine disrupting chemicals (EDCs) on hit reaction time standard error (HRT-SE), expressed in ms, and on the glucocorticosteroids, expressed in ng/ml (HELIX subcohort; 2013-2016).**

	HRT-SE[a]	corticosterone production[a]	cortisol production[a]	cortisone producti
OP pesticide metabolites				
DEP	0.019 (-0.022, 0.061)	-0.082 (-0.276, 0.113)	-0.139 (-0.374, 0.096)	-0.104 (-0.312, 0.1
DETP	0.025 (-0.054, 0.104)	-0.16 (-0.332, 0.011)	-0.071 (-0.264, 0.123)	-0.097 (-0.269, 0.0
DMP	-0.034 (-0.093, 0.025)	0.007 (-0.217, 0.231)	-0.031 (-0.119, 0.057)	-0.069 (-0.207, 0.0
DMTP	0.005 (-0.095, 0.106)	-0.014 (-0.165, 0.137)	-0.21 (-0.326, -0.094)	-0.166 (-0.353, 0.0
Phenols				
BPA	0.032 (-0.026, 0.09)	-0.153 (-0.291, -0.015)	-0.125 (-0.269, 0.018)	-0.085 (-0.216, 0.0
BUPA	-0.022 (-0.067, 0.024)	-0.117 (-0.247, 0.012)	-0.129 (-0.209, -0.048)	-0.013 (-0.112, 0.0
ETPA	0.012 (-0.021, 0.045)	-0.254 (-0.416, -0.092)	-0.184 (-0.39, 0.022)	-0.219 (-0.472, 0.0
MEPA	-0.001 (-0.061, 0.058)	-0.129 (-0.271, 0.013)	-0.127 (-0.258, 0.004)	-0.144 (-0.257, -0.
OXBE	0.032 (0.004, 0.061)	-0.213 (-0.486, 0.059)	-0.077 (-0.306, 0.153)	-0.064 (-0.274, 0.1
PRPA	0.015 (-0.045, 0.074)	-0.12 (-0.262, 0.022)	-0.043 (-0.238, 0.151)	-0.102 (-0.223, 0.0

TRCS	-0.017 (-0.076, 0.042)	-0.142 (-0.251, -0.034)	-0.13 (-0.248, -0.012)	-0.152 (-0.207, -0.0
Phthalate metabolites				
MBzP	-0.066 (-0.126, -0.007)	-0.026 (-0.098, 0.047)	-0.018 (-0.143, 0.108)	-0.079 (-0.174, 0.0
MECPP	0.008 (-0.076, 0.092)	-0.014 (-0.165, 0.136)	-0.043 (-0.084, -0.002)	0.017 (-0.055, 0.0
MEHHP	0.028 (-0.075, 0.131)	-0.052 (-0.264, 0.161)	-0.091 (-0.208, 0.026)	-0.006 (-0.087, 0.0
MEHP	0.017 (-0.082, 0.115)	-0.165 (-0.259, -0.071)	-0.221 (-0.289, -0.153)	-0.177 (-0.298, -0.0
MEOHP	0.02 (-0.068, 0.107)	-0.061 (-0.232, 0.111)	-0.075 (-0.157, 0.006)	0.009 (-0.063, 0.0
MEP	-0.053 (-0.138, 0.033)	-0.05 (-0.408, 0.308)	-0.083 (-0.384, 0.218)	-0.119 (-0.338, 0.
MiBP	-0.02 (-0.138, 0.098)	0.037 (-0.175, 0.249)	-0.041 (-0.267, 0.184)	-0.021 (-0.162, 0.1
MnBP	-0.035 (-0.11, 0.041)	0.029 (-0.186, 0.243)	0.063 (-0.134, 0.26)	0.017 (-0.076, 0.1
oh-MiNP	0.046 (-0.009, 0.102)	-0.127 (-0.335, 0.08)	-0.181 (-0.33, -0.033)	-0.164 (-0.304, -0.0
oxo-MiNP	-0.026 (-0.059, 0.008)	-0.12 (-0.315, 0.076)	-0.146 (-0.303, 0.011)	-0.127 (-0.238, -0.0

[a]Estimate and 95% CI.

Table 5: **Pairwise differences between marginal contrasts on the logarithmic scale of males and females, for the effect of a increase from the 10th to the 90th percentile of the glucocorticosteroids on hit reaction time standard error (HRT-SE) expressed in ms (HELIX subcohort; 2013-2016).**

	HRT-SE[a]
Glucocorticosteroids	
corticosterone production	0.126 (0.009, 0.243)
cortisol production	0.097 (-0.045, 0.238)
cortisone production	0.14 (0.019, 0.261)

[a]Estimate and 95% CI.

6 Figures for main results

6.1 Marginal contrasts

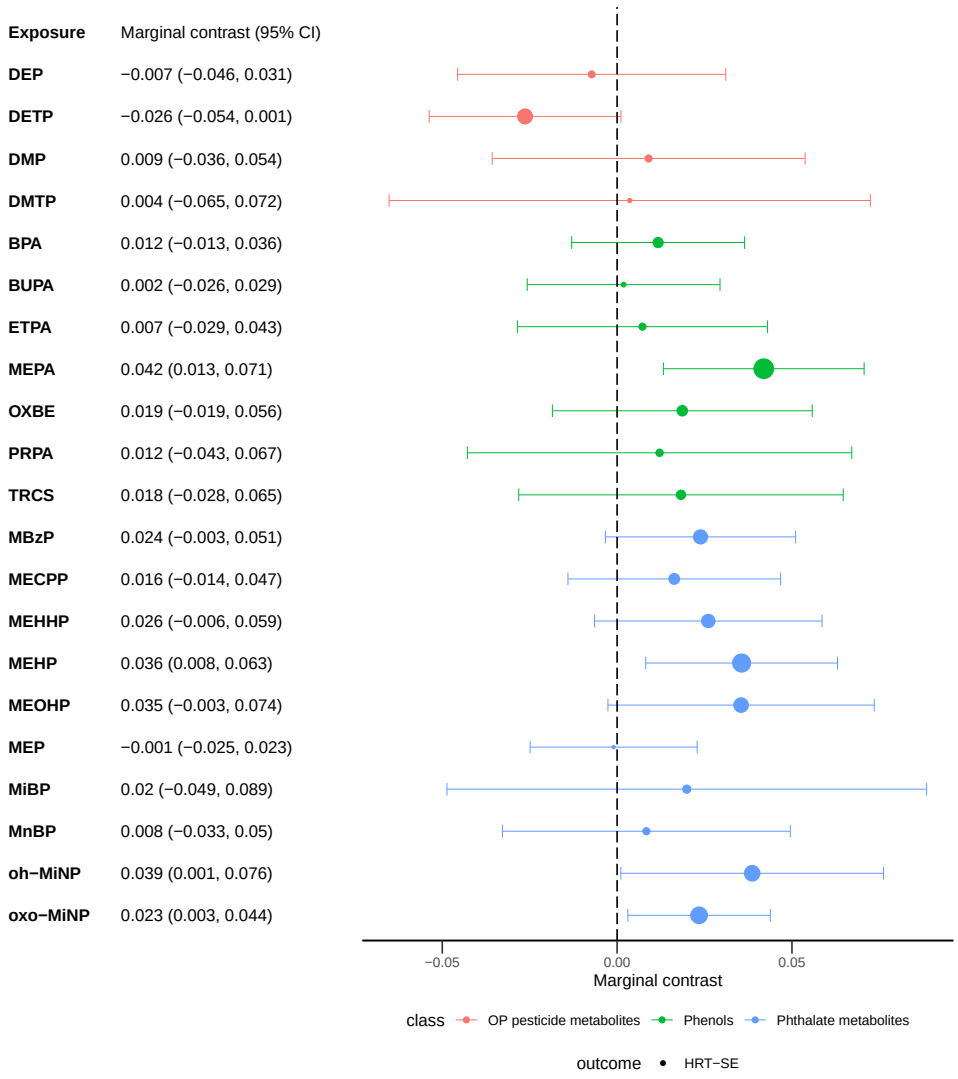

Figure 1: **Marginal contrasts on the logarithmic scale for the effect of a increase from the 10th to the 90th percentile of the endocrine disrupting chemicals (EDCs) on hit reaction time standard error (HRT-SE) expressed in ms (HELIX subcohort; 2013-2016).** Circles indicate effect estimates. Solid lines indicate the 95% CI. The size of the circles represents the S value of the effect estimate (56).

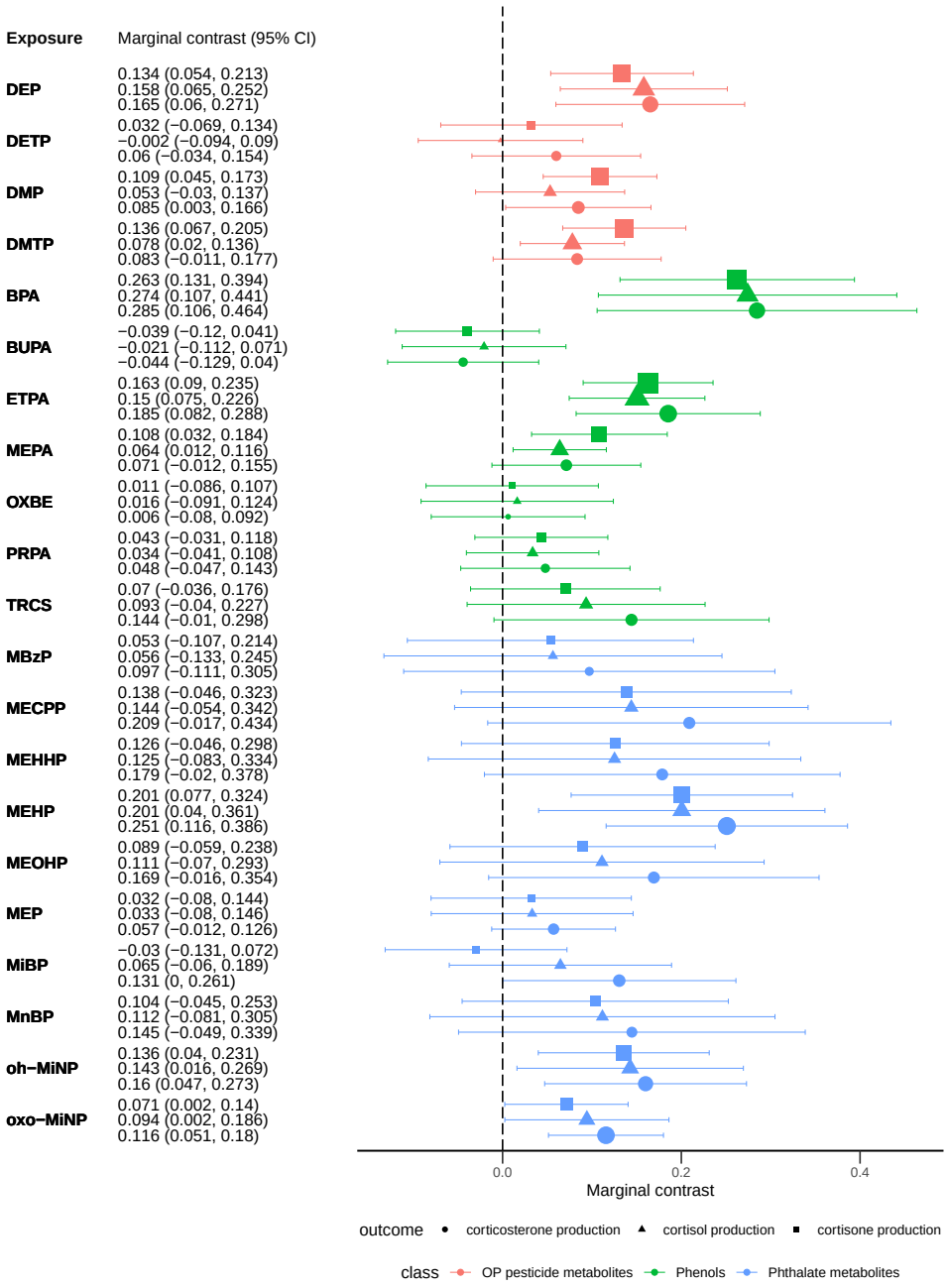

Figure 2: **Marginal contrasts on the logarithmic scale for the effect of a increase from the 10th to the 90th percentile of the endocrine disrupting chemicals (EDCs) on the glucocorticosteroids expressed in ng/ml (HELIX subcohort; 2013-2016).** Circles, triangles, and squares indicate effect estimates. Solid lines indicate the 95% CI. The size of the circles represents the S value of the effect estimate (56).

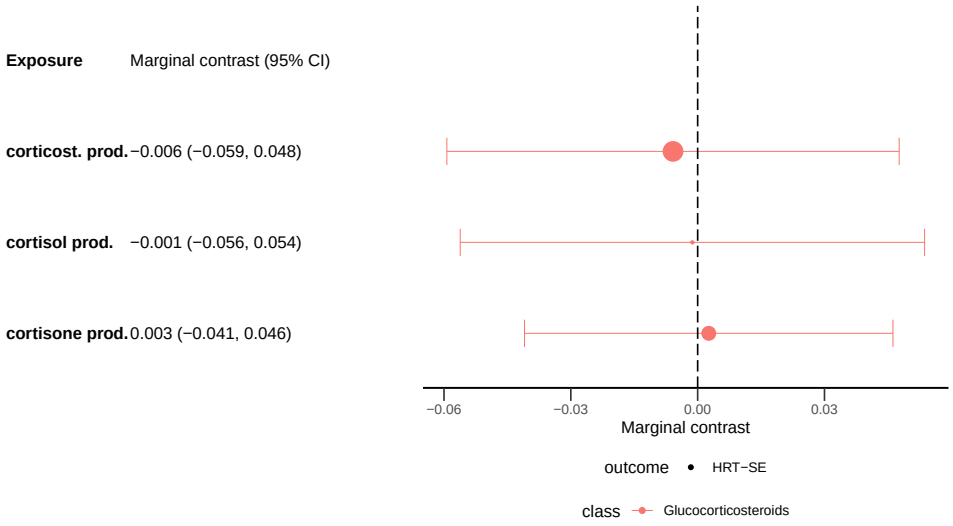

Figure 3: **Marginal contrasts on the logarithmic scale for the effect of a increase from the 10th to the 90th percentile of the glucocorticosteroids on hit reaction time standard error (HRT-SE) expressed in ms (HELIX subcohort; 2013-2016).** Circles indicate effect estimates. Solid lines indicate the 95% CI. The size of the circles represents the S value of the effect estimate (56). Abbreviations: cortisone production (cortisone prod.); cortisol production (cortisol prod.); corticost. prod. (corticosterone production).

7 Supplementary information

7.1 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
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
}
```

8 Supplementary tables

8.1 Tables for descriptive data

8.1.1 Information about the endocrine disruptors

8.1.2 Information about the glucocorticosteroids

8.1.3 Codebooks

8.1.4 Lower limits of quantification of the glucocorticosteroids

8.1.5 Study populations

8.1.6 Concentrations of the glucocorticosteroids

8.2 Tables for main results

8.2.1 Balancing weights: sample sizes

8.2.2 Balancing weights: summary statistics

8.3 Tables for other results

8.3.1 Balancing weights for effect modification: summary statistics

9 Supplementary figures

9.1 Figures for descriptive data

9.1.1 Study populations

9.1.2 Description of endocrine disruptors

9.1.3 Description of glucocorticosteroids

9.2 Figures for other results

9.2.1 Marginal contrasts for effect modification

Compound	Symbol	Variable name	PubChem CID	Parental compoun
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	
n-butyl-paraben	BUPA	bupa	7184	
ethyl-paraben	ETPA	etpa	8434	
methyl-paraben	MEPA	mepa	7456	
oxybenzone	OXBE	oxbe	4632	
propyl-paraben	PRPA	prpa	7175	
triclosan	TRCS	trcs	5564	
Phthalate metabolites				
mono benzyl phthalate	MBzP	mbzp	31736	BBzP
mono-2-ethyl 5-carboxypentyl phthalate	MECPP	mecpp	148386	DEHP
mono-2-ethyl-5-hydroxyhexyl phthalate	MEHHP	mehhp	170295	DEHP
mono-2-ethylhexyl phthalate	MEHP	mehp	21924291	DEHP
mono-2-ethyl-5-oxohexyl phthalate	MEOHP	meohp	119096	DEHP
monoethyl phthalate	MEP	mep	75318	DEP
mono-iso-butyl phthalate	MiBP	mibp	92272	DiBP
mono-n-butyl phthalate	MnBP	mnbp	8575	DnBP
mono-4-methyl-7-hydroxyoctyl phthalate	oh-MiNP	ohminp	102401880	MiNP
mono-4-methyl-7-oxooctyl phthalate	oxo-MiNP	oxominp	102401881	MiNP

Table S1: **Information about non-persistent endocrine disrupting chemicals (EDCs), including the full compound name, the standard symbol, the used variable name, the identifier from PubChem, and the parental compound.**

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

Abbreviations: Human Metabolome Database (HMDB); Chemical Abstracts Service (CAS).

Table S2: **Information about the glucocorticosteroids, including the full metabolite name, the standard symbol, the identifier from the HMDB, and the CAS number.**

	type	description	coding
age_child			
hs_age_years	numerical	Age	
breastfeeding			
hs_bf	categorical	Child breastfeeding	0,1
characteristics_child			
hs_c_height	numerical	Height	
hs_c_weight	numerical	Weight	
hs_head_circ	numerical	Head circumference	
child_diet			
hs_fastfood	numerical	Fast food/take away	
hs_org_food	numerical	Organic food	
hs_total_fish	numerical	Fish and seafood	
hs_total_fruits	numerical	Fruits	
hs_total_veg	numerical	Vegetables	
child_smoking			
hs_tob	categorical	Tobacco consumption	1,2,3,4,5
cohort			
cohort	character	Cohort	SAB,EDEN,BIB,RHEA
creatinine			
hs_creatinine_cg	numerical	Creatinine pooled sample	
envFactors_visit			
hs_mood	categorical	Mood before assessment	1,2
hs_rest_nth	categorical	Rest before assessment	1,2
ethnicity_child			
h_ethnicity_c	character	Child ethnicity	1,2,3,4,5,6,7
ethnicity_mother			
h_ethnicity_m	integer	Mother ethnicity	1,2,3,4,5,6,7
familySEP			
FAS_score	numerical	Family Affluence Scale	
hs_finance	categorical	Financial situation	1,2,3,4,5,6
maternalAlcohol_preg			
e3_alcpreg_g	numerical	Alcool during pregnancy	
maternalDiet_preg			
h_cereal_preg	numerical	Cereal consumption during pregnancy	
h_dairy_preg	numerical	Dairy consumption during pregnancy	
h_fastfood_preg	numerical	Fast food consumption during pregnancy	
h_fish_preg	numerical	Fish consumption during pregnancy	
h_fruit_preg	numerical	Fruit consumption during pregnancy	
h_legume_preg	numerical	Legume consumption during pregnancy	
h_meat_preg	numerical	Meat consumption during pregnancy	
h_veg_preg	numerical	Vegetables consumption during pregnancy	
maternalSEP_preg			
e3_edum	categorical	Maternal education	0,1,2
e3_marital	categorical	Marital status	0,1,2
e3_ses	categorical	Socioeconomic status of the parents	1,2,3
maternalSmoking_preg			
e3_asmokyn_p	categorical	Pregnancy maternal active smoking	0,1
e3_psmokanyt	categorical	Pregnancy maternal passive smoking	0,1

	type	description	coding
age_child			
hs_age_years	numerical	Age	
characteristics_child			
hs_c_height	numerical	Height	
hs_c_weight	numerical	Weight	
hs_head_circ	numerical	Head circumference	
child_diet			
hs_fastfood	numerical	Fast food/take away	
hs_org_food	numerical	Organic food	
hs_total_fish	numerical	Fish and seafood	
hs_total_fruits	numerical	Fruits	
hs_total_veg	numerical	Vegetables	
child_smoking			
hs_tob	categorical	Tobacco consumption	1,2,3,4,5
cohort			
cohort	character	Cohort	SAB,EDEN,BIB,RHEA,KANC,MOBA
creatinine			
creatinine_to_helix	numerical	Creatinine night sample	
hs_creatinine_cg	numerical	Creatinine pooled sample	
ethnicity_child			
h_ethnicity_c	character	Child ethnicity	1,2,3,4,5,6,7
ethnicity_mother			
h_ethnicity_m	integer	Mother ethnicity	1,2,3,4,5,6,7
familySEP			
FAS_score	numerical	Family Affluence Scale	
hs_finance	categorical	Financial situation	1,2,3,4,5,6
season_visit			
hs_date_neu	date	Date of test	
sex_child			
e3_sex	categorical	Sex	0,1
time_lastMeal			
hs_dift_mealblood_imp	numerical	Fasting time	

[a]Percentage of confounders included in the models: 95%.

Table S4: **Codebook for the covariates used in the estimation of the marginal comparisons of endocrine disrupting chemicals (EDCs) on the glucocorticosteroids.**

	type	description	coding
age_child			
hs_age_years	numerical	Age	
breastfeeding			
hs_bf	categorical	Child breastfeeding	0,1
characteristics_child			
hs_c_height	numerical	Height	
hs_c_weight	numerical	Weight	
hs_head_circ	numerical	Head circumference	
chemical			
hs_bpa_c	numerical	Bisphenol A (BPA)	
hs_bupa_c	numerical	N-Butyl paraben (BUPA)	
hs_dedtp_cadj	numerical	Diethyl dithiophosphate (DEDTP) adjusted for creatinine	
hs_dep_c	numerical	Diethyl phosphate (DEP)	
hs_detp_c	numerical	Diethyl thiophosphate (DETP)	
hs_dmdtp_craw	numerical	Dimethyl dithiophosphate (DMDTP)	
hs_dmp_c	numerical	Dimethyl phosphate (DMP)	
hs_dmtp_c	numerical	Dimethyl thiophosphate (DMTP)	
hs_etpa_c	numerical	Ethyl paraben (ETPA)	
hs_mbzp_c	numerical	Mono benzyl phthalate (MbzP)	
hs_mecpp_c	numerical	Mono-2-ethyl 5-carboxypentyl phthalate (MECPP)	
hs_mehhp_c	numerical	Mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP)	
hs_mehp_c	numerical	Mono-2-ethylhexyl phthalate (MEHP)	
hs_meohp_c	numerical	Mono-2-ethyl-5-oxohexyl phthalate (MEOHP)	
hs_mep_c	numerical	Monoethyl phthalate (MEP)	
hs_mepa_c	numerical	Methyl paraben (MEPA)	
hs_mibp_c	numerical	Mono-iso-butyl phthalate (MiBP)	
hs_mnbp_c	numerical	Mono-n-butyl phthalate (MnBP)	
hs_ohminp_c	numerical	Mono-4-methyl-7-hydroxyoctyl phthalate (OHMiNP)	
hs_oxbe_c	numerical	Oxybenzone (OXBE)	
hs_oxominp_c	numerical	Mono-4-methyl-7-oxooctyl phthalate (OXOMiNP)	
hs_prpa_c	numerical	Propyl paraben (PRPA)	
hs_trcs_c	numerical	Triclosan (TRCS)	
child_diet			
hs_fastfood	numerical	Fast food/take away	
hs_org_food	numerical	Organic food	
hs_total_fish	numerical	Fish and seafood	
hs_total_fruits	numerical	Fruits	
hs_total_veg	numerical	Vegetables	
child_smoking			
hs_tob	categorical	Tobacco consumption	1,2,3,4,5
cohort		43	
cohort	character	Cohort	SAB,EDEN,
creatinine			
creatinine_to_helix	numerical	Creatinine night sample	
envFactors_visit			
hs_mood	categorical	Mood before assessment	1,2
hs_rest_nth	categorical	Rest before assessment	1,2
ethnicity_child			
h_ethnicity_c	character	Child ethnicity	1,2,3,4,5,6,7
ethnicity_mother			
h_ethnicity_m	integer	Mother ethnicity	1,2,3,4,5,6,7

Metabolite	LLOQ
5aTHF	5.00
5bTHE	5.00
5b20acortolone	5.00
5b20bcortolone	5.00
5a20acortol	2.50
5a20bcortol	2.50
5b20acortol	2.50
5b20bcortol	2.50
11OHAndros	2.00
17HP	2.00
PT	2.00
20bDHF	0.50
5bTHF	0.50
6OHF	0.50
E	0.50
20aDHE	0.50
20bDHE	0.50
5aTHE	0.50
6OHE	0.50
5aTHB	0.50
5bTHB	0.50
17DOcortolone	0.50
5bTHS	0.50
Andros	0.50
Etio	0.50
F	0.25
20aDHF	0.25
5bDHF	0.10
A	0.10
S	0.10
5bDHS	0.10
T	0.10
AED	0.10

Abbreviations: lower limit of quantification (LLOQ).

Table S6: **Lower limits of quantification expressed in ng/ml for the glucocorticosteroids (HELIX subcohort; 2013-2016).**

Characteristic		**Overall**, N = 1,297[a]	**BIB**, N = 204[a]	**E**
Child age (years)		8.1 (6.5, 8.9)	6.6 (6.5, 6.8)	
Child breastfeeding		1,093.0 (84.7%)	147.0 (72.4%)	
Unknown		6	1	
Child ethnicity				
Caucasian		1,157.0 (90.0%)	87.0 (42.6%)	
Pakistani		80.0 (6.2%)	80.0 (39.2%)	
Asian		21.0 (1.6%)	13.0 (6.4%)	
Other		19.0 (1.5%)	17.0 (8.3%)	
African		7.0 (0.5%)	7.0 (3.4%)	
Native American		2.0 (0.2%)	0.0 (0.0%)	
White non European		0.0 (0.0%)	0.0 (0.0%)	
Unknown		11	0	
Child head circumference (cm)		51.8 (50.6, 52.9)	51.4 (50.3, 52.3)	
Unknown		3	0	
Child height (m)		1.3 (1.2, 1.4)	1.2 (1.2, 1.2)	
Child neuropsychological diagnosis		95.0 (7.3%)	3.0 (1.5%)	
Child rest before assessment				
Yes		1,209.0 (93.3%)	192.0 (94.1%)	
Not as well as usual		87.0 (6.7%)	12.0 (5.9%)	
Unknown		1	0	
Child sex				
Male		710.0 (54.7%)	112.0 (54.9%)	
Female		587.0 (45.3%)	92.0 (45.1%)	
Child weight (kg)		26.9 (22.9, 32.6)	22.3 (20.3, 25.0)	
Chiod mood before assessment				
Usual		1,232.0 (95.1%)	198.0 (97.1%)	
Not usual		64.0 (4.9%)	6.0 (2.9%)	
Unknown		1	0	
Creatinine night sample (g/l)		1.7 (0.9, 3.0)	0.8 (0.6, 1.1)	
Unknown		321	72	
Creatinine pooled sample (g/l)		1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	
Date of test (season)				
Spring		358.0 (27.7%)	48.0 (23.5%)	
Winter		339.0 (26.2%)	40.0 (19.6%)	
Autumn		300.0 (23.2%)	49.0 (24.0%)	
Summer		297.0 (23.0%)	67.0 (32.8%)	
Unknown		3	0	
Family affluence scale				
6		410.0 (31.7%)	34.0 (16.7%)	
5		325.0 (25.1%)	48.0 (23.5%)	
7		248.0 (19.2%)	26.0 (12.7%)	
4		174.0 (13.4%)	40.0 (19.6%)	
3		92.0 (7.1%)	34.0 (16.7%)	
2		28.0 (2.2%)	16.0 (7.8%)	
1		12.0 (0.9%)	4.0 (2.0%)	
0	45	6.0 (0.5%)	2.0 (1.0%)	
Unknown		2	0	
Fast food/take away (times/week)		0.1 (0.1, 0.5)	0.5 (0.1, 1.0)	
Unknown		7	0	
Fasting time before visit (hours)		3.3 (2.8, 4.0)	3.3 (2.8, 4.1)	
Financial situation of the parents				
Doing alright		414.0 (32.1%)	73.0 (35.8%)	
Living comfortably		412.0 (31.9%)	59.0 (28.9%)	
Getting by		331.0 (25.6%)	59.0 (28.9%)	
Finding it quite difficult		86.0 (6.7%)	8.0 (3.9%)	
Finding it very difficult		40.0 (3.1%)	5.0 (2.5%)	
Does not wish to answer		8.0 (0.6%)	0.0 (0.0%)	
Unknown		6	0	
Fish and seafood (times/week)		2.0 (1.1, 3.5)	2.0 (1.0, 3.1)	

Characteristic	**Overall**, N = 1,004[a]	**BIB**, N = 154[a]	**EDEN**, N = 137[a]	**INN**
Glucocorticosteroid				
A	4.3 (2.4, 8.2)	4.8 (2.8, 9.0)	5.1 (2.6, 9.1)	3.
Unknown	1	0	0	
E	22.9 (13.1, 38.5)	25.7 (14.5, 41.4)	28.6 (14.1, 42.0)	17.
F	5.5 (3.2, 9.5)	6.3 (4.2, 10.4)	7.8 (4.2, 11.4)	4.
Unknown	2	0	0	
Glucocorticosteroid metabolite				
11OHAndros	234.2 (130.3, 390.5)	259.7 (151.9, 375.0)	413.0 (221.7, 617.0)	256.7
Unknown	3	0	0	
17-DO-cortolone	57.5 (29.1, 101.7)	56.1 (32.8, 100.6)	76.5 (46.0, 137.6)	61.3
Unknown	2	0	0	
20aDHE	16.6 (9.7, 27.5)	14.2 (7.0, 25.8)	25.8 (15.1, 37.8)	15.
Unknown	11	7	0	
20aDHF	6.6 (3.3, 13.3)	7.2 (3.8, 14.0)	10.0 (5.7, 19.5)	5.
Unknown	7	4	0	
20bDHE	9.5 (6.2, 14.3)	8.7 (4.8, 14.8)	13.2 (9.7, 17.3)	9.
Unknown	17	14	0	
20bDHF	15.2 (9.1, 24.8)	16.5 (10.8, 26.5)	19.9 (12.0, 32.0)	13.
5a20acortol	88.9 (52.1, 141.6)	109.8 (61.7, 177.3)	103.0 (58.0, 153.8)	83.0
Unknown	9	9	0	
5a20bcortol	122.4 (70.4, 185.0)	131.0 (66.3, 182.3)	148.8 (108.8, 226.1)	124.
Unknown	5	5	0	
5aTHB	133.1 (76.1, 222.4)	159.8 (101.7, 241.3)	144.2 (87.9, 255.3)	115.
5aTHE	73.9 (39.7, 124.0)	82.0 (52.1, 145.7)	83.9 (41.5, 132.7)	62.
Unknown	1	0	0	
5aTHF	2,870.0 (1,663.7, 4,389.0)	3,394.6 (2,288.1, 5,308.1)	3,474.2 (1,856.1, 5,253.4)	2,756.9
5b20acortol	147.7 (83.5, 225.8)	177.4 (98.9, 302.3)	169.7 (91.1, 252.9)	141.
Unknown	11	11	0	
5b20acortolone	641.9 (366.0, 983.1)	638.3 (385.0, 1,028.2)	903.7 (574.5, 1,296.1)	654.6
5b20bcortol	195.7 (120.1, 302.4)	242.7 (152.0, 356.8)	225.2 (142.1, 371.5)	199.9
Unknown	3	3	0	
5b20bcortolone	546.9 (336.3, 837.1)	561.3 (331.3, 889.9)	682.3 (452.0, 1,031.1)	534.1
5bDHF	1.4 (0.9, 2.0)	1.4 (0.9, 2.2)	1.8 (1.3, 2.6)	1.
Unknown	2	0	0	
5bTHB	49.3 (28.0, 82.7)	53.3 (27.5, 98.3)	60.9 (34.9, 94.5)	50.
Unknown	1	0	0	
5bTHE	3,138.3 (1,889.5, 4,694.0)	3,552.8 (2,335.3, 4,797.4)	3,649.6 (2,293.5, 5,317.1)	2,911.6
5bTHF	906.5 (548.0, 1,416.1)	1,116.2 (660.8, 1,644.8)	1,238.6 (743.1, 1,578.3)	882.9
Unknown	2	2	0	
6OHE	11.9 (6.5, 18.4)	13.2 (7.6, 20.6)	12.2 (6.1, 17.4)	9.
6OHF	42.8 (22.5, 76.7)	51.9 (29.8, 93.9)	55.8 (29.8, 82.3)	32.
Glucocorticosteroid precursor				
S	0.4 (0.3, 0.8)	0.5 (0.3, 0.9)	0.4 (0.3, 0.7)	0.
Unknown	94 46	6	5	
Glucocorticosteroid precursor metabolite				
17HP	22.3 (15.1, 33.5)	17.0 (11.1, 27.6)	33.2 (23.5, 44.0)	20.
Unknown	1	0	0	
5bDHS	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.3 (0.2, 0.5)	0.
Unknown	132	5	20	
5bTHS	30.7 (18.5, 50.5)	35.7 (20.7, 59.2)	34.5 (19.8, 52.1)	27.
Unknown	2	0	0	
PT	200.6 (112.8, 342.0)	149.1 (87.6, 246.3)	378.8 (230.8, 542.8)	253.4
Androgen				
AED	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)	0.3 (0.2, 0.5)	0.
Unknown	407	0	34	
T	0.5 (0.3, 1.0)	0.7 (0.5, 1.0)	1.0 (0.5, 1.9)	0.

Exposure	Unadjusted	Adjusted[a]
Phenols		
PRPA	1,297	1,297
ETPA	1,297	1,289
OXBE	1,297	1,277
BUPA	1,297	1,276
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		
oxo-MiNP	1,297	1,199
oh-MiNP	1,297	1,171
MBzP	1,297	1,114
MEHP	1,297	1,090
MEP	1,297	1,054
MnBP	1,297	1,035
MEHHP	1,297	1,010
MEOHP	1,297	1,000
MECPP	1,297	980.4
MiBP	1,297	927.3

[a]Truncated weights.

Table S9: **Effective sample size before and after balancing weights estimation (exposures: endocrine disrupting chemicals (EDCs); outcome: hit reaction time standard error (HRT-SE)) (HELIX subcohort; 2013-2016).**

Exposure	Unadjusted	Adjusted[a]
Phenols		
OXBE	976.0	960.1
PRPA	976.0	956.0
MEPA	976.0	953.7
BUPA	976.0	952.3
ETPA	976.0	951.7
TRCS	976.0	942.4
BPA	976.0	856.4
OP pesticide metabolites		
DEP	976.0	922.1
DETP	976.0	922.1
DMTP	976.0	907.3
DMP	976.0	893.3
Phthalate metabolites		
oh-MiNP	976.0	877.9
oxo-MiNP	976.0	873.6
MBzP	976.0	828.8
MEHP	976.0	827.3
MEP	976.0	796.3
MEHHP	976.0	784.8
MECPP	976.0	768.1
MEOHP	976.0	761.5
MnBP	976.0	745.7
MiBP	976.0	690.9

[a]Truncated weights.

Table S10: **Effective sample size before and after balancing weights estimation (exposures: endocrine disrupting chemicals (EDCs); outcomes: glucocorticosteroids) (HELIX subcohort; 2013-2016).**

Exposure	Unadjusted	Adjusted[a]
cortisone production	976.0	777.2
corticosterone production	976.0	757.5
cortisol production	976.0	751.5

[a]Truncated weights.

Table S11: **Effective sample size before and after balancing weights estimation (exposures: glucocorticosteroids; outcome: hit reaction time standard error (HRT-SE)) (HELIX subcohort; 2013-2016).**

	Median (IQR)	Range
Characteristic[a]	**N = 1,297**[a]	**N = 1,297**[a]
OP pesticide metabolites		
DMP	0.99 (0.73, 1.25)	0.49, 1.50
DMTP	1.00 (0.81, 1.20)	0.59, 1.39
DEP	1.01 (0.81, 1.19)	0.59, 1.39
DETP	0.99 (0.81, 1.18)	0.61, 1.41
Phenols		
MEPA	1.01 (0.90, 1.13)	0.74, 1.25
ETPA	1.01 (0.96, 1.07)	0.88, 1.14
PRPA		
2143289344	1,297 (100%)	1,297 (100%)
BPA	0.99 (0.70, 1.27)	0.39, 1.57
BUPA	1.01 (0.91, 1.11)	0.81, 1.22
OXBE	1.01 (0.92, 1.09)	0.79, 1.21
TRCS	1.01 (0.87, 1.13)	0.68, 1.28
Phthalate metabolites		
MEP	0.93 (0.61, 1.27)	0.27, 1.77
MiBP	0.91 (0.46, 1.38)	0.05, 1.92
MnBP	0.98 (0.59, 1.33)	0.20, 1.74
MBzP	0.98 (0.66, 1.27)	0.35, 1.62
MEHP	0.98 (0.64, 1.28)	0.31, 1.68
MEHHP	0.96 (0.54, 1.35)	0.16, 1.76
MEOHP	0.96 (0.52, 1.35)	0.15, 1.78
MECPP	0.95 (0.50, 1.34)	0.14, 1.84
oh-MiNP	1.00 (0.74, 1.24)	0.47, 1.51
oxo-MiNP	1.01 (0.78, 1.20)	0.52, 1.43

[a]Truncated weights.

Table S12: **Summary statistics of the estimated balancing weights (exposures: endocrine disrupting chemicals (EDCs); outcome: hit reaction time standard error (HRT-SE)) (HELIX subcohort; 2013-2016).**

Characteristic[a]	Median (IQR) **N = 976**[a]	Range **N = 976**[a]
OP pesticide metabolites		
DMP	0.99 (0.75, 1.23)	0.51, 1.46
DMTP	1.00 (0.78, 1.23)	0.56, 1.41
DEP	0.99 (0.81, 1.20)	0.64, 1.41
DETP	0.99 (0.82, 1.18)	0.62, 1.41
Phenols		
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)	0.76, 1.26
BPA	1.00 (0.70, 1.26)	0.40, 1.58
BUPA	1.01 (0.90, 1.13)	0.75, 1.27
OXBE	1.01 (0.92, 1.10)	0.78, 1.21
TRCS	1.01 (0.86, 1.14)	0.68, 1.29
Phthalate metabolites		
MEP	0.92 (0.60, 1.27)	0.28, 1.74
MiBP	0.88 (0.44, 1.38)	0.09, 1.98
MnBP	0.97 (0.52, 1.35)	0.14, 1.84
MBzP	0.94 (0.68, 1.29)	0.35, 1.68
MEHP	0.98 (0.65, 1.29)	0.33, 1.64
MEHHP	0.98 (0.56, 1.35)	0.21, 1.69
MEOHP	0.98 (0.53, 1.35)	0.18, 1.77
MECPP	0.96 (0.55, 1.36)	0.19, 1.76
oh-MiNP	0.99 (0.73, 1.25)	0.45, 1.49
oxo-MiNP	1.01 (0.71, 1.25)	0.45, 1.52

[a]Truncated weights.

Table S13: **Summary statistics of the estimated balancing weights (exposures: endocrine disrupting chemicals (EDCs); outcomes: glucocorticosteroids) (HELIX subcohort; 2013-2016).**

	Median (IQR)	Range
Characteristic[a]	**N = 976**[a]	**N = 976**[a]
cortisol production	1.00 (0.54, 1.39)	0.14, 1.80
cortisone production	1.00 (0.59, 1.39)	0.19, 1.73
corticosterone production	0.98 (0.56, 1.39)	0.15, 1.78

[a]Truncated weights.

Table S14: **Summary statistics of the estimated balancing weights (exposures: glucocorticosteroids; outcome: hit reaction time standard error (HRT-SE)) (HELIX subcohort; 2013-2016).**

	Median (IQR)		Range	
Characteristic[a]	**females**, N = 587[a]	**males**, N = 710[a]	**females**, N = 587[a]	**males**, N = 710[a]
OP pesticide metabolites				
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, 1.18)	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
Phenols				
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)	0.42, 1.50	0.42, 1.50
BUPA	1.02 (0.95, 1.10)	1.01 (0.81, 1.20)	0.67, 1.29	0.67, 1.29
OXBE	1.03 (0.92, 1.12)	1.02 (0.94, 1.09)	0.81, 1.19	0.81, 1.19
TRCS	1.03 (0.92, 1.13)	1.01 (0.89, 1.12)	0.73, 1.25	0.73, 1.25
Phthalate metabolites				
MEP	0.96 (0.67, 1.26)	0.93 (0.62, 1.30)	0.31, 1.68	0.31, 1.68
MiBP	0.93 (0.51, 1.39)	0.96 (0.52, 1.40)	0.16, 1.85	0.16, 1.85
MnBP	1.00 (0.63, 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, 1.27)	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 (0.56, 1.36)	0.26, 1.72	0.26, 1.72
MEOHP	1.00 (0.63, 1.29)	0.95 (0.53, 1.40)	0.23, 1.74	0.23, 1.74
MECPP	1.00 (0.59, 1.33)	0.95 (0.50, 1.37)	0.23, 1.76	0.23, 1.76
oh-MiNP	1.02 (0.78, 1.22)	1.00 (0.76, 1.23)	0.51, 1.46	0.51, 1.46
oxo-MiNP	1.02 (0.84, 1.17)	1.01 (0.76, 1.21)	0.58, 1.39	0.58, 1.39

[a]Truncated weights.

Table S15: **Summary statistics of the estimated balancing weights for effect modification (exposures: endocrine disrupting chemicals (EDCs); outcome: hit reaction time standard error (HRT-SE); modifier: sex) (HELIX subcohort; 2013-2016).**

	Median (IQR)		Range	
Characteristic[a]	**females**, N = 434[a]	**males**, N = 542[a]	**females**, N = 434[a]	**males**, N = 542[a]
OP pesticide metabolites				
DMP	0.98 (0.77, 1.23)	1.01 (0.76, 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, 1.18)	0.67, 1.36	0.67, 1.36
DETP	1.00 (0.77, 1.22)	1.01 (0.86, 1.17)	0.57, 1.40	0.57, 1.40
Phenols				
MEPA	1.01 (0.88, 1.16)	1.03 (0.94, 1.11)	0.73, 1.26	0.73, 1.26
ETPA	1.04 (0.92, 1.12)	1.02 (0.91, 1.12)	0.78, 1.22	0.78, 1.22
PRPA	1.03 (0.87, 1.16)	1.02 (0.95, 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, 1.20)	0.64, 1.30	0.64, 1.30
OXBE	1.03 (0.86, 1.16)	1.02 (0.95, 1.09)	0.76, 1.22	0.76, 1.22
TRCS	1.03 (0.92, 1.13)	1.01 (0.88, 1.14)	0.73, 1.25	0.73, 1.25
Phthalate metabolites				
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, 1.39)	0.15, 1.84	0.15, 1.84
MnBP	0.97 (0.51, 1.40)	0.98 (0.57, 1.32)	0.21, 1.78	0.21, 1.78
MBzP	0.99 (0.70, 1.26)	0.98 (0.66, 1.31)	0.38, 1.58	0.38, 1.58
MEHP	1.01 (0.72, 1.29)	0.98 (0.61, 1.34)	0.36, 1.58	0.36, 1.58
MEHHP	1.02 (0.65, 1.31)	1.00 (0.59, 1.35)	0.30, 1.63	0.30, 1.63
MEOHP	1.01 (0.62, 1.32)	1.01 (0.51, 1.41)	0.24, 1.68	0.24, 1.68
MECPP	0.98 (0.62, 1.32)	0.98 (0.54, 1.40)	0.29, 1.67	0.29, 1.67
oh-MiNP	1.00 (0.73, 1.26)	1.00 (0.78, 1.24)	0.49, 1.44	0.49, 1.44
oxo-MiNP	1.03 (0.74, 1.27)	1.02 (0.76, 1.24)	0.47, 1.45	0.47, 1.45

[a]Truncated weights.

Table S16: **Summary statistics of the estimated balancing weights for effect modification (exposures: endocrine disrupting chemicals (EDCs); outcomes: glucocorticosteroids; modifier: sex) (HELIX subcohort; 2013-2016).**

Characteristic[a]	Median (IQR)		Range	
	females, N = 434[a]	**males**, N = 542[a]	**females**, N = 434[a]	**males**, N = 542[a]
cortisol production	0.97 (0.57, 1.41)	1.01 (0.59, 1.35)	0.24, 1.71	0.24, 1.71
cortisone production	1.00 (0.61, 1.40)	1.00 (0.59, 1.38)	0.27, 1.69	0.27, 1.69
corticosterone production	1.00 (0.60, 1.39)	1.03 (0.56, 1.37)	0.23, 1.71	0.23, 1.71

[a]Truncated weights.

Table S17: **Summary statistics of the estimated balancing weights for effect modification (exposures: glucocorticosteroids; outcome: hit reaction time standard error (HRT-SE); modifier: sex) (HELIX subcohort; 2013-2016).**

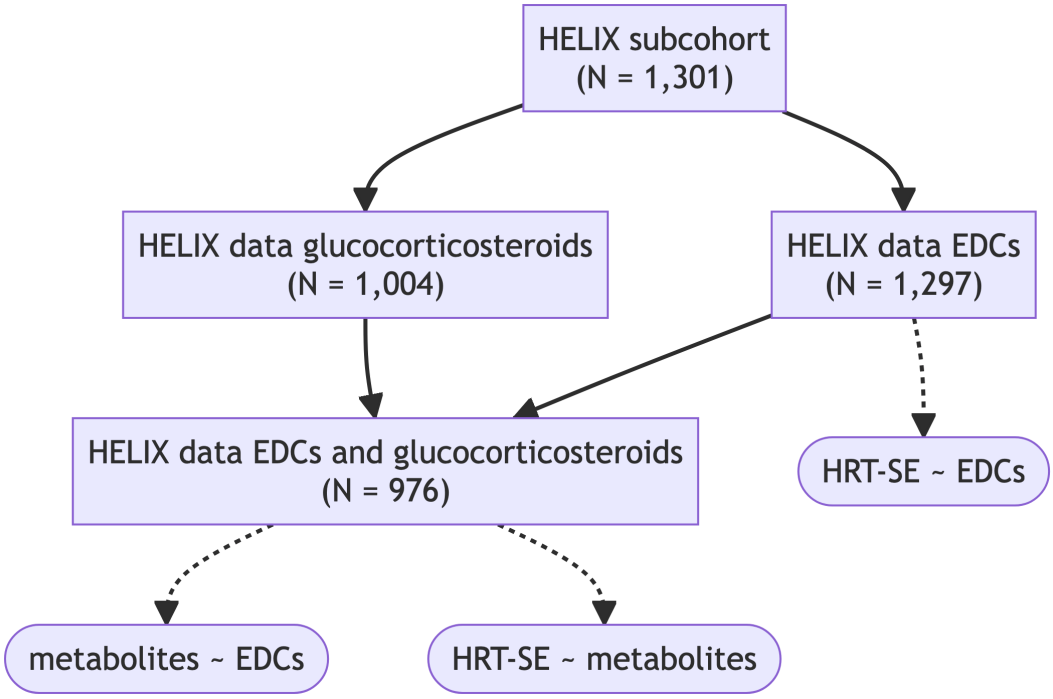

Figure S1: Flowchart describing the sample size for each research question.

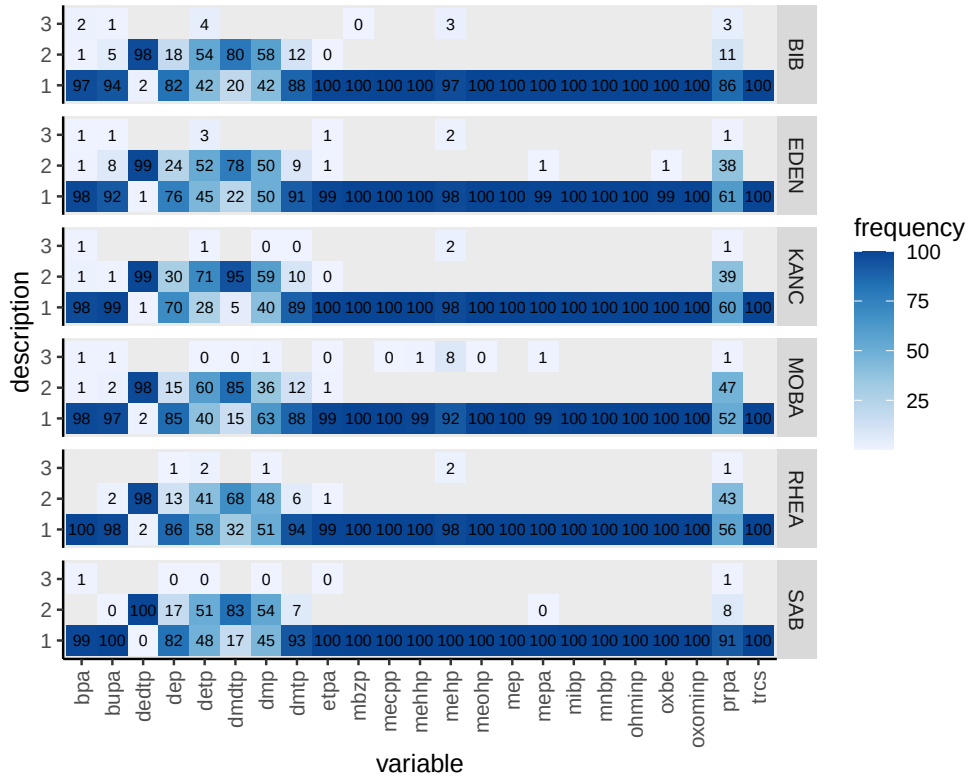

Figure S2: **Measurement classification of endocrine disrupting chemicals (EDCs), by cohort (HELIX subcohort; 2013-2016).** Coding: 1, quantifiable; 2, <LOD; 3, interference or out of range; 4. not analysed.

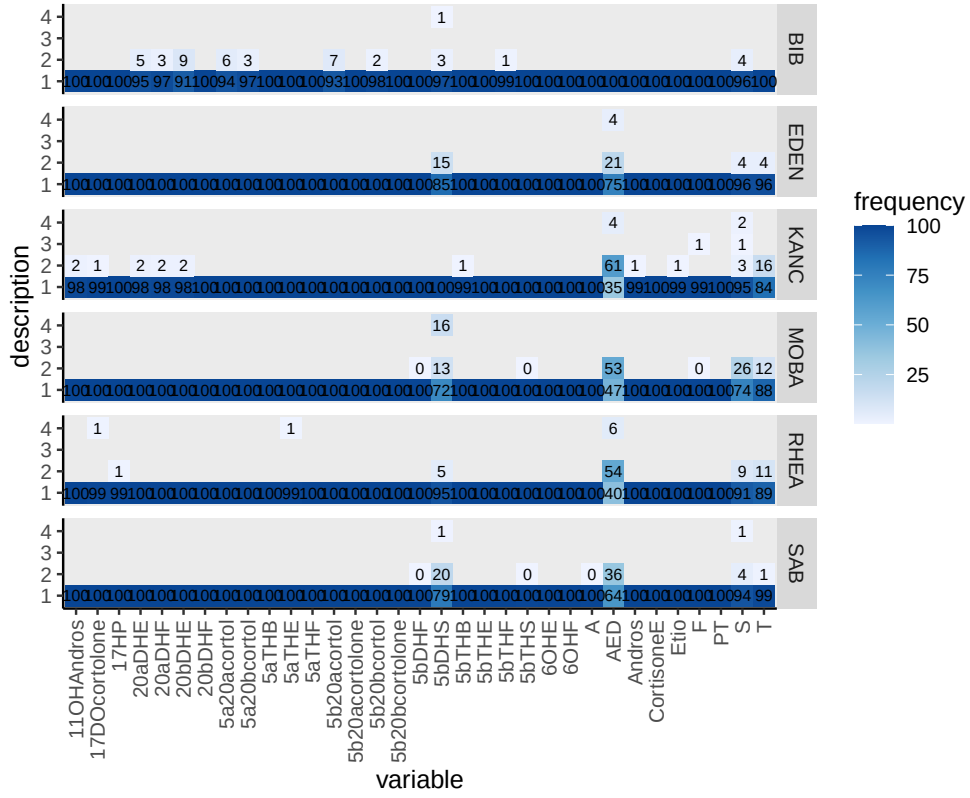

Figure S3: **Measurement classification of the glucocorticosteroids, by cohort (HELIX subcohort; 2013-2016).** Coding: 1, quantifiable; 2, <LOQ; 3, interference or out of range; 4, not detected.

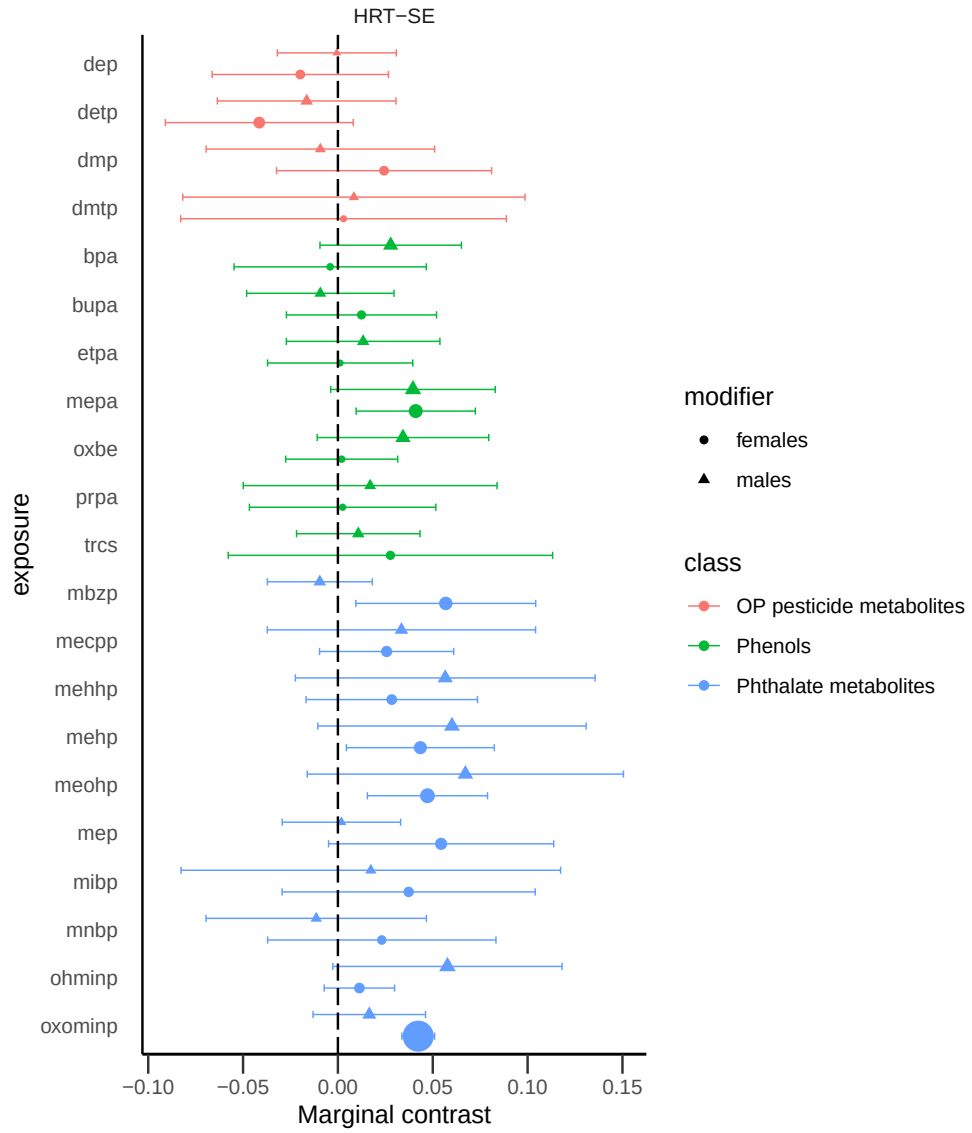

Figure S4: **Marginal contrasts on the logarithmic scale for effect modification by sex of a increase from the 10th to the 90th percentile of the endocrine disrupting chemicals (EDCs) on hit reaction time standard error (HRT-SE) expressed in ms (HELIX subcohort; 2013-2016).** Circles and triangles indicate effect estimates. Solid lines indicate the 95% CI. The size of the circles represents the S value of the effect estimate (56).

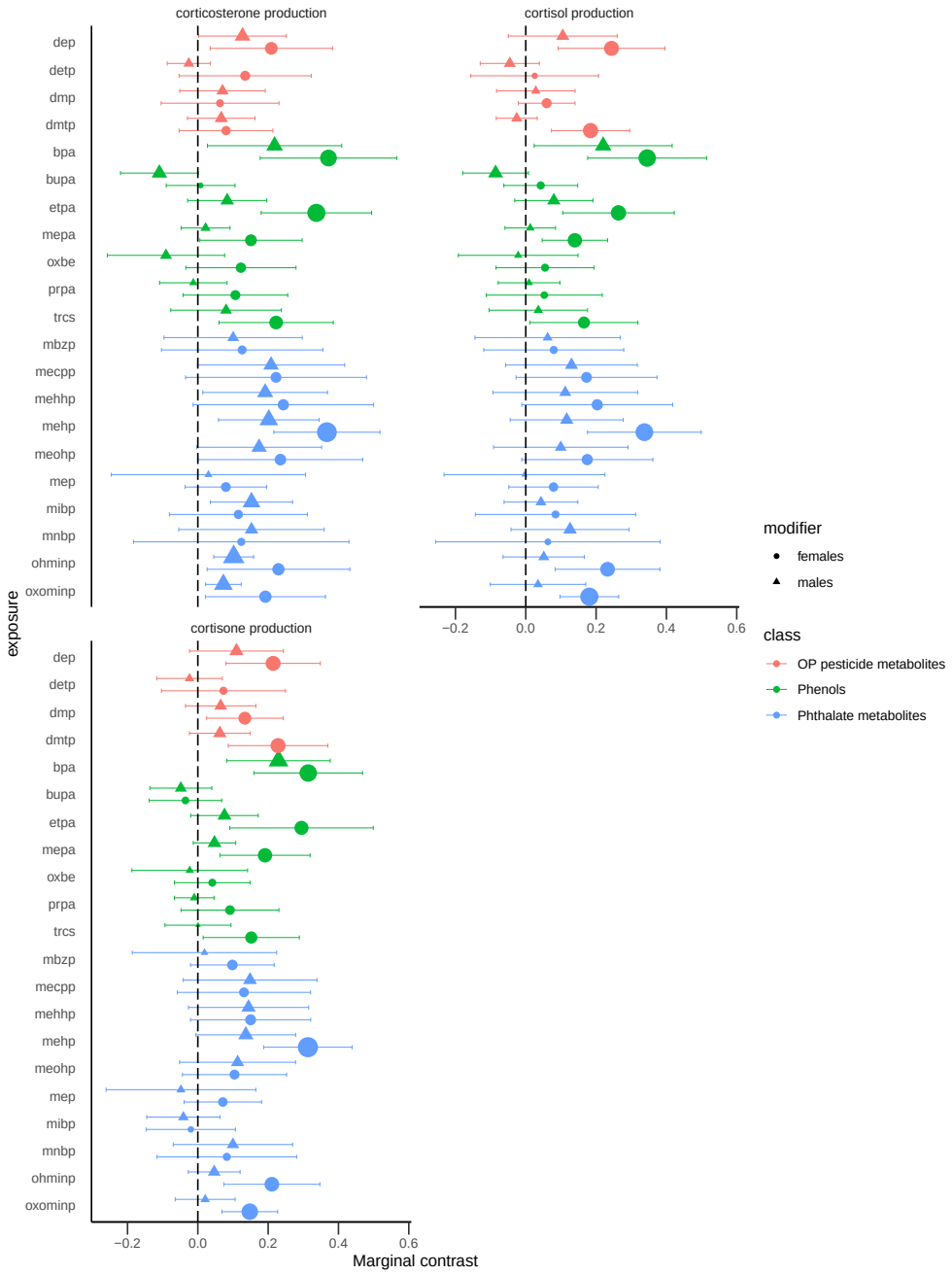

Figure S5: **Marginal contrasts on the logarithmic scale for effect modification by sex of a increase from the 10th to the 90th percentile of the endocrine disrupting chemicals (EDCs) on the glucocorticosteroids expressed in ng/ml (HELIX subcohort; 2013-2016).** Circles and triangles indicate effect estimates. Solid lines indicate the 95% CI. The size of the circles represents the S value of the effect estimate (56).

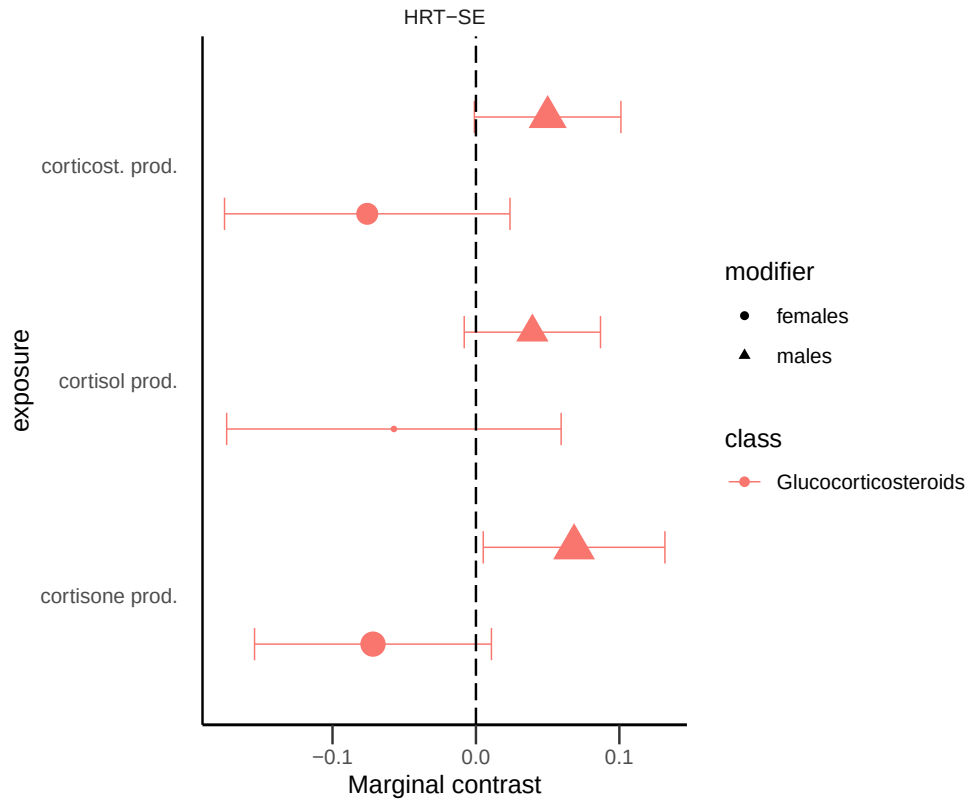

Figure S6: **Marginal contrasts on the logarithmic scale for effect modification by sex of a increase from the 10th to the 90th percentile of the glucocorticosteroids on hit reaction time standard error (HRT-SE) expressed in ms (HELIX subcohort; 2013-2016).** Circles and triangles indicate effect estimates. Solid lines indicate the 95% CI. The size of the circles represents the S value of the effect estimate (56). Abbreviations: cortisone production (cortisone prod.); cortisol production (cortisol prod.); corticost. prod. (corticosterone production).